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New insights into autoinflammatory diseases: From bench to bedside

Edited by
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New insights into autoinflammatory diseases: From bench to bedside

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Editorial: New insights into autoinflammatory diseases: from bench to bedside

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Editorial on the Research Topic
New insights into autoinflammatory diseases: from bench to bedside

The concept of autoinflammation was introduced in McDermott et al. (1) and refers to primary diseases of innate immunity caused by the activation of the inflammasome with the production of cytokines. The diseases are induced by inappropriate activation of antigen-independent inflammatory mechanisms. However, cells associated with adaptative immunity (e.g., T lymphocytes) may also contribute to autoinflammation (2, 3).

The demonstration of the genetic origin of these rare diseases has made it possible to better understand the immunopathogenesis of autoinflammatory diseases (AIDs).

Monogenic AIDs are caused by mutations of genes coding for proteins, which play a role in the regulation of the inflammatory response. Most AIDs have an early onset and make a clinical picture of recurrent fevers associated with inflammatory cutaneous, mucosal, serosal, and osteoarticular involvement and a long-term risk of secondary amyloidosis. These clinical abnormalities occur in the form of repeated attacks and are associated with a biological inflammatory syndrome not explained by an infectious or autoimmune cause. Apart from crises, patients are asymptomatic without systemic inflammation (4).

Familial Mediterranean fever (FMF), cryopyrin-associated periodic fever syndrome or NLRP3-associated AIDs, mevalonate-kinase deficiency, and TNFRSF1A-receptor associated periodic fever syndrome are the first four described monogenic diseases and are considered under the term periodic fevers. They correspond to a disorder of the inflammasomes and are related to IL-1 family cytokines.

Other AIDs associate systemic inflammation and skin damage such as urticaria rash with other clinical manifestations. It is the case of familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and chronic infantile neurological cutaneous and articular syndrome (CINCA).

New diseases are also currently being described, due to advances in genetics analysis and may be categorized into three working groups depending on the pathogenic mechanisms involved. Thus, we distinguish the pathologies mediated by IL-1 family cytokines (e.g., the case of FMF or mevalonate-kinase deficiency), the diseases of interferon production and signaling called interferonopathies [e.g., Aicardi-Goutières syndrome and STING-associated vasculitis with onset in infancy (SAVI)], and the diseases of NFkB activation [e.g., Blau syndrome and haploinsufficiency of A20/tumor necrosis factor alpha-induced protein 3 (TNFAIP3)]. The clinical presentation of these diseases is variable, with recurrent fever and with dominant skin involvement or as an immune deficiency (2–5). The principal

inflammatory mechanism linked to each disease is targeted for treatment and includes the use of biological agents that block different cytokines.

Additional disorders are also classified as autoinflammatory syndrome with or without identifiable genetic cause. However, some autoinflammatory diseases result from multiple mechanisms and do not neatly fall into the categories listed above.

For example, etiologic defects have been identified for cyclic neutropenia, pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome, pyoderma gangrenosum, acne and suppurative hidradenitis (PASH) syndrome, deficiency of the IL-1 receptor antagonist (IL-1Ra) (DIRA), deficiency of the IL-36R antagonist (DITRA) and recently identified vacuoles, E1 enzyme/X-linked autoinflammatory somatic (or VEXAS) syndrome (5, 6). Those without a known cause include, for example, systemic-onset juvenile idiopathic arthritis, adult-onset Still disease, periodic fever, aphthous stomatitis, pharyngitis and adenopathy (PFAPA), non-infectious uveitis, non-infectious scleritis, undifferentiated autoinflammatory diseases, Behçet disease, and Schnitzler syndrome.

Given the rarity of systemic monogenic and multifactorial AIDs, the creation of international registries was a necessity. These registries have the advantage of including a larger number of patients and of globally sharing broad knowledge on the management of these rare diseases through the sharing of experience of clinicians and researchers. This is the case of the AutoInflammatory Disease Alliance (AIDA) network that will be presented in this issue (7).

The current Research Topic presents several registries including The Autoinflammatory Disease Alliance Registry of Monogenic Autoinflammatory Disease, the AIDA International Registry for patients with Schnitzler's syndrome, with Behçet's disease, with undifferentiated systemic autoInflammatory disease, and with Still's disease, the AIDA International registry for patients with VEXAS syndrome, and the AIDA registry for patients with axial spondyloarthritis in patients with recurrent fever attacks.

In addition, the current collection includes a prospective multicenter study from France about vasculitis and familial Mediterranean fever. The study, which includes 22 patients with both FMF and vasculitis, showed that polyarteritis nodosa (PAN) ($n = 10$) and IgA vasculitis ($n = 8$) were predominant with a high frequency of bleeding in FMF-associated PAN. The authors concluded that FMF should be investigated in case of persistent symptoms and/or inflammatory syndrome despite vasculitis treatment in Mediterranean patients.

We also invite you to read in this issue, a very interesting review by Naga et al. about the diagnosis and management of Behçet uveitis.

Contributors and editors of this Research Topic invite readers to take advantage of this collection and read up-to-date information about a variety of research areas on AIDs. Clinical advances, including advances in the treatment of AIDs, will be covered with a focus on all new insights in the field.

Disease-specific therapeutic strategies are established for some AIDs, but new therapeutic approaches are needed. An article included in this Research Topic reviewed the effectiveness and safety of JAK Inhibitors (JAKi) in AIDs. Through a systematic review of the literature in accordance with the PRISMA guidelines, the results show that JAKi can be beneficial in certain AIDs. The risk of viral infections should be considered. To accurately assess the risk-benefit ratio of JAKi for AIDs, clinical trials should be conducted.

The effectiveness of JAK inhibitors was evaluated in a Chinese study involving six patients with trisomy 8 and autoinflammatory features, with a favorable response in 4/6 patients with glucocorticoid sparing effect and good tolerance.

Additionally, a real-life study from the International AIDA Registry assessed any difference in the effectiveness of the IL-1β antagonist (canakinumab) prescribed as a first-line biologic agent between systemic and chronic-articular Still's disease. The results of the study of 26 patients showed that, when used as a first-line biotechnological agent, canakinumab has proved to be effective in controlling both clinical and laboratory manifestations regardless of the type of disease course.

In conclusion, approaches to diagnosis and therapeutic management of AIDs are rapidly developing. It is expected that this research will spark new and very interesting studies to better understand AIDs and how to manage patients.

Author contributions

WA designed, wrote and reviewed the article, and collaborated with the writing and the revision of the manuscript.

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Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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STUDY PROTOCOL
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Development and Implementation of the AIDA International Registry for Patients With Still's Disease

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Objective: Aim of this paper is to present the design, construction, and modalities of dissemination of the AutoInflammatory Disease Alliance (AIDA) International Registry for patients with systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD), which are the pediatric and adult forms of the same autoinflammatory disorder.

Methods: This Registry is a clinical, physician-driven, population- and electronic-based instrument implemented for the retrospective and prospective collection of real-world data. The collection of data is based on the Research Electronic Data Capture (REDCap) tool and is intended to obtain evidence drawn from routine patients' management. The collection of standardized data is thought to bring knowledge about real-life clinical research and potentially communicate with other existing and future Registries dedicated to Still's disease. Moreover, it has been conceived to be flexible enough to easily change according to future scientific acquisitions.

Results: Starting from June 30th to February 7th, 2022, 110 Centers from 23 Countries in 4 continents have been involved. Fifty-four of these have already obtained the approval from their local Ethics Committees. Currently, the platform counts 290 users (111 Principal Investigators, 175 Site Investigators, 2 Lead Investigators, and 2 data managers). The Registry collects baseline and follow-up data using 4449 fields organized into 14 instruments, including patient's demographics, history, clinical manifestations and symptoms, trigger/risk factors, therapies and healthcare access.

Conclusions: This international Registry for patients with Still's disease will allow a robust clinical research through collection of standardized data, international consultation, dissemination of knowledge, and implementation of observational studies based on wide cohorts of patients followed-up for very long periods. Solid evidence drawn from "real-life" data represents the ultimate goal of this Registry, which has been implemented to significantly improve the overall management of patients with Still's disease. NCT 05200715 available at https://clinicaltrials.gov/.

Keywords: autoinflammatory diseases, precision medicine, personalized medicine, rare diseases, research, treatment

INTRODUCTION

Data available on rare disorders are mainly excerpted from case reports, case series and small observational studies. This represents a harsh struggle for physicians and researchers dedicated to such diseases, as recruiting a sufficient number of patients may be challenging. A direct consequence is the lack of solid evidence on long-term disease course, borderline or atypical clinical manifestations, proper clinical management, short and long-term outcomes, prognostic factors, and the most appropriate therapeutic solutions. This is also evident for patients with autoinflammatory disorders (1, 2).

As a matter of fact, new research tools based on the Internet are going to overcome traditional research approaches in the field of rare diseases; patients' registries have taken a first-in-charge position among new electronic tools due to their capacity to recruit numerous patients followed-up for very long periods. The primary importance of patients' registries has also been recognized by the European Union, which has included these tools among the effective strategies to implement for rare diseases and has also provided guidelines aimed at ensuring high quality registries (3–5).

As a whole, these reasons have brought about the development of an international platform hosting specific registries dedicated to monogenic and multifactorial autoinflammatory diseases. This

project has taken the name of AIDA from the acronym of AutoInflammatory Disease Alliance. The primary objective of the project has been the creation of an International Network of researchers and physicians interested in sharing knowledge and expanding current evidence about autoinflammatory diseases, including systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD), which are the pediatric and adult forms of the same autoinflammatory disorder. The AIDA Network may be reached at the following website: https://aidanetwork.org/en/.

AOSD and sJIA are rare diseases characterized by the triad of daily spiking fever, arthritis, and evanescent salmon-colored skin rash, but serositis, lymphoadenopathy, hepatomegaly, splenomegaly, and lung inflammatory involvement may also be encountered (6, 7). Life-threatening complications, such as macrophage activation syndrome (MAS) and interstitial lung disease, may complicate both diseases (8, 9).

Laboratory investigations typically show an elevated white blood cell count with neutrophil predominance, increased inflammatory markers, and high levels of serum ferritin. Serum liver enzymes are also increased in some patients (10). To date, diagnosis of AOSD and sJIA are clinical and require the exclusion of infectious, neoplastic and autoimmune diseases. Different sets of criteria have been developed for diagnostic and classification purposes, with Yamaguchi's criteria and Fautrel's criteria being the most frequently employed for adult patients (11, 12), while the Pediatric Rheumatology INternational Trials Organization (PRINTO) provisional criteria and the International League of Associations for Rheumatology (ILAR) criteria are used for pediatric patients (13).

In this paper we are going to illustrate the steps that led to the development and activation of the International AIDA Registry conceived for patients with Still's disease, focusing on the rationale, design, material, and methods employed along with the diffusion of the project.

MATERIALS AND METHODS

Study Design

This AIDA Registry has been thought as an international, clinical, physician-driven, population- and electronic-based registry for patients diagnosed with Still's disease, disregarding the age at disease onset.

Data collection includes both a retrospective and a prospective phase. The former refers to demographic, clinical laboratory and therapeutic data accrued up to the time of enrollment in the Registry; the latter is about progressive updates in clinical, therapeutic, and socioeconomic conditions reported thereafter. The prospective data collection consists of regular updates (at least one per year), but is particularly recommended when changes in treatment options, including dosage modifications and different molecules combinations, occur.

As part of its observational design, the Registry requires the collection of demographic, genetic, clinical, laboratory and treatment data collected over the past months/years of disease activity and over the future years of disease. Data will be exclusively captured from the routine assessments performed in the context of the standard management included in the daily clinical practice and no additional information will be requested. Furthermore, all of the therapeutic choices and eventual treatment changes proposed to patients will not be affected by adherence to the project itself, but will only be guided by physicians' clinical judgment to preserve and improve patients' health.

Participation in the AIDA project is free and open to any Center that deals with the management, diagnosis, and treatment of pediatric or adult-onset Still's disease; no limits as to the clinical specialty, location, and type of practice setting have been provided and no costs or financial fees are settled, since data inserted are usually collected throughout standard practice. As a prerequisite for adherence to the project, each Center should obtain approval from the local Ethics Committee and should define a Principal Investigator and at least a Site Investigator, which will, respectively, manage the local coordination of the study and documentation at data entry. After having presented a formal request about the involvement in the AIDA Network to the study Promoter, all Centers receive the proper credentials to access the Registry and start patients' enrollment.

Registry Objectives

The Registry for Still's disease is primarily intended to gather as much data as possible from a robust cohort of patients enrolled on an international basis, in order to homogenize the research efforts and obtain significant results from real-world experience, disregarding specific geographic contexts. The first research paper obtained from data recruited in this Registry will focus on better characterizing prognostic factors capable of identifying patients more likely to develop complications in the short- and long-term. Future objectives would include matching the best treatment approach with patient's characteristics.

Other objectives of this Registry are: (a) to identify disease features in the light of a possible evolution toward different patterns of disease course based on the current diagnostic and therapeutic acquisitions; (b) to look for any change in the prognosis in relationship with an earlier diagnosis owing to a better knowledge and awareness of this disease; (c) to try to cluster disease features in order to identify subgroups of patients showing different prognosis or requiring different treatment strategies; (d) to highlight differences in the modalities of disease expression and severity according to the geographical context; (e) to identify any possible predisposing factors and triggers responsible for the onset and the acute exacerbation of the disease, quantifying and layering the intensity of the manifestations and response to treatments; (f) to describe old and new therapeutic regimens, specifically focusing on their global efficacy and their impact on different features of the disease; (g) to define a treat-to-target strategy in relationship with how to use corticosteroids, conventional immunosuppressants and biotechnologic agents in the earliest phase of disease; (h) to evaluate the best timing to start biotechnologic treatment in order to improve prognosis and induce a long-term remission; (i) to carefully study posologies and their adjustments to create standardized treatment protocols; (j) to look for evidence on the tapering and withdrawal of treatment strategies

for any of the therapeutic approaches currently employed (especially conventional immunosuppressants, interleukin-1 and interleukin-6 inhibitors); (k) to assess the socioeconomic influence of the disease in terms of access to healthcare and patients' absenteeism due to the disease; (l) to identify different diagnostic strategies fitting with regional areas and evaluating the treatment response according to the resources available worldwide; (m) to better characterize the behavior of the disease during pregnancy and the trend of disease activity during the postpartum; (n) to monitor the cardiovascular risk in patients with Still's disease; (o) to identify clinical and biological factors predisposing to MAS development, which is the most frequent life-threatening complication of Still's disease; (p) to explore the therapeutic options and results about the pharmacological agents used in this severe condition; (q) to assess the reproducibility (sensitivity/specificity) of the different classification/diagnostic criteria currently used for sJIA and AOSD.

Finally, pioneering studies may eventually be designed according to the population extent of patients enrolled, with the perspective of selecting patients that may fit to future Randomized Control Trials (RCTs), whose realization is nowadays challenging because of the low epidemiological disease impact worldwide. **Table 1** summarizes primary, additional and ancillary objectives of this Registry.

Inclusion/Exclusion Criteria

Patient's inclusion into the Registry strictly requires the fulfillment of Yamaguchi's criteria and/or Fautrel criteria and/or Cush criteria (11, 12, 14). Patients with pediatric disease onset (<16 years old) have to fulfill the International League of Associations for Rheumatology (ILAR) criteria for sJIA and/or the Pediatric Rheumatology INternational Trials Organization (PRINTO) provisional criteria for sJIA (13, 15).

Moreover, the patient has to provide her/his written and informed consent after a previous detailed explanation from the referring physician. The physician should carefully inform the patient about the project and its aims; the absence of implications of the study on her/his own clinical management; the free choice to deny the consent without this may affect the relationship with the reference Center; the international laws guaranteeing patients' privacy, anonymity and security of data, in line with the local and/or European legislation; and the chance to withdraw from the project at any time.

For minor patients or patients unable to provide their consent, this should be given by parents or legally authorized representatives, as long as they will observe the study requirements highlighted in the protocol for the entire duration of the study. No other exclusion criteria or conditions are previewed for the enrollment.

Patients not fulfilling diagnostic and classification criteria for AOSD and sJIA along with subjects who will not fully and freely agree with the project can not be recruited in the Registry dedicated to Still's disease.

Online Data Collection

The Research Electronic Data Capture (REDCap) tool has been employed to collect and store data for the AIDA Project. REDCap is an electronic data collector produced at Vanderbilt University Medical Center (VUMC) and currently residing at the Virginia Commonwealth University (Award Number UL1TR002649). The access to the REDCap platform is free to all members of the REDCap consortium, which may use the tool in exchange for technical support. To date, over 5800 worldwide institutions from 145 countries already take part in the REDCap consortium (16). The access to the Registry website (at page: https://sitbio.med.unisi.it/redcap/redcap_v12.2.1/index.php?pid=41) is password-protected and the recruited information is stored on the servers of the University of Siena, Siena, Italy. The Registry may be reached via REDCap web interface using the private credentials supplied to each Principal and Site Investigator. The Registry's browser interface provided for data entry is entirely supplied in English in order to facilitate collection and reduce any language barriers. Privacy is granted for each Center's data: Principal and Site Investigators of a given Center cannot access the information collected by other Centers.

Variables included in the Registry depends on the fixed objectives. On this assumption, the number and nature of data elements included have been carefully determined based on the literature analysis and the evaluation of current unmet needs. The number of variables has been determined considering the costs of data collection, the potential burden of missing data, any loss of investigators' compliance, but also the need for a high detailed and specialized research and the will to develop an all-inclusive scientific tool.

In order to enhance registry feasibility and sustainability, variables included in the Registry have been distinguished into "mandatory" and "should have", with the former being data to be collected compulsory and the latter being desirable, but not essential.

Data Quality Management

Central to the development of a registry is maintenance of a high quality of the data entered, which is essential to obtain robust information and definitive study results (17). When developing this Registry, many precautions have been adopted to ensure data quality: quality assurance, quality control, and quality improvement. Quality assurance refers to the activities aimed at obtaining the highest quality of data that have preceded data collection, including the search for the essential variables required to describe patients with Still's disease and the critical revision of such variables. Quality assessment refers to periodical revisions of data included in the Registry, to minimize missing data and avoid discrepancies in data collected. Quality improvement consists of a constant effort to keep up to date the variables required to answer to address the future unmet needs. Also, Site Investigators will be continuously trained to collect and enter data in the most correct and complete manner possible.

Ethics

In June 2019 the Ethics Committee of the Azienda Ospedaliero-Universitaria Senese, Siena, Italy (Ref. N. 14951; NCT05200715) granted the first national regulatory approval. After that,

TABLE 1 | List of the objectives that have driven the implementation of the AIDA Registry for patients with Still's disease.

Primary objectives		To gather as much data as possible from a large cohort of patients enrolled on an international basis
		To obtain real-world experience applicable to all geographic contexts
		To identify prognostic factors capable of tapering patients' management and treatment in the light of a personalized medicine approach
Additional objectives	Regarding diagnosis	To highlight disease differences in the severity and modalities of presentation of the disease according to the geographical context
		To assess the reproducibility (sensitivity/specificity) of the different classification/diagnostic criteria currently used for sJIA and AOSD
		To cluster disease features in order to identify subgroups of patients with different prognosis or requiring different treatment strategies
	Regarding prognosis	To look for any impact of diagnostic delay on disease prognosis
		To identify any possible predisposing factor and trigger inducing disease exacerbations
		To better characterize the behavior of the disease during pregnancy and postpartum period
		To monitor the cardiovascular risk, adjusting for treatments employed
		To identify clinical and biological factors predisposing to MAS development, which is the most frequent life-threatening complication of Still's disease
		To assess whether and how disease course has changed due to the current diagnostic and therapeutic evolution
	Regarding therapy	To define a treat-to-target strategy regarding how to use corticosteroids, conventional immunosuppressants and biotechnologic agents in the earliest phase of the disease
		To evaluate the best timing to start biotechnologic treatment
		To assess starting posologies and posologies adjustments
		To look for evidence on the tapering and withdrawal of treatment strategies
		To assess the socioeconomic impact of the disease before and after treatment
		To explore the therapeutic options and results about the pharmacological agents used in this severe condition
		To identify different diagnostic strategies fitting with regional areas and evaluating the treatment response according to the resources available worldwide
		To describe old and new therapeutic regimens, specifically focusing on their global efficacy and role on the different features of the disease
Ancillary objectives		To quickly find patients to be potentially included in randomized controlled trials
		To think about retrospective and prospective studies capable of answering future unmet needs

Primary objectives have been distinguished from additional objectives: the former represents the general purposes at the basis of the Registry development, while the latter consist of the main lines of research the AIDA Network will follow in next years.

Centers experienced in diagnosis, clinical management and treatment of AOSD from Europe, the Middle East, the far East, Africa and North and South America have been invited to approve the project in order to join the AIDA Network.

Patients' data are kept in accordance with the EU General Data Protection Regulations (GDPR), or other counterparts, on the processing of personal data and the protection of privacy (2016/679/EU) (18).

The Registry protocol meets the recommendations from the Declaration of Helsinki. In particular, patients enrolled have to give their voluntary informed consent; otherwise, assent is required from minor patients aged $\geq$ 12 years or when the participant is not competent to provide the consent. In these last cases, parents/legal guardians have to give their approval to be part of the project.

Consent for the use of data for statistical analyses may be withdrawn at any time by patients or Principal Investigators. If the patient revokes the consent, no more data will be collected into the Registry; moreover, the patient has the right to obtain the erasure of personal data. In this regard, all data already gathered in the Registry will be deleted soon after the patient's notification to the study Promoter.

Participation in the study does not involve any kind of financial remuneration neither for the patient nor for the physician or Center, and there should be no evidence of any billing relationships with the national health system or insurance companies.

Statistical Analysis

Statistical analysis will depend on the specific goals to pursue. However, the analysis will embrace general principles of descriptive statistics, correlations between groups and comparisons between subgroups. Also learning machine systems will be used in the future to enhance real-world evidence.

An unacceptable level of missing data is set to 25%. Variables not reaching at least 75% of compilation will be excluded from statistical analysis. For variables reaching a higher than 75% level of compilation, pair-wise deletion will be used to manage missing data, basing on the assumption that lacking data are completely missing at random (the probability that data are missing is not related to either the specific value which is

supposed to be obtained or to the set of observed responses) or missing at random (the probability that the responses are missing depends on the set of observed responses, but is not related to the specific missing value which is expected to be obtained) (19).

RESULTS

The creation and activation of this AIDA Registry is a first fundamental result of the AIDA project. Actually, the development of this Registry fulfills the main purpose to create an online tool capable of gathering real-world data aimed at obtaining strong scientific evidence through the recruitment of a large number of patients diagnosed with Still's disease.

That being so, 23 nations distributed in 4 continents (Algeria, Argentina, Belgium, Brazil, Chile, Egypt, Germany, Ghana, Greece, Iran, Italy, Lebanon, Mexico, Morocco, Poland, Portugal, Romania, Saudi Arabia, Spain, Taiwan, Turkey, United States, Zimbabwe) have already joined the AIDA Network. **Figure 1** highlights the worldwide distribution of the AIDA network. Overall, 110 Centers around the world have joined the project; 20 of those have currently (February 14th, 2022) entered data on the Registry; 290 users (111 Principal Investigators, 175 Site Investigators, 2 Lead Investigators, 2 Data Managers) have applied for credentials to access the Registry.

At present, 178 patients (74 males/104 females) with Still's disease have been enrolled in the Registry in about 8 months from the activation (June 30th, 2021).

Registry Development

When establishing clinical variables to include in the Registry, it was pursued the ultimate purpose of comprehensively tracing the whole clinical and therapeutic history of the patient enrolled, in order to provide answers to the unmet needs deriving from current clinical practice. To date (February 14th, 2022), the Registry consists of 4,449 common data elements (each representing a study variable) organized into 14 instruments. While 9 instruments are dedicated to the retrospective phase, 4 instruments are built for both retrospective and prospective phases; the last instrument is specifically intended for longitudinal data collection. The Instruments included in the Registry and the corresponding phases (i.e., retrospective/prospective) at which they should be referred to are shown in **Table 2**.

Registry Structure and Organization

Common data elements consist of demographic, instrumental, laboratory, therapeutic and any other clinical variable useful to completely describe patients' history. In particular, variables are organized to define family history, symptoms and clinical/laboratory signs at disease onset, symptoms developed during patient's history, Still's disease classification criteria (11–15), genetic features (including human leukocyte antigens and genes not related to the most common autoinflammatory diseases, such as CSF1 and IL18, suggested to be associated to Still's disease), comorbidities, cardiovascular risk, detailed information about treatments, including dosage changes, combinations, withdrawals or additions carried out over time. Data about disease course during and soon after pregnancy, long-term clinical outcomes and access to health care have also been included. Both the retrospective and prospective instruments require laboratory parameters such as daily routine investigation and more specific laboratory exams (lactate dehydrogenase, β2-microglobulin, ferritin serum level, percentage of glycosylated ferritin and 24 h-proteinuria). The filling-in of the following clinimetric scores: Pouchot score and modified Pouchot score by Rau et al. (10, 20), visual analog scale (VAS) for articular pain, patient global assessment (PGA), evaluator's global assessment (EGA), Health Assessment Questionnaire score (HAQ) or childhood HAQ (CHAQ); disease activity score based on 28 joints (DAS28) calculated with erythrocyte sedimentation rate (ESR) and with C reactive protein (DAS28-CRP) or juvenile disease activity score on 27 joints (JADAS27) with ERS and CRP. Laboratory parameters include daily routine investigation, such as inflammatory markers, liver enzymes and 24 h proteinuria. In addition, more specific laboratory exams are required: lactate dehydrogenase, β2-microglobulin, ferritin serum level and percentage of glycosylated ferritin.

Using a branching mechanism, the various fields are organized in such a way as to appear only when clinical history makes it necessary. In this way, only a few parts of the 4310 fields will appear during data entry, and the number of questions the investigator will have to answer is closely related to the complexity of patient's clinical history.

Many common data elements are shared with other AIDA registries dedicated to different autoinflammatory diseases, enhancing the merging of data among different Registries and the consequent optimal use of information for different research projects.

Patients' Involvement

During the last decades patients have become aware of the importance in stimulating and supporting research. Patients have an active and pivotal role also in this project, as they may advocate the participation of Centers, help and support recruitment providing their own time, enhance data recruitment supplying patients reported outcomes as well as past information, and support a further diffusion of the project. For these reasons, patients' associations can be of outstanding help, as happens for ANMAR (Associazione Nazionale Malati Reumatici) and APMARR (Associazione Nazionale Persone con Malattie Reumatologiche e Rare), that are Italian associations of patients suffering from rheumatologic diseases.

Noteworthy, based on patients' suggestions, an electronic system for collecting patient-reported data (AIDA for patients) is under development. Among other things, AIDA for patients will also lead to a better data collection, minimizing the amount of missing values and substantially reducing the work burden for the Site Investigators, along with the risk for selection bias, the loss of prospective follow-up data and challenges resulting from physicians' time constraints.

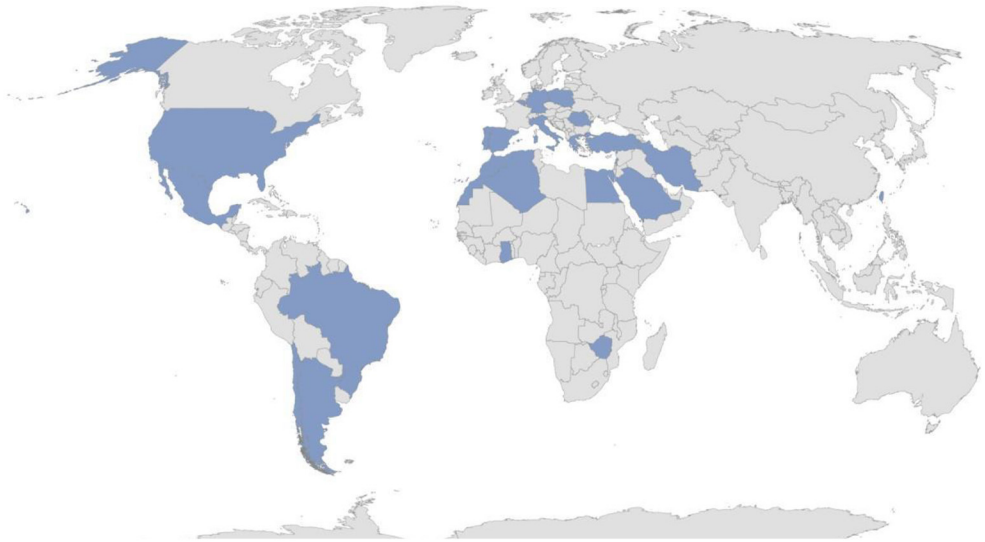

FIGURE 1 | Worldwide distribution of the AIDA network in February 2022.

TABLE 2 | List of instruments included in the Registry dedicated to patients with Still's disease, with the corresponding number of common data elements, the phase (i.e., retrospective/prospective) at which they should refer to and the number of mandatory variables included.

Instruments	Variables	Retrospective/prospective phase	N. of mandatory variables
Demographics	11	Retrospective phase	4
Consents	4	Retrospective phase	1
Diagnostic data and family history	25	Retrospective phase	2
Clinical and laboratory features of Still's disease	160	Retrospective phase	0
Clinical diagnostic scores and criteria	16	Retrospective phase	1
Cardiovascular risk	24	Retrospective/prospective phase	2
Past and current treatments	1	Retrospective/prospective phase	0
Corticosteroids as monotherapy/main therapy—the retrospective phase	227	Retrospective phase	1
Treatment with cDMARDs not associated to biologic agents—the retrospective phase	591	Retrospective phase	6
Treatment with small molecules not associated to biologic agents—the retrospective phase	1048	Retrospective phase	12
Treatment with biotechnological agents—the retrospective phase	1212	Retrospective phase	14
Fertility and pregnancy	14	Retrospective/prospective phase	1
Disease course and treatment during pregnancies	66	Retrospective/prospective phase	1
Follow-up visits: clinical manifestations and treatment—the prospective phase	897	Prospective phase	51

DISCUSSION

Still's disease is a rare multifactorial autoinflammatory disorder mainly characterized by fever, skin manifestations (salmon-colored evanescent rash and/or heterogeneous atypical cutaneous lesions), arthralgia, arthritis, lymphadenopathy, liver involvement, serositis, neutrophilic leukocytosis and prominent increase of laboratory inflammatory markers and ferritin serum levels (15). Despite the good overall prognosis of the disease, life-threatening complications may sometimes occur, especially when macrophage activation syndrome (MAS) develops (8).

Diagnosis is based on the fulfillment of internationally accepted criteria to apply only after the exclusion of neoplastic, infectious, autoimmune, and other monogenic and multifactorial autoinflammatory diseases (11–15). AOSD is a very uncommon disease with an annual incidence estimated between 0.1 and 0.4 cases per 100,000 people in Europe (21). Also sJIA, which is

considered the pediatric counterpart of AOSD, is a rare condition and may be encountered in about 10–20% of all cases of juvenile idiopathic arthritis (22).

As for other rare diseases, the low epidemiological burden of Still's disease determines major difficulties in scientific research, due to the limited number of patients available for RCTs or even for retrospective "real-life" studies. Therefore, gathering patients together through the new web-based technologies is an invaluable opportunity to perform cutting edge and ambitious studies capable of obtaining solid results, also in the field of Still's disease. Noteworthy, this Registry is not only intended to enable a broad population-based data collection, but also to stimulate the scientific community in focusing research efforts on specific targets reflecting the current unmet needs in the clinical practice. The project includes patients disregarding the age at disease onset and age at the enrollment.

The Registry represents a potential opportunity to assess the performance of currently available classification criteria in different geographic realities and to eventually elaborate new diagnostic/classification criteria for sJIA and AOSD specifically tailored on patient subsets or contexts. Looking at the clinical management of patients with Still's disease, many doubts about proper care and treatment should be solved at present. For instance, the Registry would provide valuable information about how to taper the different treatment strategies in patients with Still's disease. In this regard, the identification of predictive variables capable of correlating with disease relapses after drug tapering or withdrawal is crucial to establish whether and when to successfully reduce treatments.

The increasing number of therapeutic opportunities for patients with Still's disease has paved the way to the possible identification of treatment protocols tailored on genetic, laboratory and clinical patients' features. This could be part of a personalized medicine model specifically thought for patients suffering from Still's disease. Also, the identification of predictive variables capable of early detecting the different patterns of the disease, long-term outcomes, and any development of complications may further contribute to outline a personalized medicine approach for such condition.

Of note, only little information is available about the behavior of Still's disease during pregnancy or breastfeeding. Despite the significant efforts to better characterize Still's disease during these periods, only a few data are available regarding: (a) the timing of disease flares during pregnancy and postpartum period; (b) the different possible patterns of disease course (previously reported as first-onset type, recurrent-flare type, no-flare type) (23); (c) the best diagnostic and therapeutic approaches for first-onset disease and new flares in patients with polycyclic course; (d) the major complications possibly affecting the pregnant, the fetus and the newborn; (e) the comprehensive management of Still's disease during pregnancy and post-partum period.

The international patients' recruitment will allow the assessment of any possible change in the clinical behavior, course, prognosis and treatment response in the light of the latest treatment acquisitions and according to the specific geographical and ethnic contexts. Moreover, the sensibility and specificity of the internationally accepted classification criteria for Still's disease will be assessed according to the different settings (11–15).

Currently existing registries for patients with Still's disease are almost nation-based or borrowed from other registries created to collect information about biologic treatments. Among the others, the following projects account for some of the available registries, especially designed for pediatric patients: the UK juvenile idiopathic arthritis biologic registry, pharmacovigilance in juvenile idiopathic arthritis, the Turkish Pediatric Rheumatology Association registry, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry, the German biologic registers including the German biologics in pediatric rheumatology (BIKER) registry, the JuMBO (Juvenile Arthritis MTX/Biologics Long-Term Observation) registry, the autoinflammatory disease (AID) registry as part of the Network for autoinflammatory diseases funded by the German Federal Ministry of Education and Research (24–28). Despite these existing registries, the AIDA Registry for Still's disease is aimed at collecting data from many clinical and research perspectives with no age limitations and with the ambitious purpose to carefully report clinical history of the patients enrolled. The Registry is also intended to improve the routine patients' management, as some of the variables included are thought to investigate the best standard of care according to patients' features. The instrument dedicated to prospective follow-up visits could be also used in the clinical setting during routine visits not only to collect prospective data, but also as a guide for clinical management. In this regard, the compilation of the follow-up instrument requires from 5 to 10 min, which may perfectly fit with the visiting time.

The international basis of data recruiting is also aimed at overcoming the geographical differences due to ethnicities, environmental features and specific health strategies. In this way, it will be possible to generalize the results thanks to the wide sample size.

In thinking about this Registry, recommendations and practical guidelines provided to consider the methodological and operational aspects of patient registries were carefully followed (4, 29, 30). These practical guidances designed to consider all aspects of planning and executing patient registries helped overcome many of the obstacles and pitfalls associated with the development of this Registry.

The AIDA Registry for patients with Still's disease shows the typical limits of observational studies regarding the completeness and accuracy of data collection. At the same time, the investigators are not obliged to consecutively enroll all patients with Still's disease referred to their center; as a consequence, this may lead to unintended selection bias. Furthermore, this Registry will include only patients fulfilling currently available diagnostic/classification criteria. This may lead to the exclusion of patients with atypical Still disease. Nevertheless, three diagnostic criteria for adult patients and two classification criteria for pediatric patients have been considered for inclusion criteria in this Registry, thus minimizing the percentage of patients that will be excluded from the enrollment. Patients with suspected Still disease,

but with no diagnostic/classification criteria fulfilled, should be included in the registry dedicated to USAIDs for future and specific analysis aimed at the development of new or revised classification criteria. Of note, entering data into the Registry requires time and attention, especially when the medical history is particularly complex and many treatments have been attempted over time. Physicians and patients have to be motivated to give their time for data collection; indeed, the accuracy of data recruitment in the retrospective phase of the Registry may require many hours and the direct presence and involvement of patients during data gathering. Nevertheless, beyond its limits, this Registry has the potential and geographical basis to really achieve all the purposes proposed. Moreover, the prospective phase of the project will guarantee the recruitment of complete and easy-to-obtain data for future studies.

CONCLUSIONS

In conclusion, the International Registry for patients with Still's disease has been developed and activated for data sharing, international consultation, and knowledge diffusion. The main reasons for its deployment are to overcome the scientific and clinical fragmentation currently existing on this rare disease, and to perform solid and pioneering international studies based on wide cohorts of patients and real-world data. The final goal will be to obtain the best evidence capable of significantly improving the daily management of patients with Still's disease.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Azienda Ospedaliero-Universitaria Senese, Siena, Italy (Ref. No. 14951). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

AV wrote the first draft of the manuscript and conceived and designed the study and the Still's disease Registry. DR critically revised the manuscript. FD, GL, RP, PR, RG, GR, FL, EB, ED, CL, GE, MGo, MM, AM, JM, BO, PSfi, PSfr, CG, FI, MD, ID, LN, AAh, FC, IR, MP, EM, IM, JS, AAb, IA, and PC were involved in data recruitment in the Registry dedicated to patients with Still's disease. AT, CF, MR, MC, RK, GS, HGia, JH-R, VM, EW-S, MF, VC, ST, HGio, EG, TG, AR, SC, GC, MGe, AF, IA-M, and BF were included in the authorship as investigators from the top three contributor centers for any of the other AIDA Registries (excluding the Registry dedicated to VEXAS disease). AB is the bioengineer involved in the technical management of the platform and registries. LC conceived and designed the study and accounts for AIDA Registries Coordinator. Authorship has been established based on the number of data recruited in the AIDA Registries on February 7th, 2022. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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BRIEF RESEARCH REPORT
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Trisomy 8 Associated Clonal Cytopenia Featured With Acquired Auto-Inflammation and Its Response to JAK Inhibitors

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Objects: It has been recognized the nexus between trisomy 8 and auto-inflammatory features in myelodysplasia syndrome (MDS). Recent research about VEXAS syndrome proved clonal hematopoiesis could interfere with innate immune system far before occurrence of hematological malignancies. We reported a case series of clonal cytopenia with auto-inflammatory features in trisomy 8 patients.

Methods: A total of six patients with isolated trisomy 8 excluded from MDS was retrospectively collected from the Department of Rheumatology, Renji Hospital, Shanghai. The clinical presentations and treatment outcomes were presented.

Results: We report patients with trisomy 8 shared the auto-inflammatory features of recurrent fever, arthralgia, gastrointestinal involvement, and elevated inflammatory markers, especially hyperferritinemia, in addition to hematological findings such as macrocytic anemia and cytopenia of other lineages but without myelodysplasia. The symptoms of this disorder responded to the treatment of glucocorticoids but difficult to taper. JAK inhibitors were introduced to four patients with enhanced response along with glucocorticoids sparing effect and good tolerance.

Conclusion: Clonal cytopenia harboring trisomy 8 presenting with auto-inflammatory features was identified. JAK inhibitor may be a promising anti-inflammatory option.

Keywords: trisomy 8, auto-inflammation, myelodysplasia, clonal hematopoiesis, Janus kinase inhibitor

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INTRODUCTION

Abnormal activation of innate immune system and its associated autoinflammation had been reported in recent studies in many myeloid neoplasms (1). Trisomy 8 is one of the most common cytogenetic abnormalities in myeloid neoplasms such as myelodysplasia syndrome (MDS) and acute myeloid leukemia (AML) (2, 3). The possible link between MDS with trisomy 8 (+8-MDS) and autoinflammatory condition, Behcet's Disease (BD) in particular, has been well recognized in the past decades (4). However, Behcet's like syndrome with +8-MDS differed from classic BD with more frequent gastrointestinal (GI) but less pseudofolliculitis or ocular involvement, along with prominent MDS hematologic features (5, 6). It is noteworthy that trisomy 8 *per se,* in the absence of diagnostic MDS morphological features, is not sufficient for a MDS diagnosis (7, 8). In previous studies, researchers focused on autoimmune or autoinflammatory features only in the

confirmed +8-MDS, whereas the conditions in abnormal karyotypes without myelodysplasia had been largely overlooked.

Here, we described a case series of autoinflammatory syndrome associated with isolated +8 who were excluded from MDS. In addition, the treatment strategies of these six patients had also been discussed. Most patients responded to the glucocorticoids initially but flared in tapering. The possible efficacy of Janus kinase inhibitor for these patients was also exploited.

METHODS

We retrospectively collected patients received cytogenetics examination on bone marrow from 2014 to the present at the Rheumatology Department of Renji Hospital South Campus, Shanghai Jiao Tong University School of Medicine, Shanghai, China. Patients with isolated +8 karyotype and exclusion of other hematological disorders [according to 2016 WHO classification of myeloid neoplasms (9)], were included. Clinical and laboratory data were summarized and analyzed. The study followed local ethics committee regulations with informed consent obtained from all participants.

RESULTS

A total of seven patients with isolated +8 karyotype were identified. After morphologic evaluation of bone marrow, one patient was diagnosed as MDS-EB1 and excluded. The clinical characteristics of remaining six patients were presented in **Table 1**.

Case 1

A 69-year-old man reported recurrent fever and arthralgias without other accompanied symptom for 1 year. His C-reactive protein (CRP), procalcitonin (PCT), erythrocyte sedimentation rate (ESR), and serum ferritin (SF) levels were strikingly high, but evaluations for infectious (such as tuberculosis) or rheumatic conditions (such as giant cell arteritis) were unrevealing (**Table 1**). Peripheral blood analyses demonstrated macrocytic anemia (Hb 92 g/L and MCV 112.8 g/L) and mild thrombocytopenia (Plt $76*10^9$/L). Bone marrow (BM) examination showed no myelodysplasia but presence of +8. Additionally, a next-generation sequencing panel for autoinflammatory diseases was performed and found a heterozygous *NLRP3* R675Q missense mutation. Family history was unremarkable. This mutation of *NLRP3* was not reported to be pathogenic previously and identified as uncertain significance. Bioinformatics protein function prediction indicated this mutation was benign. A working diagnosis of autoinflammatory syndrome with trisomy 8 was established and the patient has a prompt response to dexamethasone 10 mg per day. Methotrexate 10 mg per week was subsequently added to facilitate glucocorticoids (GCs) tapering. However, fever and CRP resurged during reduction of GCs. Methotrexate was stopped and a therapeutic trial of tofacitinib 5 mg twice daily was initiated at the treatment of 25 mg prednisone per day, after discussion and agreement achieved with the patient. During the following 16-month follow up, tofacitinib was titrated to 15 mg/day and prednisone reduced to 15 mg per day as maintenance. Attempts to reduce either tofacitinib or prednisone to a lower dosage incurred flare of symptom or inflammatory markers. The patient remained stable and underwent regular follow up to date (**Figure 1A**).

Case 2

A 36-year-old man, with a history of immune thrombocytopenia purpura 10 years ago and platelets recovered after splenectomy, who suffered from chronic anemia followed by intermittent fever and arthralgias for more than 1 year. The patient was suspected having autoimmune disease and received treatment of prednisone 15 mg per day with only suboptimal improvement. He developed lower abdominal pain and diarrhea 1 month prior to admission. No oral or ocular or genital lesions were presented. His CRP, PCT, ESR, and SF were elevated, along with macrocytic anemia (Hb 66 g/L and MCV 120.1 g/L) and mild leukopenia (WBC $3.22*10^9$/L). The autoantibody panel was negative. Despite of finding +8 in karyotype, hematological malignancy was not suggested by BM examination. Abdominal CT indicated ileocecal edema, and colonoscopy confirmed large solitary ulceration on ileocecal valve. A working diagnosis of intestinal Behcet-like syndrome with trisomy 8 was made. Tofacitinib 10 mg per day was added in the first month and increased to 15 mg/day in the following 3 months, while prednisone maintained in 15 mg/day in the beginning and tapered to 10 mg/day from the second month. Continued to be symptom free with stable inflammatory markers and improvement of anemia, the patient declined to have a colonoscopy reexamination and tofacitinib was reduced to 10 mg/day in the 4th month (**Figure 1B**).

Case 3

A 67-year-old man with recurrent fever, arthralgias and abdominal pain, who was diagnosed as having 'mesenteric panniculitis' and treated with thalidomide for 1.5 years prior to the presentation. The symptoms recurred with elevated CRP, ESR, and SF. He received first BM examination due to mild leukopenia (WBC $3.77*10^9$/L) and macrocytic anemia (Hb 117 g/L and MCV 116 g/L). Karyotype showed +8 but no myelodysplasia was detected. He was prescribed prednisone 30 mg per day and thalidomide but with suboptimal response. Tofacitinib of 15 mg per day was added. The fever and arthralgia were improved. Inflammatory markers also decreased. Unfortunately, patient stopped all medications by himself due to a car accident which resulted in a ulna fracture A month later, his hemoglobin level reduced from 101 g/L to 59 g/L despite of resuming prednisone and tofacitinib treatments (**Figure 1C**). A second BM examination was performed 13 months after the first biopsy. Ring sideroblast comprised 15% of nucleated erythroid cells and *SF3B1* H662D mutation (Variant Allele Frequency, VAF 11.2%) was identified in BM cells. The diagnosis of MDS-RS was made, and hematology consultation decided no chemotherapy or demethylation therapy at this stage. Thus, he continued the anti-inflammatory treatment of prednisone

TABLE 1 | The clinical and laboratory findings in patients.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age/sex	69/M	36/M	67/M	62/M	66/M	40/F
Symptoms	Fever, arthralgia	Fever, lower abdominal pain, arthralgia, diarrhea	Fever, arthralgia, abdominal distension	Fever, rash, arthralgia, abdominal pain	Fever, oral uclers abdominal pain, hematochezia	Fever, rash, erythema nodosum, abdominal pain, thrombosis
Gastrointestinal findings	None	Ileocecal ulcer and edema	Mesenteric panniculitis	Mesenteric panniculitis	Terminal ileum ulcer	Terminal ileal nercrosis
Past history	None	Immune thrombocytopenia purpura	None	None	None	Takayasu arteritis
WBC (*10^9/L) (3.5–9.5)	5.17	3.22	3.77	6.11	4.89	3.04
Hb (g/L) (130–175)	92	66	117	79	63	100
MCV (g/L) (82–100)	112.8	120.1	116	127	108.2	111.2
MCH (pg) (27–34)	35.2	40.8	39.3	39.3	36.1	36.8
Plt (*10^9/L) (125–350)	76	478	131	120	79	232
CRP (mg/L) (0–10)	139.6	101.74	18.34	165.66	150	194.9
ESR (mm/h) (0–15)	106	140	65	63	84	62
Ferrtin (ng/ml) (24–336)	1564	1605	2160	1134	861	1620.9
PCT (ng/ml) (0–0.1)	19.2	0.9	0.18	0.09	4.02	0.6
ANA	Negative	Negative	Negative	Negative	Negative	Negative
Additional gene mutation	*NLRP3* R675Q	\	*SF3B1* H662D	\	\	*U2AF1* S34Y
Previous treatment	GCs, MTX, colchicine	GCs	GCs, thalidomine	GCs, NSAIDs	GCs, 5-ASA	GCs, CTX, tocilizumab, tacrolimus
Last treatment	prednisone + tofacitinib	prednisone + tofacitinib	prednisone + tofacitinib	prednisone + thalidomine + CTX	prednisone + baritinib	prednisone + adalimumab
Follow-up time after JAKi (months)	22	6	8	\	4	\
Outcome	Improved	Improved	Improved with inflammation but progressed to MDS-RS	Loss of follow-up	Improved	Improved

WBC, white blood cell; Hb, hemoglobin; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; Plt, platelet; CRP, C-reaction protein; ESR, erythrocyte sedimentation rate; PCT, procalcitonin; ANA, anti-nuclear antibody; GCs, glucocorticoids; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; 5-ASA, 5-aminosalicylic acid; CTX, cyclophosphamide; MDS-RS, Myelodysplastic Syndrome with ring sideroblasts.

and tofacitinib with a watchful follow up. His hemoglobin dramatically recovered to over 110 g/L and kept sustained remission in the following 3 months. Tofacitinib was declined to 10 mg/day with prednisone 20 mg/day in 6th month.

Case 4

A 62-year-old man presented with recurrent episodes of fever accompanied by evanescent pink rashes, joint pain, intermittent abdominal pain, and painful erythema nodules on extremities (spontaneous subsided after fever episode) in the past 1 year. Systematic examination in another medical center was otherwise unrevealing except for increased ESR/CRP and "mesenteric panniculitis" indicated by abdominal CT. Treatment of prednisone 60 mg per day was initiated with symptoms relieved. However, fever recurred and was not responded to NSAIDs add-on when prednisone tapered to 30 mg per day. Repeat blood test in our hospital confirmed high ESR, CRP, SF, and negative ANAs. Macrocytic anemia (Hb 79 g/L and MCV 127 g/L) was detected but leukocytes and platelets were within normal ranges. No hematological neoplasia was found except isolated +8 in karyotype through BM examination. A skin nodule biopsy of lower extremity proved panniculitis. After treatment of methylprednisolone 40 mg per day and one dose of cyclophosphamide 0.6 g, symptoms were controlled. The patient was lost of follow-up after discharge.

Case 5

A 66-year-old man presented with intermittent fever, oral ulcers, and anemia for 6 months. He developed abdominal pain and hematochezia 1 month prior to admission. Laboratory investigations showed macrocytic anemia (Hb 63 g/L and MCV 108.2 g/L) with markedly increased CRP, ESR, PCT, and

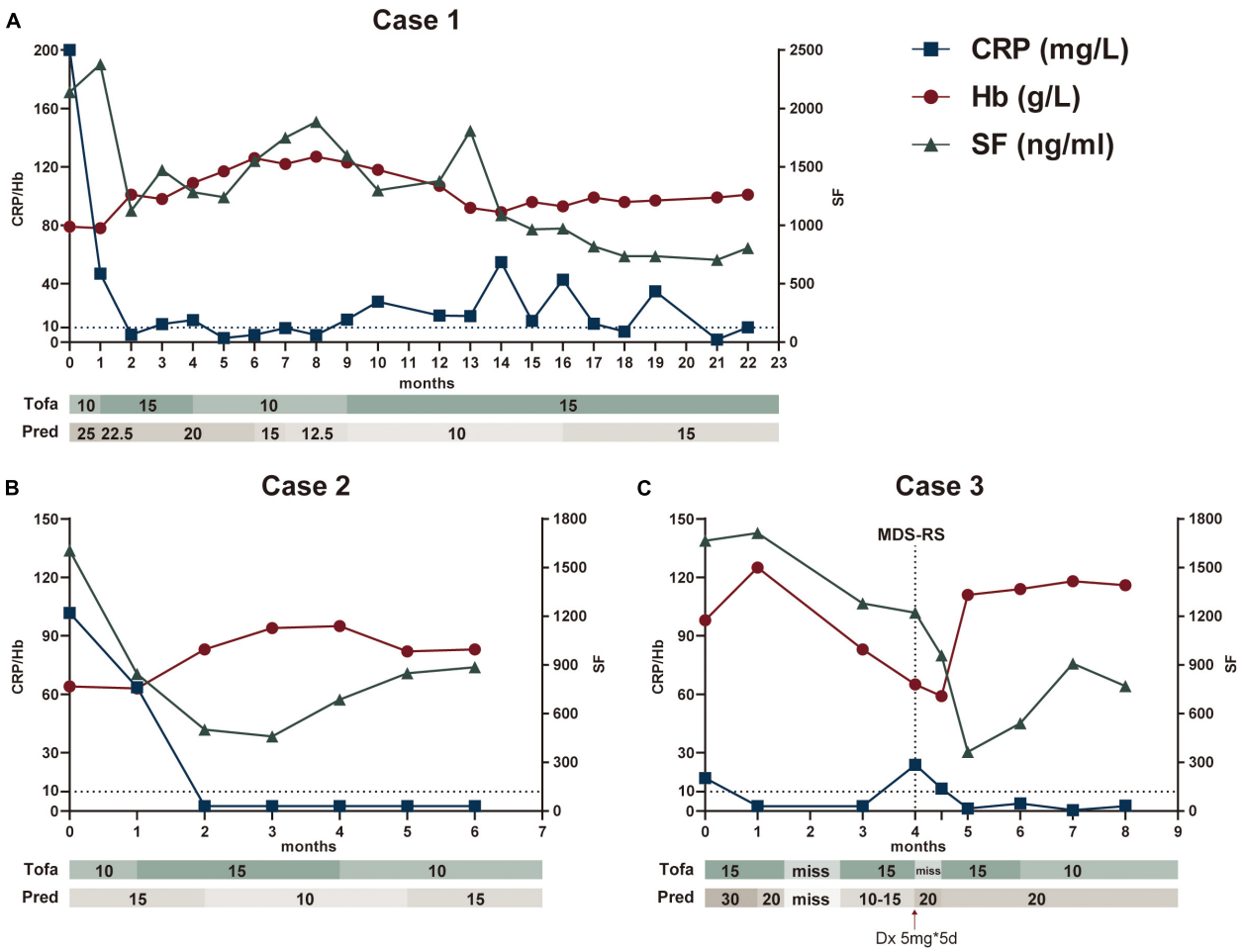

FIGURE 1 | Main clinical and biologic findings and therapeutic interventions in three patients treated with tofacitinib. The Figures illustrated Case 1 **(A)**, Case 2 **(B)**, and Case 3 **(C)**, respectively. CRP and Hb referred to the left *Y* axis, SF referred to the right *Y* axis. CRP, C-reaction protein; Hb, hemoglobin; SF, serum ferritin; Tofa, tofacitinib (mg/day); Pred, prednisone (mg/day); Dx, dexamethasone; MDS-RS, Myelodysplastic Syndrome with ring sideroblasts.

SF. The karyotype of trisomy 8 was detected but MDS was excluded by BM biopsy. No connective tissue disease, infection or malignancy was evident. Endoscopy was performed and showed multiple oval ulcers in lower jejunum and terminal ileum (**Figures 2A,B**). Biopsy revealed eosinophil infiltration in mucosa and submucosa and no epithelioid granuloma was found (**Figure 2C**). Methylprednisolone 40 mg per day was started followed by gradual reduction. Baricitinib 4 mg per day was added at the 4th month to facilitate GC tapering. The patient attained symptom-free with the hemoglobin recovered to 114 g/L (remained macrocytic), while inflammatory markers returned to normal at the 8th months. The maintenance dose of methylprednisolone was 4 mg/day.

Case 6

A 40-year-old woman was reported with recurrent high fever with rash and elevated CRP for half a year. She was diagnosed as Takayasu arteritis in other medical center because of carotid and subclavian artery stenosis and increased metabolism in PET-CT. Therefore, she received CTX first but swift to tocilizumab in combination with glucocorticoids. 3 months later, the patient developed abdominal pain, which was considered as a bowel obstruction and underwent partial resection of the small bowel near the ileocecal region. Treatment of prednisone with tacrolimus was initiated but fever flared in steroid tapering. Subsequently, the patient was admitted to our hospital. Laboratory investigations showed obviously increased CRP and SF with slightly macrocytic anemia (Hb 100 g/L and MCV 111.2 g/L) and leukopenia (WBC $3.04*10^9$/L). BM biopsy indicated trisomy 8 and *U2AF1* S34Y mutation (VAF 36.4%) without myelodysplasias. Adalimumab was selected in combination with prednisone to better control gastrointestinal symptoms.

Summary

We described a case series of six patients harboring sole trisomy 8 in BM cells without myelodysplasia to begin with. Most cases were male with an average age of 57 years at

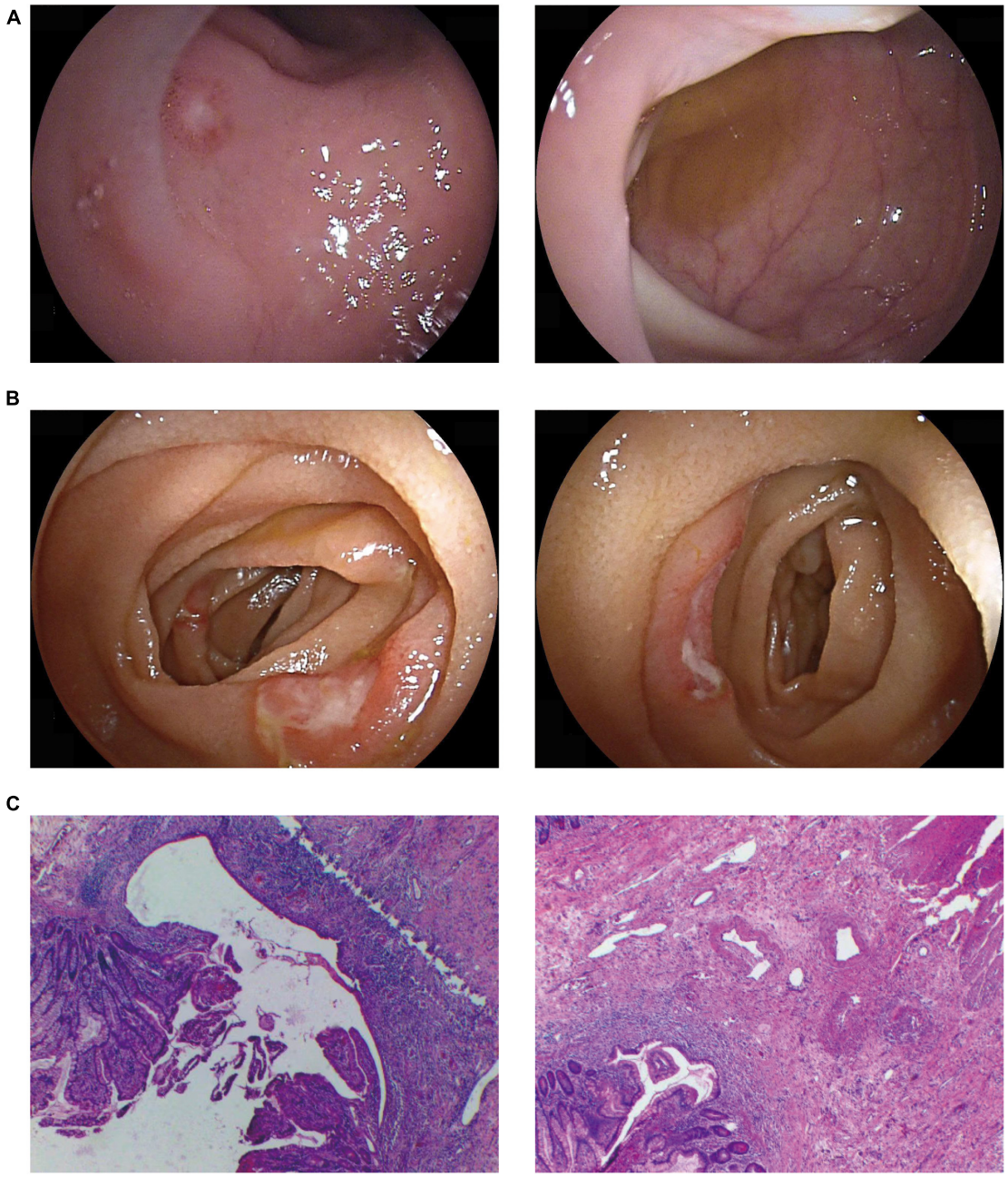

FIGURE 2 | Representative gastrointestinal involvement in our cases. Typical endoscopic findings showed multiple ulcers of terminal ileum **(A)** and the lower jejunum **(B)**. Pathology suggested multiple shallow ulcers in the small intestinal mucosa **(C)**.

disease onset and shared the symptoms of recurrent non-infectious fever with arthralgia or rash. Five of them had gastrointestinal manifestations of which three had ileocecal ulcerations, while another two only revealed having "mesenteric panniculitis" by CT scan but otherwise unremarkable after extensive GI evaluations. All patients had significantly elevated inflammatory markers including CRP, ESR, and SF. The autoantibody penal was negative, such as rheumatoid factor, autoantibodies binding to citrullinated antigens, antinuclear antibody, extractable nuclear antigen, antineutrophil cytoplasmic antibodies, or antiphospholipid antibody. Notably, macrocytic anemia was detected with or without other cytopenia. The initial MDS finding in BM smear and biopsy was lacking, although one patient evolved into MDS over time. Most manifestations could be ameliorated by 0.5 mg/kg prednisone but relapse was common during GC tapering. Except for one patient who lost-to-followup and one treating with adalimumab, the rest 4 patients received a JAK inhibitor add-on (tofacitinib in 3 and baricitinib

for 1), which in turn enhanced anti-inflammatory effect and facilitated GC tapering. A dose-dependent phenomenon was observed, i.e., 15 mg per day of tofacitinib might be more efficacious than 10 mg per day in certain patients. No alarming adverse event was observed during the follow-up period up to 22 months.

DISCUSSION

Autoinflammation refers to abnormal chronic systematic inflammation mediated by innated immune system in the absence of persistent infection stimuli (10, 11). Monogenic systemic autoinflammatory diseases (SAIDs) are considered prototype of autoinflammatory disorders in contrast to autoimmune diseases. More than 50 monogenic SAIDs have been identified in the past decades. The most common feature of these diseases is recurrent febrile episodes with dramatically increased acute phase reactants and various manifestations affecting mucocutaneous, gastrointestinal, and/or musculoskeletal system typically among pediatric patients (12, 13). Current opinions believe the pro-inflammatory cytokines produced and released by innate immune cells are responsible for autoinflammation (12); for example, NLRP3 inflammasome and IL-1β pathway are at the central place in the pathogenesis of classic SAIDs (14, 15).

As comparison, the discovery of VEXAS syndrome extends the understandings of SAIDs (16). It proved that somatic mutation restricted to hematopoietic stem and progenitor cells could induce late-onset autoinflammatory disease (16, 17). Thus, a new concept of hemato-inflammatory disease is proposed to define systematic inflammatory disease caused by somatic mutations in blood cells, which may progress toward to hematopoietic disorders (17, 18). Trisomy 8 is common in myelodysplasia neoplasms and has variable phenotype. Notably, sole +8 is neither sufficient nor necessary to induce leukemogenesis, or in other words, to be diagnostic for MDS (8, 9). Likewise, not all +8-MDS presented with autoinflammatory features; moreover, only a minority of +8-MDS showing BD-like disease, which indicates trisomy 8 is also not sufficient to cause autoinflammatory or BD-like phenotype. Interestingly, almost all BD-like disease occurred in +8-MDS differed from classical BD with less eye lesion but more intestinal (ileocecal predominant) inflammation (4, 17). The detailed contribution of +8 to both autoinflammation and myelodysplasia remained unclear and need further investigations.

We herein summarized a small series of patients with hemato-inflammatory syndrome related to somatic trisomy 8 without myelodysplasia to begin with. All patients presented with macrocytic anemia and mild cytopenia involved other lineages; one patient eventually progressed to MDS-RS during the follow-up. It is likely that the syndrome represents an undifferentiated gray zone between autoinflammatory rheumatic condition and hematological disease (**Figure 3**). Clonal hematopoiesis could induce auto-inflammation far before it evolved into MDS or leukemia. Patients may suffer from severe clinical symptoms requiring active treatment before the settlement of diagnosis of hematological malignancies and the initiation of chemotherapy. It should be noted that only half of our patients received the gene mutation detection in BM cells or peripheral blood cells. A series of accompanying additional mutations with trisomy 8 were also identified. The contributions of these mutations to the clinical manifestations remain unclear. Futural detailed molecular examination was required to overcome this limitation.

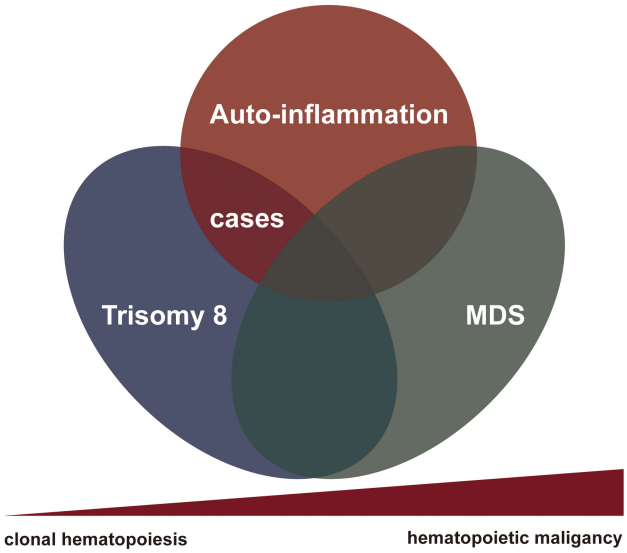

FIGURE 3 | The nexus between rheumatological conditions and clonal hematopoiesis toward to myelodysplasia.

The management of this rare autoinflammatory condition is tricky. Although still served as the most potent anti-inflammatory drug, glucocorticoid is always problematic especially with high-dose and long-term exposure. JAK inhibitors, on the other hand, might down-regulate multiple pro-inflammatory cytokines dependent on JAK/STAT signaling (19). The blockage of JAK has been proved to be promising in both SAIDs and myeloproliferative disorders with an established safety profiling (13, 19, 20). In our observations, JAK inhibitors displayed signals in terms of ameliorating systemic inflammations and facilitating glucocorticoids tapering without severe side effects in short terms. However, glucocorticoid seemed to be irreplaceable despite the combination of JAK inhibitors. No severe adverse event was reported with tofacitinib 15 mg/day, but the incident of adverse event of tofacitinib was related to go higher dosage. We attempted to keep tofacitinib in a regular dosage for safety precautions and pharmacoeconomic considerations, although 15 mg per day of tofacitinib might be more effective. Lager scale investigations and long-term follow up data are required to truly address the safety and efficacy of this rare syndrome in the future.

In conclusion, a new clonal cytopenia with autoinflammatory features characterized as recurrent fever, elevated inflammatory markers, and macrocytic anemia, with or without intestinal BD-like manifestations, is described harboring trisomy 8 in BM cells. JAK inhibitors might be a promising GC sparing drug to ameliorate the autoinflammatory symptoms.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee, Renji Hospital, Shanghai Jiao Tong University School of Medicine. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

YF, WW, and SY contributed to the study design. YF, WW, ZC, and LG collected the clinical data. YF and SY wrote the manuscript. All authors have revised and agreed to the final version of the manuscript.

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Development and Implementation of the AIDA International Registry for Patients With Undifferentiated Systemic AutoInflammatory Diseases

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Objective: This paper points out the design, development and deployment of the AutoInflammatory Disease Alliance (AIDA) International Registry dedicated to pediatric and adult patients affected by Undifferentiated Systemic AutoInflammatory Diseases (USAIDs).

Methods: This is an electronic registry employed for real-world data collection about demographics, clinical, laboratory, instrumental and socioeconomic data of USAIDs patients. Data recruitment, based on the Research Electronic Data Capture (REDCap) tool, is designed to obtain standardized information for real-life research. The instrument is endowed with flexibility, and it could change over time according to the scientific acquisitions and potentially communicate with other similar tools; this platform ensures security, data quality and data governance.

Results: The focus of the AIDA project is connecting physicians and researchers from all over the world to shed a new light on heterogeneous rare diseases. Since its birth, 110 centers from 23 countries and 4 continents have joined the AIDA project. Fifty-four centers have already obtained the approval from their local Ethics Committees. Currently, the platform counts 290 users (111 Principal Investigators, 179 Site Investigators, 2 Lead Investigators, and 2 data managers). The Registry is collecting baseline and follow-up data using 3,769 fields organized into 23 instruments, which include demographics, history, symptoms, trigger/risk factors, therapies, and healthcare information access for USAIDs patients.

Conclusions: The development of the AIDA International Registry for USAIDs patients will facilitate the online collection of real standardized data, connecting a worldwide group of researchers: the Registry constitutes an international multicentre observational groundwork aimed at increasing the patient cohort of USAIDs in order to improve our knowledge of this peculiar cluster of autoinflammatory diseases. NCT 05200715 available at https://clinicaltrials.gov/.

Keywords: autoinflammatory diseases, personalized medicine, precision medicine, rare diseases, International Registry

INTRODUCTION

Undifferentiated Systemic AutoInflammatory Diseases (USAIDs) represent a group of undefined medical conditions increasingly reported in medical literature. The acronym USAIDs identifies a subset of patients characterized by self-limiting episodes of inflammation that fail to meet criteria for the established monogenic or multifactorial autoinflammatory diseases, but display features of autoinflammatory disorders. Patients with USAIDs do not carry confirming pathogenic mutations in genes associated with monogenic autoinflammatory diseases and do not fulfill any of the diagnostic or classification criteria currently available for multifactorial autoinflammatory disorders. There are neither definite diagnostic criteria available, nor specific laboratory investigations for identifying USAIDs (1, 2). USAIDs can be suspected after ruling out infectious, neoplastic, autoimmune, and other monogenic and multifactorial autoinflammatory diseases. The concept of USAIDs has not been fully delineated neither in terms of diagnosis, nor in terms of optimal therapeutic approach, while long-term clinical evolution and prognosis have not been established at all. In this regard, the AutoInflammatory Diseases Alliance (AIDA) project is aimed at shedding new light on these conditions, potentially allowing their better definition and classification, and aimed at improving overall knowledge. To this aim, the creation of an International Network of expert physicians in autoinflammatory disorders combining together scientific efforts and sharing ideas, information, and the development of an International Registry to collect data from dedicated centers around the world would be precious.

Priority of the AIDA project is the development and maintenance of international registries for patients affected by monogenic and multifactorial autoinflammatory disorders and ocular inflammatory diseases. To date, nine international registries have been launched, including Behçet's disease (BD), monogenic autoinflammatory diseases, Still's disease, Schnitzler's syndrome, Periodic Fever, Aphthous stomatitis, Pharyngitis and cervical Adenitis (or PFAPA) syndrome, non-infectious

uveitis, non-infectious scleritis, vacuoles, E1 enzyme/X-linked autoinflammatory somatic (or VEXAS) syndrome and undifferentiated autoinflammatory diseases. The use of these registries will allow sharing of knowledge, experience, and different perceptions on the clinical, therapeutic and research approaches in the field of rare diseases (3, 4).

This paper purposes to point out the design, development and deployment of the AIDA International Registry dedicated to patients with USAIDs, which corresponds to a multicentre, non-interventional, population- and electronic-based observational clinical study. The registry will include patients with unexplained systemic inflammation suggested by laboratory, clinical or therapeutic clues which will be widely clarified in the methods section.

MATERIALS AND METHODS

Study Design

The AIDA Registry for USAIDs patients has been conceived to collect both retrospective and prospective data. In particular, retrospective phase refers to demographic, clinical, laboratory, instrumental and therapeutic information available at the time of enrollment into the Registry; prospective phase includes clinical, therapeutic and socioeconomic data acquired thereafter.

Variables included in the Registry have been selected on the basis of clinical and laboratory features generally described in patients with autoinflammatory diseases; evidence currently available in literature; therapeutic details required to comprehensively describe treatment options proposed for monogenic and multifactorial autoinflammatory diseases, and information required during the follow-up visits according with the best standard of care.

Some information may be repeated and, therefore, recorded in both the retrospective and prospective phases, as for example data about the cardiovascular risk and information about fertility, pregnancy and breastfeeding period. The retrospective assessment includes clinical and laboratory data referring to the start of symptoms, the time at the diagnosis, and the time at the enrollment into the Registry; for each treatment performed during the patient's history, clinical and laboratory data would be required referring to the start of the treatment, the 3-, 6- and 12-month visits and at the last assessment while on the treatment. Conversely, the follow-up visits will be added at the patient re-evaluations following the inclusion in the AIDA Registry; a follow-up re-evaluation should take place at least every year and at any change in the treatment strategy, as for the introduction of new drugs and posology changes.

Since only data related to the standard routine management are recorded and no additional specific investigations are required, no funds are provided for patient's enrollment and no further impact on national healthcare will be determined by the participation in the AIDA project. Similarly, treatments administered prior or after the enrollment in the AIDA Registry are drawn by the best standard of care and are not influenced by the study protocol.

Any center managing USAIDs may participate in the project without limitations regarding the location, medical specialty, or type of practice setting. The centers that would like to participate, can make a request by contacting the Promoter directly or by sending an email from the web page contact the AIDA Team by writing to support@aidaregistry.org or using a specific form at the bottom of the following page: https://aidanetwork.org/en/aida.

The only required prerequisite is obtaining approval from the local Ethics Committee and appointing a Principal Investigator whose function is coordinating the study locally, and Site Investigators responsible for the documentation and data entry for that site.

Registry Objectives

Among the objectives of the USAIDs Registry, the primary one is to enroll the largest number of patients with systemic inflammation that potentially involves all organs and tissues due to dysfunction of the innate immunity, which cannot be framed in the field of monogenic or multifactorial autoinflammatory diseases. At current, criteria for enrolling patients in the basket of USAIDs include: (a) presence of recurrent stereotyped clinical manifestations with no symptoms between episodes; (b) positive family history despite lack of genetic mutations; (c) hematological disorders associated with somatic mutations (e.g., *RUNX1*, *BCOR*, *WTI* or *TP53* genes); (d) increased inflammatory markers during attacks (serum amyloid-A, erythrocyte sedimentation rate, C-reactive protein); (e) laboratory-proved evidence of *NLRP3* inflammasome activation; (f) increased serum levels of interleukin (IL)-1 and/or IL-6 during clinical manifestations; (g) effectiveness of colchicine or corticosteroid administration; (h) response to IL-1 or IL-6 inhibitors; (i) absence of cyclic neutropenia, immunodeficiency, chronic infections, inflammatory bowel diseases, autoimmune diseases or neoplasms explaining the systemic inflammatory picture.

Further objectives include: (a) the identification of new genetic syndromes in addition to those currently included among monogenic autoinflammatory diseases; (b) the categorization into subgroups characterized by similar signs and symptoms and response to therapies according to a clustering method; (c) the search for new diagnostic or classification criteria; (d) the assessment of disease complications and life-threatening sequelae; (e) the identification of predisposing factors for a worse outcome and systemic amyloidosis development; (f) the detection of biomarkers and predictive factors for disease monitoring; (g) the identification of variables capable of identifying patients more likely responsive to different therapeutic approaches; (h) the description of the socioeconomic impact of these diseases in association with the epidemiologic burden in different geographic contexts; (i) the evaluation of current clinimetric tools in different diseases and contexts alongside with assessment of new clinimetric instruments specific for USAIDs patients; (j) the behavior of disease during pregnancy and post-partum period; (k) the impact of chronic disease inflammation on the cardiovascular risk. **Table 1** summarizes all objectives of USAIDs Registry.

When a substantially high number of patients is enrolled, more specific and more cutting-edge studies will be proposed in the context of the AIDA network.

TABLE 1 | Objectives of the USAIDs registry.

Main objective	Built an International Registry to overcome limitation of small number of USAIDs patients in each single center
Other objectives	Identification of new genetic syndromes
	Categorization into subgroups characterized by similar signs and symptoms and response to therapies
	Search for new diagnostic or classification criteria
	Assessment of disease complications and life-threatening sequelae
	Identification of predisposing factors to a worse outcome and systemic amyloidosis development
	Detection of biomarkers and predictive factors for disease monitoring
	Identification of variables capable of identifying patients more likely responsive to different therapeutic approaches
	Description of socioeconomic impact of these diseases
	Assessment of new clinimetric instruments specific for USAIDs patients
	Behavior of disease during pregnancy and post-partum period
	Impact of chronic disease inflammation on the cardiovascular risk

Inclusion/Exclusion Criteria

Primary inclusion criterion is the presence of systemic inflammation driven by innate immunity (5) with the identification of clinical features resembling other autoinflammatory diseases. Furthermore, as USAIDs are based on an exclusion diagnostic approach (1), patients with monogenic and multifactorial autoinflammatory diseases, alongside patients with infections, malignancies or autoimmune diseases, are excluded from the Registry. Multifactorial autoinflammatory diseases will have to be ruled out when the diagnostic/classification criteria are not fulfilled for Behçet's disease (6, 7), Still's disease (8, 9), PFAPA syndrome (10, 11), Schnitzler's disease (12), and Chronic Recurrent Multifocal Osteomyelitis (13).

Infectious, neoplastic and autoimmune diseases have to be firstly excluded according to the best standard of care for any of those clinical conditions.

Patients included in the USAIDs Registry should have been preliminarily assessed in order to exclude monogenic autoinflammatory diseases through a Next Generation Sequencing (NGS) approach, when available, or using other methods of genetic sequencing based on the specific patient's clinical framework. In addition, patients fulfilling clinical diagnostic criteria for Familiar Mediterranean Fever (14–16), have to be excluded.

Ethics

The first national regulatory approval of the AIDA project has been obtained in June 2019 by the Ethics Committee of Azienda Ospedaliera Universitaria Senese, Siena, Italy (Ref. N. 14951). Later, expert centers for the diagnosis, clinical management and treatment of autoinflammatory diseases have approved the project across Europe, the Middle East, North Africa and the North America and the South America and actively participate in the AIDA International Registry.

This project, already registered at ClinicalTrials.gov (ID: NCT05200715), follows Declaration of Helsinki recommendations. All patients enrolled have to provide their written informed consent after having been carefully informed about the project and its aims, long-term purposes, lack of any impact on their clinical and therapeutic course. The possibility to refuse entering or withdrawing from the study at any time with no impact on the clinical management is well-cited and patients have to be informed about the personal data privacy and security in accordance with the local and/or European regulations. As far as adolescents are concerned, their parents (or legal representatives) have to comply with the study requirements during the whole study.

Both patients and Principal Investigators may withdraw their consent to use of data for statistical analyses at any time. If a patient withdraws the consent, no further data for that patient will be entered into the Registry and, if requested by the patient, all prior data will be deleted soon after her/his request to the Promoter. Patients' data are collected and stored in accordance with the EU General Data Protection Regulations (GDPR) on the processing of personal data and protection of privacy (2016/679/EU) (17)."

Online Data Collection and Management

Data are collected through Research Electronic Data Capture (REDCap), which is an electronic data capture tool developed at the Vanderbilt University Medical Center. It is hosted at Virginia Commonwealth University (Award Number UL1TR002649) and can be also used to develop patients' registries. The software is distributed at no costs and currently about over 5,700 Institutions in 145 Countries have already joined this online opportunity (18).

Investigators included into the AIDA project can log in the Registry through the REDCap web-interface and later insert data on the Instruments (pages) of the Registry. None of the recruited Principal Investigators and Site Investigators are allowed to see information inserted by other Centers. The electronic data entry system of the Registry is in English.

While public website of the AIDA Network (https://aidanetwork.org/en/) may be accessed by anyone who wants to learn about this Project, the Registry website (https://sitbio.med.unisi.it/redcap/redcap_v12.2.1/index.php?pid=40) is hosted separately and requires credential to meet data privacy regulations.

The Investigators will be responsible for entering the own study data in the online Registry. They will be also responsible for the accuracy of the information accrued, with the Principal Investigator required to supervise the accuracy of the data. The security of the patients' information is guaranteed by the online access through personal username and password and by the compliance of the Investigators with local legislation. Each Principal Investigator and Site Investigator may provide their study proposal during dedicated meetings.

Figure 1 provides a summary of the three main phases describing the creation of the Registry, pointing

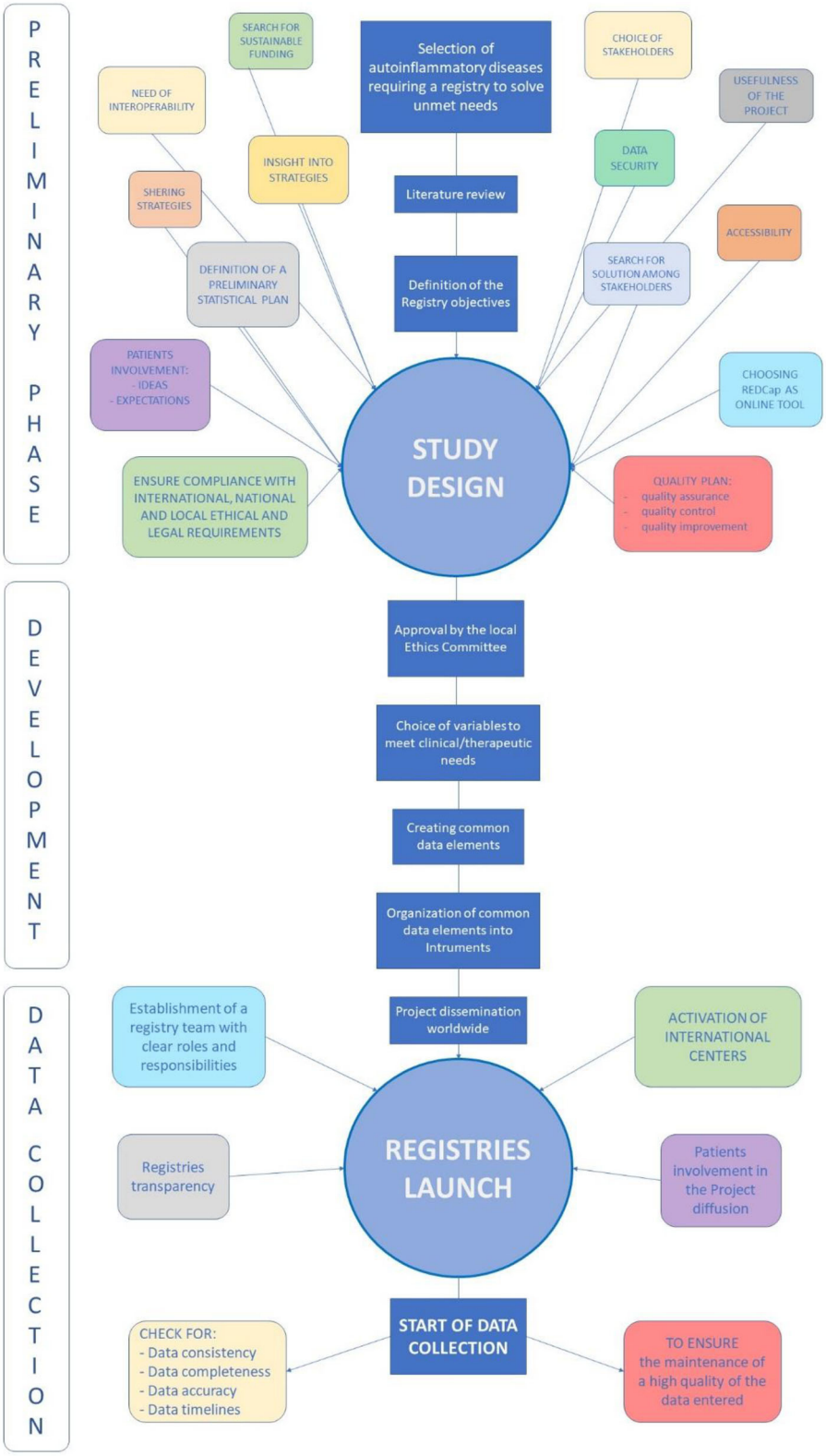

FIGURE 1 | Summary of the main phases corresponding to the creation of the Registry: the preliminary phase with all the elements required to carry out the project; the development phase during which common data elements and instruments of the Registry were realized; the data collection phase following the launch of the Registry accompanied by the efforts to maintain the high quality of data entered and of the Registry according to the new scientific acquisition.

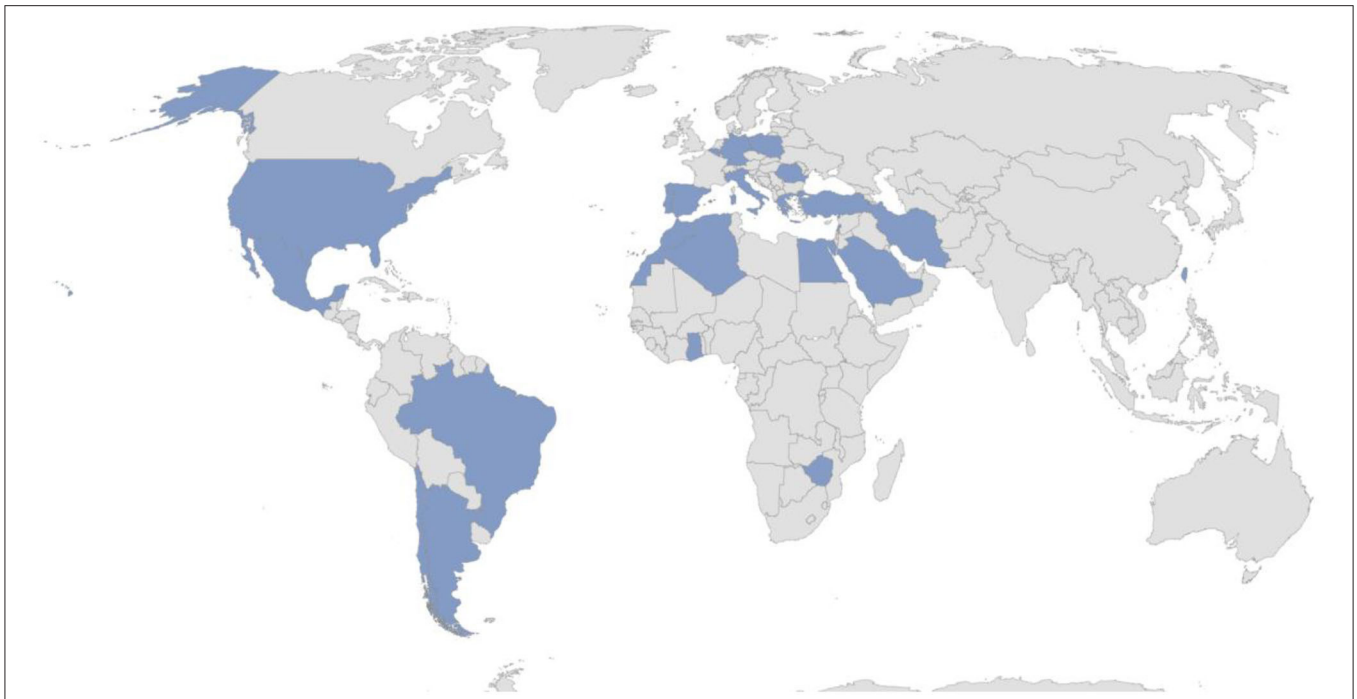

FIGURE 2 | Country involved in the AIDA Network (update February 7th, 2022).

out all the elements contributing to development of the project, realization of the online tool based on REDCap, and launch of the Registry followed by data collection.

Statistical Analysis

Statistical analysis will include, in addition to descriptive statistics, also correlations between groups and comparisons among subgroups; furthermore, machine learning principles will be applied to complement the conventional data analysis. Other statistical analysis will depend on the objectives to be achieved over time and on the type and number of data collected.

Each Principal Investigator may analyze data collected in the own center, does conducting prospective and retrospective studies of the behalf of the AIDA Network; the totality of data collected in the Registry will be managed by statistics and physicians involved in the network, selected by the Promoter on a case-by-case basis according with their field of expertise. All the variables related to the study's objectives will be provided to the Investigators who will take care of the study. Analysis of data will take place according with the aims of the study, scientific relevance, biologic plausibility, and the number of data collected.

RESULTS

This International Registry was created with the essential purpose to obtain solid scientific information about rare autoinflammatory disorders not thoroughly studied yet. Indeed, this project may quickly reach a wide geographic coverage, as shown during the last 20 months. In particular, Centers from 23 Countries (Algeria, Argentina, Belgium, Brazil, Chile, Egypt, Germany, Ghana, Greece, Iran, Italy, Lebanon, Mexico, Morocco, Poland, Portugal, Romania, Saudi Arabia, Spain, Taiwan, Turkey, United States, Zimbabwe) in 4 Continents have already joined the Project sharing their knowledge and experience about autoinflammatory diseases. At current (February 7th, 2022), 110 centers around the world corresponding to 290 users (111 Principal Investigators, 175 Site Investigators, 2 Lead Investigators, 2 data managers) have already joined the network (**Figure 2**).

Registry Development

In order to better record patients' clinical and therapeutic history, a wide number of variables has been included into the Registry to describe in detail the whole disease course; general and specific items have been included to shed light on a still unknown clinical entity. Therefore, a total number of 3,357 common data elements (fields corresponding to variables) have been created and organized into 23 instruments (forms corresponding to different pages) to constitute the USAIDs Registry.

The common data elements refer to patient's demographics, medical history, laboratory features, genetic characteristics, comorbidities, symptoms at disease onset, symptoms developed over time, cardiovascular risk, work-up examinations, pregnancies after symptoms onset, disease complications, long-term clinical outcomes, treatments administered, short- and long-term responses to treatments, management

of different therapeutic strategies in terms of posology changes and drug combinations, and impact on national healthcare. Specific fields appear only if required based on patient's clinical history, thanks to a branching system of questions. Therefore, only a small part of the 3,769 fields appears to the Investigators for each patient, and the number of questions to be answered depends exclusively on the complexity of the patient's clinical history. With regard to the prospective phase of the AIDA project, longitudinal data are acquired using a specific follow-up instrument, which includes details about clinical and laboratory features and treatments update.

Data elements from AIDA Registries for other autoinflammatory diseases are shared, while specific data elements for USAIDs have been added to describe the specific field of these entities.

Furthermore, a specific instrument includes items possibly setting up an early form of clinical diagnostic scores and criteria; this instrument describes the reasons leading to the enrolment of the patient among USAIDs. In addition, the Eurofever scores and diagnostic/classification criteria for other multifactorial autoinflammatory diseases have been included in this instrument (10, 11, 14, 15, 19).

The Instruments constituting the Registry and their reference time-points are listed in **Table 2.**

Patients' Involvement

In the last few years, the role of patients has progressively been increasing to become central in stimulating the research effort and quality of clinical management (20); furthermore, the role of patient advocacy organizations has added an important new dynamic to the patient care (21). Currently, patient advocacy groups may help in many ways, by disseminating information, supporting the recruitment of patients, and taking part in regulatory processes. There are different associations actively involved in the AIDA project, including the Italian Association of Periodic Fever (A.I.F.P., *Associazione Italiana Febbri Periodiche*), the National Association of People with Rheumatic and Rare Diseases (A.P.M.A.R., *Associazione Nazionale Persone con Malattie Reumatologiche e Rare*) and the National Association of Rheumatic Patients (A.N.M.A.R., *Associazione Nazionale Malati Reumatici*). More in detail, the associations of patients were asked to provide their opinion since the very beginning of the AIDA project; patients' point of view and impressions were required before starting the project, while concerns, especially regarding the protection of personal data, were carefully answered. Patients did not desire a registry mainly focused on therapeutic aspects; in fact, we expanded the focus to all the different issues of the disease. To date patient organizations are of Italian origin only; however, other international centers have been invited to facilitate the participation of other organizations worldwide by diffusing the project among patients.

TABLE 2 | List of instruments (forms) included in the AIDA International Registry dedicated to USAIDs patients, with the corresponding number of common data elements, time-points at which they should refer to and number of mandatory fields included.

Instruments	Fields	Retrospective/prospective phase	N. of mandatory fields
Demographics	10	Retrospective phase	4
Consents	4	Retrospective phase	2
Diagnostic data and family history	24	Retrospective phase	2
General genetic information	5	Retrospective phase	1
Gene mutations	7	Retrospective phase	0
Features of attacks during childhood	42	Retrospective phase	0
Features of attacks at disease onset	43	Retrospective phase	0
Features of attacks up to the diagnosis	56	Retrospective phase	0
Features of attacks up from diagnosis to the time of enrolment in the AIDA Registry	56	Retrospective phase	0
Clinical diagnostic scores and criteria	10	Retrospective phase	0
Laboratory data	17	Retrospective/prospective phase	1
Cardiovascular risk	24	Retrospective/prospective phase	2
Past and current treatments	1	Retrospective phase	0
NSAIDs monotherapy-the retrospective phase	33	Retrospective phase	1
Corticosteroid monotherapy/main therapy-the retrospective phase	102	Retrospective phase	1
Colchicine treatment-the retrospective phase	50	Retrospective phase	1
Streptococcus salivarius K12 treatment-the retrospective phase	54	Retrospective phase	1
Treatment with cDMARDs (not associated to biotechnological agents)-the retrospective phase	315	Retrospective phase	6
Treatment with small molecules (not associated to biotechnological agents)-the retrospective phase	606	Retrospective phase	12
Treatment with biotechnological agents-the retrospective phase	1,029	Retrospective phase	14
Fertility and pregnancy	14	Retrospective/prospective phase	1
Disease course and treatment during pregnancies	66	Retrospective/prospective phase	1
Follow-up visits: clinical manifestations and treatment-the prospective phase	766	Prospective phase	58

DISCUSSION

In the last years, the use of online networks has gradually increased, facilitating the spreading of knowledge and establishing worldwide research collaboration between researchers, clinicians, pharmaceutical companies, patients' advocatory groups, and patients with their families. This constitutes a great revolution in the field of rare diseases, where the small number of cases and the difficult-to-reach diagnosis are barriers to translational research and the identification of a large patient cohorts. In this context, the AIDA network and the corresponding registries dedicated to rare diseases have been created as a unifying agent in the field of autoinflammatory diseases to gather forces currently spread across the various referring centers. This highly concerns USAIDs, which correspond to a cluster of medical conditions lacking a widely shared classification and definition along with an internationally accepted protocol for management and treatment. Indeed, the concept of USAIDs itself is at an early stage of development and the knowledge on this clinical group of diseases is embryonic at current.

The AIDA network has been also created to facilitate the international consultation and involvement of all medical figures dealing with the management of autoinflammatory diseases in general, and USAIDs in particular. Actually, the AIDA network already includes and enhances the communication between different specialties, such as rheumatologists, immunologists, gastroenterologists, dermatologists, ophthalmologists, internal medicine physicians, geneticists and pediatric rheumatologists for patients with childhood onset disease. This project represents a demonstration of how well a web-based worldwide collaboration can overcome the fragmentation of clinical and research experiences, expanding and improving our knowledge in the field of rare and complex diseases.

The AIDA project has met the expectations for the development of an online platform dedicated to patients with autoinflammatory diseases, including those characterized by a clear but undifferentiated clinical picture. This represents the first fundamental step to overcome the limitations related to the poor number of patients included in case-series and small individual studies currently available (22). This is even more remarkable when considering that current research aspires to a personalized medicine aimed at choosing the most proper treatment according to the baseline features and risk of developing severe manifestations or complications. In this light, a large-scale, long-term patient's Registry is essential to provide additional evidence on still unknown autoinflammatory diseases included in the USAID acronym. In this regard, a wide number of patients is required to assess atypical and borderline cases especially when aiming at identifying common clinical features that cluster in a specific new nosologic entity. The identification of new genetic syndromes and/or diagnostic/classification criteria is one of the most ambitious goals of this Registry. A further goal is to better characterize specific phenotypes of patients, as for musculoskeletal and abdominal pain, which have been frequently described in USAIDs (2, 23).

Though an International Registry enables the recruitment of a high number of patients that is required to assess response to treatment and prognostic variables among specific subgroups of patients. A long-term observational Registry could allow assessing any change in the natural history of USAIDs as a consequence of the new therapeutic approaches available at current. Furthermore, the efficacy of a therapeutic strategy might suggest the involvement of a particular molecular pathway in disease pathogenesis of specific patient subgroups.

The Registry may also be a precious source of real-life data regarding the role of chronic inflammation on the cardiovascular risk as well as disease behavior during pregnancy and postpartum. The prospective phase will also provide data about the socioeconomic impact of these diseases and benefits that national healthcare could obtain from different therapeutic strategies.

As a whole, achieving all the goals aspired by this Registry will improve the knowledge about this peculiar basket of inflammatory disorders and facilitate their early diagnosis, with a consequent decrease of long-term or life-threatening complications, such as amyloidosis, and a positive impact on quality of life and life expectations (2). Noteworthy, the Registry is flexible to include other future unmet needs and implement protocol variations according with future clues and suggestions deriving from future scientific progress. Indeed, this Registry could potentially communicate with other existing or future similar instruments.

The AIDA Registry for USAIDs patients has the usual shortcomings typically present in observational studies, especially selection biases deriving from the number of missing data and any non-consecutive enrolment of patients. In addition, entering data into the Registry requires time and attention, especially when patient's medical history is particularly complex, as for patients with long-term disease course, multiple treatment approaches attempted over time and many posology changes to report. Nevertheless, entering retrospective data requires 2–3 h, while completing the form at follow-up visits takes a maximum of 10–15 min. Despite its limitations, this Registry has the potential, given also its geographical extension, to eventually achieve all the objectives thus shedding light on a quite unknown field of autoinflammation.

Of note, a branch of the AIDA project defined as "AIDA for patients" is under development. "AIDA for patients" is an online tool based on the REDCap technology primarily aim at involving patients in the collection of the data, especially regarding the impact of the disease on the quality of life and on socio-economic aspects and the current status of the disease with specifically built patients reporting outcome (PROs). Moreover, "AIDA for patients" was born to enhance patients' participation in the decision-making process when establishing the lines of research and the strategies to follow, in order to seek the growth of the AIDA project.

In conclusion, the AIDA International Registry for USAIDs patients has been developed and activated to facilitate the collection of standardized data and enable international multicentre collaborative research. Data sharing, implementation, and optimisation of research about autoinflammatory diseases, along with international consultation, and dissemination of knowledge represent pivotal goals that may be easier to achieve via this international effort offered by the AIDA network.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Azienda Ospedaliera Universitaria Senese, Siena, Italy (Ref. No. 14951). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

FD wrote the first draft of the manuscript. AV conceived and designed the study and revised the draft of the manuscript. DR revised the draft of the manuscript. LC conceived and designed the study and accounts for AIDA Registries Coordinator. AB is the bioengineer involved in the technical management of the platform and registries. GL, PR, FCi, GE, MC, EW-S, MM, BO, PS, AT, SA-M, ED, EA, FL, JS, SC, ID, DI, IM, KJ-R, RJ, KL, CG, AAb, PC, GRo, and AAl were involved in data recruitment in the Registry dedicated to patients with USAIDs. DY, MT, GRa, FR, FCa, MK, MF, VC, MS, RP, VB, SGe, SGu, TG, VG, FI, HG, IA, RK, DA-I, BF, and CF included in the authorship as investigators from the top contributor centers for any of the other seven AIDA Registries. Authorship has been established based on the number of data recruited in the AIDA Registries on February 7th, 2022. All authors contributed to the article and approved the submitted version.

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Effectiveness and Safety of JAK Inhibitors in Autoinflammatory Diseases: A Systematic Review

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Introduction: Autoinflammatory diseases (AID) are rare diseases presenting with episodes of sterile inflammation. These involve multiple organs and can cause both acute organ damage and serious long-term effects, like amyloidosis. Disease-specific anti-inflammatory therapeutic strategies are established for some AID. However, their clinical course frequently includes relapsing, uncontrolled conditions. Therefore, new therapeutic approaches are needed. Janus Kinase inhibitors (JAKi) block key cytokines of AID pathogenesis and can be a potential option.

Methods: A systematic review of the literature in accordance with the PRISMA guidelines was conducted. Three databases (MEDLINE, Embase and Cochrane Central Register of Controlled Trials) were searched for publications regarding the use of JAKi for AID. Data from the included publications was extracted and a narrative synthesis was performed. Criteria for defining treatment response were defined and applied.

Results: We report data from 38 publications with a total of 101 patients describing the effects of JAKi in AID. Data on Type I Interferonopathies, Adult-Onset Still's Disease (AOSD), Systemic Juvenile Idiopathic Arthritis (sJIA), Familial Mediterranean Fever (FMF), and Behçet's Syndrome (BS) was identified. From a total of 52 patients with type I interferonopathies, in seven patients (7/52, 13.5%) a complete response was achieved, most (35/52, 67.3%) showed a partial response and a minority (10/52, 19.2%) showed no treatment response. For AOSD, a complete or a partial response was achieved by eleven (11/26, 42.3%) patients each. Two sJIA patients achieved complete response (2/4, 50%) and in two cases (2/4, 50%) a partial response was reported. Half of FMF patients showed a complete response and the other half had a partial one (3/6, 50.0%). Amongst BS patients most achieved a partial response (8/13, 61.5%). Five patients showed no response to therapy (5/13, 38.5%). Overall, the most frequent AEs were upper respiratory tract infections (17), pneumonia (10), BK virus viremia (10) and viruria (4), herpes zoster infection (5), viral gastroenteritis (2) and other infections (4).

Conclusion: The results from this systematic review show that JAKi can be beneficial in certain AID. The risk of AEs, especially viral infections, should be considered. To accurately assess the risk benefit ratio of JAKi for AID, clinical trials should be conducted.

Keywords: autoinflammation, interferonopathy, monogenic autoinflammatory disease, Janus Kinase inhibition, *innate immunity*

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INTRODUCTION

Autoinflammatory diseases (AID) are characterized by seemingly unprovoked inflammatory attacks in absence of pathogenic autoantibodies or antigen-specific T-cells. Defined as *mono- and polygenic disorders of innate immunity,* AID comprise a broad spectrum of rare diseases which may present with episodes of fever and sterile inflammation potentially causing severe morbidity and mortality. Due to advances in gene sequencing technology and the development of diagnostic criteria, new syndromes continue emerging (1, 2).

Depending on the dominating cytokine pattern, AID can be grouped in IL-1 (inflammasomopathies) (3), NFκB (relopathies) (4) or type I interferon (IFN)-driven diseases (interferonopathies) (5). However, in multiple syndromes such as Adult-Onset Still's Disease [AOSD; IL-1, IL-6, IL-18 (6, 7)], Behçet's syndrome [BS; IL-1, IL-6 (8), IFNγ (9)] or Familial Mediterranean Fever [FMF; IL-1 (10) and IL6 (11)] more than one cytokine plays a key role in pathogenesis. Due to the broad disturbance of cytokine signaling, AID can affect various organs and are thus associated with a high disease burden and severe physical, but also socioeconomic limitations (12). Furthermore, AID patients with persistent inflammation have a high risk of developing AA amyloidosis (13, 14).

Current management of AID includes targeted inhibition of specific cytokine signaling. For example, targeted IL-1 inhibition has been shown to be effective for some conditions such as cryopyrin-associated periodic syndromes (CAPS) (15) and AOSD (16). Unfortunately, some AID patients do not respond to targeted inhibition of specific cytokines and other treatment options are needed (17).

Janus Kinase inhibitors (JAK inhibitors, JAKi) interfere with signal transduction of the Janus Kinase-Signal transducer and activator of transcription (JAK-STAT) pathway causing effective suppression of downstream cytokine signaling. JAK-STAT signaling can be triggered by two types of cytokine receptors: type I receptors bind mainly cytokines (IL-2,−6,−9,−12,−15), hormones (growth hormone, GH) and colony stimulating factors, while type 2 receptors are activated mostly by interferon and IL-10 (18). They act as competitive antagonists at activation sites for Janus kinases and as such interrupt downstream signals along the JAK-STAT pathway, effectively leading to suppression of cytokine production. The JAK-STAT pathway includes several kinases and JAKi can be grouped by their kinase-specific effects: tofacitinib—JAK1, JAK2 and JAK3, baricitinib and ruxolitinib- selective inhibition of JAK1 and JAK2, upadacitinib and filgotinib—selective for JAK1. While JAKi are considered as "targeted therapies," there is almost no other substance class that exerts an effect on such a large number of cytokines. The resulting immunomodulatory effects can be clinically illustrated by the fact that the drugs have already been approved for a number of rheumatic diseases such as rheumatoid arthritis (RA), psoriatic arthritis (19, 20), polyarticular juvenile arthritis (tofacitinib) (21) and ankylosing spondylitis (upadacitinib, tofacitinib) (22, 23).

First reports from an expanded access program study on the beneficial effects of JAKi in type I interferonopathies (24) have also been published. Due to their broad blockade of proinflammatory pathways, JAKi may ameliorate autoinflammatory processes and thus lead to clinical remission in otherwise refractory AID cases. The aim of this systematic literature review is to identify and analyze the available evidence on JAKi for the treatment of autoinflammatory diseases.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed for preparing the manuscript (25).

Protocol and Registration

A study protocol was registered at PROSPERO (CRD42021270369) prior to the systematic search (26).

Data Sources and Searches

The following databases were systematically searched for publications investigating the role of JAKi in AID treatment: MEDLINE *via* PubMed, EMBASE *via* Ovid, Cochrane Central Register of Controlled Trials (via Cochrane Library). The search was conducted on 30 June 2021 and updated on 16 October 2021. The results were supplemented by a backwards search of relevant publications (reference screening).

The search strings were built based on two components using the Boolean operator *and* (AID *and* JAKi). Within those components, multiple terms were linked by *or*. For each syndrome, the full and the abbreviated terms were used including at least one synonym for each condition. For MEDLINE both Medical Subject Headings (MeSH) terms and free-text words were used. All keywords were used to search within titles and abstracts of publications.

Details of the complete search strategy for all searched databases can be found in the **Supplementary Materials**.

Study Selection

Criteria for inclusion were developed using the Patient, Intervention, Comparator, Outcome (PICO) scheme (27). Of interest were following diseases/syndromes:

- Adult-Onset Still's disease (AOSD)
- Systemic Juvenile Idiopathic Arthritis (sJIA)
- Familial Mediterranean Fever (FMF)
- Cryopyrin-associated Periodic Syndromes (CAPS)
- TNF-Receptor Associated Periodic Syndrome (TRAPS)
- Mevalonate Kinase Deficiency (MKD)
- Pyogenic Arthritis, Pyoderma Gangrenosum and Acne (PAPA) Syndrome
- Periodic Fever, Aphthous Stomatitis, Pharyngitis and Adenitis (PFAPA) Syndrome
- Genetic Interferonopathies: Aicardi Goutières Syndrome (AGS), Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) Syndrome, STING associated vasculitis with onset in infancy (SAVI) Syndrome
- Behçet's Syndrome

TABLE 1 | Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
a) *Patient population*: Patients with AID (AOSD, sJIA, FMF, BS, CAPS, TRAPS, PAPA, PFAPA, Type I Interferonopathies)	a) *Patient population*: animal/ *in-vitro* study, AID other than specified
b) *Intervention*: tofacitinib, baricitinib, upadacitinib, filgotinib, ruxolitinib, other JAKi	b) *Intervention*: other than specified
c) *Comparators:* any other treatment	c) *Outcomes*: no/insufficient clinical results
d) *Outcomes*: effectiveness, safety	d) *Publication type:* review articles
e) *Study design*: retrospective (e.g., case reports, case-series, case-control studies, cohort studies); prospective studies (e.g., randomized controlled trials, non-randomized controlled trials, prospective observational studies)	e) *Language*: other
f) *Language*: English	

Defined as *Intervention* was the usage of JAKi (tofacitinib, upadacitinib, baricitinib, filgotinib or ruxolitinib). As *Comparator* we accepted any other treatment. For *Outcome* we analyzed treatment response (see below) and safety (considered were reports on any adverse events).

No restrictions were applied concerning publication date, age, and number of recruited patients. Only studies published in English were included. Considered for inclusion were both retrospective (e.g., case reports, case-series, case-control studies) and prospective studies (e.g., randomized controlled trials, non-randomized controlled trials, prospective observational studies).

Assessment for eligibility was performed by two independent reviewers (AP and ZB), following inclusion and exclusion criteria (**Table 1**). First, only title and abstract were screened. Suitable publications were then assessed in full text. Where there were discrepancies in the evaluation of the eligibility of a publication by the two reviewers, a third reviewer acted as an arbiter (MK).

Data Collection Process and Data Items

Data extraction and management was performed with Microsoft Excel 2016. A standardized data extraction sheet was designed and used for extraction of study characteristics and outcome data, which was carried out by one of the reviewers (ZB). Data was extracted from each publication on: (1) study characteristics; (2) patient characteristics at baseline; (3) patient characteristics after intervention.

Summary Measures, Synthesis

Due to the lack of randomized controlled trials and the heterogeneity of data, a narrative synthesis was carried out. Results were reported based on the Synthesis Without Meta-analysis (SWiM) guideline (28).

Here, the treatment response of each patient was classified as *complete, partial* or *none* based on the available data on clinical symptoms and laboratory parameters prior/post intervention. A *complete* response was defined as resolution of all clinical symptoms and normalization of inflammatory parameters (Erythrocyte Sedimentation Rate, ESR, and/or C-Reactive Protein, CRP); as *partial* when either clinical symptoms resolved or laboratory markers normalized, and as *none* when both remained unchanged or worsened.

RESULTS

The first database search identified 582 records of which 70 were removed (duplicate records). The 512 records were screened. Reference screening of included publications additionally identified 4 suitable publications. The updated search (June to October 2021) identified further 80 publications, of which 75 were screened.

Overall, 38 original publications were included for data extraction and analysis. A total of 101 AID patients treated with a JAKi could be identified. **Figure 1** provides details on the selection process of included studies.

Evidence on Effectiveness and Safety for Chronic Atypical Neutrophilic Dermatosis With Lipodystrophy and Elevated Temperature (CANDLE) Syndrome

The database search identified four case reports (full text $n = 3$, conference abstracts $n = 1$) (29–32) and two articles reporting results of the same compassionate use study (24, 33). A total of fourteen patients were treated with a JAKi. Median age of JAKi initiation was 8.5 years (1.5–17 years, reported for 4 patients). Eleven patients received baricitinib (11/13, 84.6%), and three received tofacitinib (3/14, 21.4%). Mean treatment duration was 92.4 months (reported for 13 patients). All but one patient received glucocorticoids (GC) in addition to a JAKi. Data on baseline characteristics, treatment and response are shown in **Supplementary Table 1**.

Six of the patients (6/14, 42.9%) had a complete response to therapy, half (7/14, 50.0%) showed a partial response and one (1/14, 7.1%) did not respond at all. GC dosage at the end of follow up was reported for eleven patients (11/13, 84.6%), of whom seven (7/11, 63.6%) successfully discontinued GC. In four patients (4/11, 36.4%) GC dose reduction was possible.

Data on adverse events (AEs) was available for thirteen patients (13/14, 92.9%). One patient experienced transient muscle pain. One other developed gamma-GT elevation with dyslipidemia. The latter was managed with atorvastatin. Both cases did not require therapy discontinuation. The most common AEs were infections: BK virus viremia (6/13, 46.2%), herpes zoster (2/13, 15.4%), upper respiratory tract infections (UTI) (10/13, 76.9%) and pneumonia (4/13, 30.8%) none of which required treatment discontinuation. Of all AEs hospitalization was required in 3 cases (3/25, 12%): for BK viremia, herpes zoster and pneumonia.

One patient discontinued therapy after 67.5 months because of acute kidney injury following a series of infections (pneumocystis jirovecii pneumonia, clostridium difficile, influenza, and rotavirus). Details on AEs are summarized in **Table 2**.

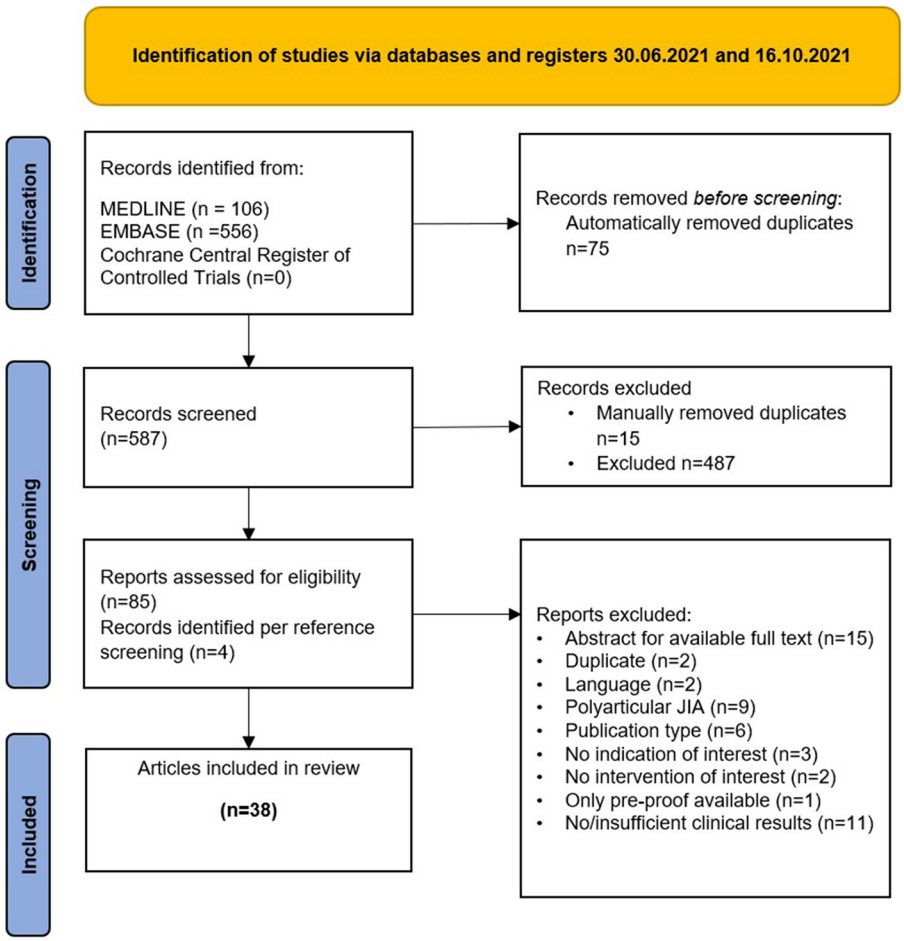

FIGURE 1 | Identification of studies *via* databases and registers 30.06.2021 and 16.10.2021.

Evidence on Effectiveness and Safety for STING Associated Vasculopathy With Onset in Infancy (SAVI) Syndrome

Six case reports (34–39) and seven case series (40–46) reporting on SAVI could be identified (full text $n = 9$, conference abstracts $n = 1$, letters $n = 3$). Additional two articles (24, 33) reported on the same study population (patients with SAVI, CANDLE, other interferonopathies).

Data was extracted and analyzed for a total of twenty-eight patients. Median age of JAKi initiation was 7.5 years (1 month-37 years, reported for 24 patients). Eighteen patients (18/28, 64.3%) received ruxolitinib, seven patients (7/28, 25%) received baricitinib, and three (3/28, 10.7%) received tofacitinib. Mean treatment duration was 23.7 months (2.5–80.1 months, reported for 27 patients). For five patients (5/28, 17.9%) data on supportive treatment was not available. A minority of patients (6/23, 26.1% of reported cases) received JAKi monotherapy. Most were on concomitant GC (16/23, 69.6% of reported cases) of whom six (5/16, 31.3% of reported cases) also received additional immunosuppression (e.g., hydroxychloroquine, IVIG, etanercept). One patient received only IVIG in combination with JAKi (1/23, 4.3%). A summary of baseline characteristics, treatment and response is shown in **Supplementary Table 1**. A quarter of the patients (7/28, 25%) showed no clinical and laboratory response. While most patients experienced improvement either in clinical symptoms, or in laboratory parameters of inflammation, no patient achieved complete remission. GC dosage at last follow-up was reported for twelve patients (12/16, 75%). For eight patients (8/12, 66.7% of reported cases) complete tapering was possible and in three cases (3/12, 25%) GC dose reduction was tolerated.

Data on AEs was available for twenty patients (20/28, 71.4%) and were mostly infectious: UTI (4), pneumonia (3), osteomyelitis (1), cutaneous infection (1), BK viremia (2), BK viruria (1) and gastroenteritis (1) all without the need for therapy discontinuation or reports of dose reduction. JAKi dose reduction was required in two cases: after recurring respiratory infections and in one case of BK viremia. Treatment

TABLE 2 | Overview of adverse events.

Disease	CANDLE	SAVI	AGS	Other type I interferonopathies	AOSD	sJIA	FMF	BS	Total
Number of patients treated	14	28	3	7	26	4	6	13	101
Adverse events—*n**	26	17	1	9	4	0	0	2	59
JAKi dose reduction	–	2	–	–	–	–	–	–	2
JAKi discontinuation	1	2	–	–	1	–	–	2	6
requiring hospitalization	3	4	–	2	–	–	–	–	9
Deaths	–	4**	–	–	1***	–	–	–	5
Types of adverse events									
Pneumonia	4	3	–	–	3	–	–	–	10
Dose reduction	–	1	–	–	–	–	–	–	1
Discontinuation	–	–	–	–	–	–		–	
UTI	10	5	–	2	–	–	–	–	17
Dose reduction	–	–	–	–	–	–	–	–	–
Discontinuation	–	–	–	–	–	–	–	–	–
BK viremia	6	3	–	1	–	–	–	–	10
Dose reduction	–	1	–	–	–	–	–	–	1
Discontinuation	–		–	–	–	–	–	–	–
BK viruria	–	1	–	3	–	–	–	–	4
Dose reduction	–	–	–	–	–	–	–	–	–
Discontinuation	–	–	–	–	–	–	–	–	–
Herpes zoster	2	–	–	1	–	–	–	2	5
Dose reduction	–	–	–	1	–	–		–	1
Discontinuation	–	–	–	–	–	–	–	2	2
Viral gastroenteritis	–	2	–	–	–	–	–	–	2
Dose reduction	–	–	–	–	–	–	–	–	–
Discontinuation	–	1	–	–	–	–	–	–	1
Other infections	1[a]	2[b]	–	1[c]	–	–	–	–	4
Dose reduction	–	–	–	–	–	–	–	–	–
Discontinuation	–	–	–	–	–	–	–	–	–
Dyslipidemia	1	–	1	–	–	–	–	–	2
Dose reduction	–	–	–	–	–	–	–	–	–
Discontinuation	–	–	–	–	–	–	–	–	–
Other AEs	2	1	–	1	1[g]	–	–	–	5
Dose reduction	–		–	–	–	–	–	–	–
Discontinuation	1[d]	1[e]	–	1[f]	1	–	–	–	4

**Information on adverse events was available for 13 CANDLE patients, 20 SAVI patients, 1 AGS patient, 5 patients with other interferonopathies, 24 AOSD patients, 3 sJIA patients, 4 FMF patients and all 13 Behçet's Syndrome patients.*

***One due to ILD and heart failure; one after humoral rejection after lung transplant due to ILD; one due to acute respiratory failure; one due to ILD.*

****One of the patients with bacterial pneumonia, after a 217-day long hospital stay.*

[a]multiple: pneumocystis jirovecii pneumonia, clostridium difficile, influenza, and rotavirus; [b]osteomyelitis; cutaneous infection with staphylococcus aureus; [c]multiple: clostridium difficile, pyelonephritis, urosepsis; [d]acute kidney injury; [e]papillary edema; [f]osteonecrosis; [g]menometrorrhagia.

discontinuation occurred in two cases (severe rotavirus enteritis, papillary edema). In both cases, JAKi therapy was later reinstated and well-tolerated. Four patients (4/28, 14.3%) died during JAKi treatment. Of all AEs, one (enteritis) occurred while the patient was hospitalized. Hospitalization was otherwise required in four cases (4/17, 23.5%): for gastroenteritis, two cases of pneumonia and recurring respiratory infections. Details on AEs are summarized in **Table 2**.

Evidence on Effectiveness and Safety for Aicardi Goutières Syndrome (AGS)

The systematic searches identified three case reports on AGS (full text $n = 2$, letters $n = 1$) (47–49). One additional letter reports preliminary results of an open-label single center study involving 35 patients with AGS (50). The publication is discussed in the Discussion section since no individual patient data was available.

Here, we report the available data on two pediatric patients and one adult. The median age of JAKi initiation was 11 years (1.5–22 years). The patients were treated for a mean duration of 28.3 months (18–43 months). A summary of baseline characteristics, treatment and response is shown in **Supplementary Table 1**. All patients (3/3, 100%) showed a partial response to therapy.

Data on AEs was available for only one patient (1/3, 33.3%) (48) who developed creatine kinase fluctuations, hypercholesterinemia, and hypertriglyceridemia, which were transient and controlled by dietary management without the need for JAKi dose reduction or hospitalization. No other AEs were reported. Details on AEs are summarized in **Table 2**.

Evidence on Effectiveness and Safety for Other Type I Interferonopathies

Three case reports (51–53) (conference abstracts $n = 1$, full text $n = 2$) and two articles reporting results of the same compassionate use study (24, 33) regarding type I interferonopathies were identified.

A total of seven patients were treated. One patient was diagnosed with DNase II deficiency. For the rest either only "other type I interferonopathy" was reported as diagnosis or a novel mutation was described (**Table 1**). Median age of JAKi initiation was 4 years (1 month −17 years, reported for 3 patients). Five patients (5/7, 71.4%) received baricitinib, and one patient each received tofacitinib or baricitinib (1/7, 14.3% each). Mean treatment duration was 33.4 months. GC were used in five patients (5/7, 71.4%), one patient received concomitant cyclosporine therapy and one patient received a combination of mepacrine and hydroxychloroquine. A summary of baseline characteristics, treatment and response is shown in **Supplementary Table 1**. A complete response was achieved by only one patient (1/7, 14.3%) under combination of baricitinib and cyclosporine A (5 mg/kg/d). Four patients (4/7, 57.1%) had a partial response and two (2/7, 28.6%) showed no response to therapy. For three patients (3/5, 60%) GC dose reduction was possible and one (1/5, 20%) successfully tapered GC.

Data on AEs was available for five patients (5/7, 71.4%), as follows: UTI (2/5, 40%), BK viruria (3/5, 60%), BK viremia (1/5, 20%). In neither case were dose reduction or therapy discontinuation reported. One case of herpes zoster (1/5, 20%) required intermittent JAKi dose reduction. Of all AEs, hospitalization was required in two cases (2/9, 22.2%): in one patient after multiple infectious events (clostridium difficile infection, pyelonephritis, urosepsis) and in one case of osteonecrosis. The latter discontinued JAKi therapy after 5.1 months due to this AE. Details on AEs are summarized in **Table 2.**

Evidence on Effectiveness and Safety for Adult-Onset Still's Disease (AOSD)

For AOSD three case reports (54–56) and three case series (57–59) were identified (conference abstracts $n = 2$, letters to the editor $n = 2$, publications in full text $n = 2$).

A total of 26 patients were treated with a JAKi. Median age of JAKi initiation was 33 years (18–82 years). Most patients (18/26, 69.2%) were treated with tofacitinib, one patient (1/26, 3.8%) received ruxolitinib, and the other patients (7/26, 26.9%) baricitinib. Mean treatment duration was 7.6 months (1–24 months). Most patients (24/26, 92.3%) received GC either alone (7/26, 26.9%) or in combination with other disease modifying antirheumatic drugs (DMARDs) (17/26, 65.4%). Two patients had methotrexate (MTX) alone as supportive treatment (2/26, 7.7%). Mean GC dose at JAKi initiation was 37.3 mg prednisone equivalent per day. A summary of baseline characteristics, treatment and response is shown in **Supplementary Table 1**. A complete response was seen in eleven patients (11/26, 42.3%), with the same number of patients showing a partial response (11/26, 42.3%). No response was seen in a minority of patients (4/26, 15.4%). GC dosage at the end of follow-up was reported for twenty-two patients (22/24, 91.7%). Mean GC dose was 13.3 mg prednisone equivalent per day. GC dose reduction was possible for most patients (18/22, 81.8% of reported cases) and complete GC tapering was achieved by three patients (3/21, 14.3% of reported cases).

Data on AEs was available for 24 patients (24/26, 92.3%) and were overall rare: pneumonia (3/24, 12.5%) and menometrorrhagia (1/24, 4.2%); the latter required therapy discontinuation in one patient. One of the patients with bacterial pneumonia died after a 217-day long hospital stay. Otherwise no AEs required hospitalization. Details on AEs are summarized in **Table 2**.

Evidence on Effectiveness and Safety for Systemic Juvenile Idiopathic Arthritis (SJIA)

Two case reports (60, 61) and one case series (57) (published as conference abstracts $n = 1$, letters $n = 1$, in full text $n = 1$) were identified.

Four patients with sJIA were treated with a JAKi. Median age at JAKi initiation was 9 years (4–13 years). Two patients received ruxolitinib (2/4, 50%), and one each received tofacitinib or baricitinib (1/4, 25% each). Mean treatment duration was 14.2 months (8–25 months). All received GC as supportive treatment. Two patients (2/4, 50%) received GC only along JAKi, and two patients—in combination with non-steroidal anti-inflammatory drugs and two patients (2/4, 50%). Data on baseline characteristics, treatment and response are shown in **Supplementary Table 1**. **Two** patients showed a complete response to therapy (2/4, 50%) and for the other two (2/4, 50%) a partial response was reported. GC dose reduction was possible for three patients (3/4, 75%) and one (1/4, 25%) successfully tapered GC to discontinuation.

Data on AEs was available for three patients (3/4, 75%), and none were reported (**Table 2**).

Evidence on Effectiveness and Safety for FMF

Two case series (62, 63) and one case report (64) (full text $n = 2$, letters $n = 1$) were identified.

A total of six patients with FMF were treated with a JAKi. Median age at JAKi initiation was 35.5 years (16–64 years). All patients were treated with tofacitinib 10 mg/d. Mean treatment duration was 4.5 months (2–12 months). One patient received no supportive treatment (1/6, 16.7%), one (1/6, 16.7%) received a combination of GC, colchicine, and sulfasalazine. Four patients (4/6, 66.7%) were prescribed colchicine. A summary of baseline characteristics, treatment and response is shown in **Supplementary Table 1**. A complete response was shown by half of the patients (3/6, 50%). The other three patients (3/6, 50%) developed no further flares, but acute phase reactants remained elevated, thus only a partial response was achieved.

Data on AEs was available for four patients (4/6, 66.7%) with none reported (**Table 2**).

Evidence on Effectiveness and Safety for Behçet's Syndrome

Only one publication on BS could be identified (65). Thirteen patients were treated with a JAKi. Median age at JAKi initiation was 42 years (22–73 years). All patients received tofacitinib 10 mg/d. Patients were treated for a mean duration of 10.8 months (5–21 months). All but one patient received concomitant GC therapy (12/13, 92.3%). Tofacitinib was administered as additional therapy to other drugs such as azathioprine, thalidomide, leflunomide, colchicine, salazosulfapyridin. A summary of baseline characteristics, treatment and response is shown in **Supplementary Table 1.**

According to the criteria used in this systematic review, most patients achieved a partial response (8/13, 61.5%). Five patients showed no response to therapy (5/13, 38.5%), of whom one patient's condition worsened (1/13, 7.7%) and tofacitinib was withdrawn after 9 months of treatment. Two cases of herpes zoster reactivation were observed, both of which led to discontinuation of tofacitinib. No other AEs were reported (**Table 2**).

Evidence on Effectiveness and Safety for Other Syndromes

No articles regarding CAPS, TRAPS, PFAPA, PAPA or MKD could be identified.

DISCUSSION

To our knowledge, this is the first systematic review analyzing the safety and effectiveness of JAKi in AID. The overview of the available clinical evidence is based on observational studies such as case reports and case series. Effectiveness was evaluated based on clinical response, defined by the authors of this systematic review as complete, partial or no response depending on (complete) symptom resolution and/or normalization of laboratory parameters for inflammation. Furthermore, AEs were described.

Type I Interferonopathies

Most reports ($n = 25$) included in this systematic review investigated the use of JAKi for type I interferonopathies. Interferonopathies represent a group of rare monogenic AID, characterized by a disturbed control of interferon-mediated immune responses, especially of type I interferons. JAKi are potent inhibitors of the JAK-STAT pathway, involved in interferon signaling (66). Thus, the application of JAKi in interferonopathies seems rational. In this analysis, reports on SAVI, CANDLE, AGS and other interferonopathies were included.

Fifty-two patients (CANDLE $n = 14$, SAVI $n = 28$, AGS $n = 3$, other interferonopathies $n = 7$) could be identified. Overall promising results were seen: seven patients (7/52, 13.5%) showed a complete response to therapy, the majority (35/52, 67.3%) showed a partial and a minority (10/52, 19.2%) showed no treatment response.

For AGS, one publication (50) was identified but individual patient data was not available. This article reported preliminary results of an open-label single center study involving 35 patients with molecularly confirmed AGS. This is to our knowledge the largest AGS cohort treated with JAKi. All patients received baricitinib. The authors report overall improvement of daily diary scores within 1 month of therapy initiation. Neurological function was evaluated based on key developmental milestones, with 20 patients (20/35, 57.1%) meeting new milestones and 12 (12/35, 34.3%) gaining two to seven new skills. In the three cases presented in this systematic review, neurological symptoms were leading in just one case (49) showing improvement under ruxolitinib. Regarding the safety profile of JAKi, in this AGS cohort (50) only one case of BK viremia was described—a relatively frequent event in interferonopathy patients discussed here (10/52, 19.2%).

Notably, amongst interferonopathy patients, JAKi was most efficient for CANDLE patients: complete remission was achieved by six patients (6/14, 42.6%). Additionally, a GC sparing effect in this group is suggested by the available data, since seven patients (7/11, 63.6%) were able to discontinue GC and in four patients (4/11, 36.4%) GC dose reduction was possible.

One hypothesis for the difference in treatment outcome between interferonopathies is that the better treatment response is owed to a higher JAKi dosage. A direct comparison is difficult since mostly pediatric patients were treated and JAKi dosage was reported as mg per kilogram without documenting weight for each individual patient. Mean baricitinib and tofacitinib dosages in CANDLE cases were 6.8 and 5 mg/d, respectively. Mean baricitinib doses for SAVI were 6 mg/d (reported for 6/7, 85.7%) up to a mean 8 mg/d in other interferonopathies. Most SAVI patients were treated with ruxolitinib at a mean dose 10.8 mg/d (reported for 13/18, 72.2% patients treated).

A head-to-head comparison of effectiveness is difficult due to (1) the small number of patients treated (2) the different choice of JAKi and the respective dosage used and (3) partial missing individual data.

Regarding safety it should be mentioned that most infectious AEs in this analysis occurred in patients with type I interferonopathies: seven cases of pneumonia (7/10, 70%), all UTIs (17/17, 100%) and all cases of BK viremia and viruria (10/10 and 4/4, respectively; 100%) (**Table 2**). The proportion of patients in this group who experienced any AE is also greater compared to other groups: around 17% of AOSD patients (4/24,

16.7%), even less in BS patients (2/13, 15.4%) and none of the FMF and sJIA patients.

Of overall 59 AEs reported, 52 (88.1%) were due to infections (**Table 2**). In general JAKi show a heterogenous risk of infectious complications. For example, a known class effect for JAKi is an elevated risk of herpes zoster (67–70). In one recent study, serious infections were more frequent with tofacitinib at a dose of 10 mg twice daily compared to TNF inhibition (71), which contradicts some available evidence pointing to a similar risk of serious infections under JAKi compared to other biological disease-modifying antirheumatic drugs (bDMARDs) (72, 73). The risk for opportunistic infections (herpes zoster, tuberculosis) under tofacitinib in this study was higher compared to a TNF-inhibitor, and even more so when tofacitinib dose was 10 mg compared to 5 mg. In this systematic review two cases of herpes infections occurred under tofacitinib and baricitinib each. One case occurred under ruxolitinib.

A controversially discussed adverse effect of JAKi are thromboembolic events. This risk has been shown to be elevated relative to TNF inhibitors, along with a clinically meaningful risk of serious heart-related AEs, cancers, blood clots and death in older patients with RA (71). However, several (meta-) analyses did not provide evidence supporting an increased risk of thromboembolism with JAKi (67, 74, 75). In this systematic review, thromboembolic events were not reported.

The discrepancy in the frequency of AEs in the different disease groups here could reflect the inconsistency in reporting of AEs, commented further below. It should be considered that for FMF, sJIA and Behçet's syndrome only a few reports were available for analysis. However, one reason for the higher incidence of infections amongst interferonopathy patients might be due to a dose dependent effect. All FMF and Behçet's syndrome patients, and most AOSD patients received a "standard dose" of tofacitinib (5 mg/d) or baricitinib (4 mg/d). As mentioned above, JAKi doses varied amongst interferonopathy patients. Nevertheless, baricitinib was often administered at doses higher than 4 mg/d—up to a mean 6.8 mg/d in CANDLE patients and a mean 6 mg/d for SAVI patients. Notably, most interferonopathy patients were pediatric patients, suggesting a higher dose pro kilogram body weight.

Another hypothesis is that interferonopathy patients generally have a higher risk for infections. While infections can be considered potential triggers for disease onset or flares (5), a predisposition for infections in interferonopathy patients is currently not proven. However, for other diseases with a prominent interferon signature, such as systemic lupus erythematosus (SLE) and dermatomyositis, a susceptibility for infections has been reported (76, 77). Thus, a possible explanation for the elevated incidence of infectious AEs in this subgroup could be an intrinsically dysfunctional immune system leaving patients exposed to an increased risk of infection.

Other AID

Part of the systematic database searches about JAKi for treating monogenic AID were CAPS, TRAPS MKD and FMF. Of those, publications were identified only for FMF. In FMF patients, JAKi resulted in a complete response in half of the patients and a partial response for the rest (3/6, 50% each). Eleven AOSD patients had a complete response and the same number of patients a partial response (11/26, 42.3% each). Two sJIA patients completely responded to JAKi therapy (2/4, 50%) and for the other two (2/4, 50%) a partial response was reported. Amongst BS a partial response was achieved by most (8/13, 61.5%), and five (5/13, 38.5%) showed no response to therapy.

Although JAKi did not lead to complete remission in all AOSD patients, the majority of them were able to taper or withdraw GC—used as supportive treatment in most patients (24/26, 92.3%). Dosage of GC at last follow up was reported for 22 patients. Mean GC dose at JAKi initiation was 37.3 mg prednisone equivalent per day, and 13.3 mg/d at last follow-up. This highlights the potential of JAKi as GC sparing drug in AOSD, especially in patients with articular phenotype. The majority of AOSD patients presented with arthritis (20/26, 76.9%), of whom most showed a complete or a partial response (8/20, 40% for each group). Additionally, all FMF patients included in this analysis had active arthritis. All of them showed clinical improvement under JAKi. Therefore, it can be hypothesized that JAKis are especially beneficial for patients with active arthritis.

Limitations and Considerations for the Future

Due to the rare nature of AID and the relatively recent availability of JAKi, there are currently no RCTs available, and most publications included were case reports or series. Therefore, conducting a risk of bias assessment was not possible. Many authors were contacted to complete missing data, however in some instances despite our best effort complete information could not be obtained. In the analyzed publications a relatively low systematization in conduct and reporting was observed, which in part resulted in limited details on individual patient characteristics at baseline and post JAKi treatment. In order to include as much information as possible on the topic, congress abstracts were also included in the analysis. Abstracts are generally considered to potentially lower the overall evidence level in a systematic review. Therefore, only abstracts providing sufficient clinical data were included in the final analysis (78).

To present the results of this systematic review, a classification based on clinical symptoms and laboratory parameters was performed. Accordingly, treatment response was classified as complete, partial or none. Although this approach has not been validated, it has been previously used by other investigators (57–59) and serves as base for objectifying and summarizing the available evidence. The body of evidence found did not suffice for quantitative analysis due to its heterogeneity. Instead, an extensive narrative synthesis was conducted.

To this date, no universal criteria for reporting outcomes in AID patients exist. To improve and standardize reporting on treatment strategies in AID we suggest the following type of reporting (**Table 3**). clinical symptoms, inflammatory parameters, concomitant diseases, previous therapies; for the use of JAKi—exact dose, as well as information on any supportive treatment, including dosage; for a precise evaluation therapeutic

TABLE 3 | Suggestions for future reporting on treatment outcome.

Pre-JAKi	**JAKi**	**Post-JAKi**
Clinical		**Clinical**
Clinical symptoms	Dosage	Change in clinical symptoms
Disease score (if available)	Supportive treatment (including dosage)	Change in disease score (if available)
Concomitant diseases	Treatment duration	Change in dosage of supportive drugs (e.g. GC)
Previous therapies		Adverse events
Inflammatory markers		**Inflammatory markers**
CRP		CRP
ESR		ESR
others (complete blood count, ferritin, IFN gene expression, if applicable)		others (complete blood count, ferritin, IFN gene expression, if applicable)

response statements on dynamics of clinical symptoms, as well as inflammatory parameters should be noted. AEs especially infections should be closely monitored. In the publications included in this systematic review reports on AEs were sometimes insufficient—those were not documented in around 15% of cases (83/101, 82.2%).

Furthermore, disease (specific) activity scores and response criteria to compare AID studies are urgently needed. For monogenetic inflammasomopathies (FMF, CAPS, TRAPS, MKD) the Auto-Inflammatory Diseases Activity Index (AIDAI) (79) is a validated score but was only reported in one study concerning JAKi use in FMF (63). An EULAR task force is currently preparing specific criteria for AOSD which should be applied for future reporting (80). Regarding type I interferonopathies Frémond, M. et al., 2016 suggested a disease activity score for SAVI patients: the Disease Activity Rating Scale of TMEM173-mutated patients (42). This score for SAVI needs to be validated and scores for the other interferonopathies need to be developed. Overall, given their rare nature, a considerable number of AID patients treated with a JAKi (101) could be identified. The available evidence showed most patients did respond to JAKi therapy. This review was conducted to summarize the available evidence on new therapeutic possibilities for AID patients and to highlight the need for well-designed clinical trials investigating JAKi in AID. Currently, one phase 3 clinical trial investigating baricitinib in CANDLE, SAVI and AGS is being conducted (81). Research is actively underway in the direction of sJIA with two ongoing phase 3 randomized double-blind, placebo-controlled studies on baricitinib and tofacitinib (82, 83).

CONCLUSION

This systematic review provides results from observational studies showing first pieces of evidence on treatment effectiveness of JAKi for AID. To validate these results and confirm efficacy and safety of JAKi for specific AID, clinical trials need to be initiated.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

ZB, GB, and MK: systematic review concept and design. ZB, NR, and MK: systematic review protocol. ZB: database search. ZB and AP: study selection. MK: arbiter during publications screening. ZB: data extraction and synthesis. ZB and MK: manuscript drafting. ZB, MK, NR, GB, and AP: manuscript revision and final review. All authors approved the final version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.930071/full#supplementary-material

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Development and Implementation of the AIDA International Registry for Patients With VEXAS Syndrome

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Objective: The aim of this paper is to present the AutoInflammatory Disease Alliance (AIDA) international Registry dedicated to Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic (VEXAS) syndrome, describing its design, construction, and modalities of dissemination.

Methods: This Registry is a clinical, physician-driven, population- and electronic-based instrument designed for the retrospective and prospective collection of real-life data. Data gathering is based on the Research Electronic Data Capture (REDCap) tool and is intended to obtain real-world evidence for daily patients' management. The Registry may potentially communicate with other on-line tools dedicated to VEXAS syndrome, thus enhancing international collaboration and data sharing for research purposes. The Registry is practical enough to be easily modified to meet future needs regarding VEXAS syndrome.

Results: To date (April 22nd, 2022), 113 Centers from 23 Countries in 4 continents have been involved; 324 users (114 Principal Investigators, 205 Site Investigators, 2 Lead Investigators, and 3 data managers) are currently able to access the registry for data entry (or data sharing) and collection. The Registry includes 4,952 fields organized into 18 instruments designed to fully describe patient's details about demographics, clinical manifestations, symptoms, histologic details about skin and bone marrow biopsies and aspirate, laboratory features, complications, comorbidities, therapies, and healthcare access.

Conclusion: This international Registry for patients with VEXAS syndrome will allow the achievement of a comprehensive knowledge about this new disease, with the final

goal to obtain real-world evidence for daily clinical practice, especially in relation to the comprehension of this disease about the natural history and the possible therapeutic approaches. This Project can be found on https://clinicaltrials.gov NCT05200715.

Keywords: autoinflammatory diseases, clinical management, precision medicine, rare diseases, research, treatment

INTRODUCTION

VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) syndrome is a recently recognized pathological entity first reported in December 2020. VEXAS represents a monogenic autoinflammatory condition caused by acquired somatic mutations in UBA1, gene encoding one of the two E1 enzyme isoforms that initiates ubiquitylation in cell's cytoplasm. Unlike other genetic autoinflammatory syndromes, which are due to germline mutations in most of cases, VEXAS syndrome is caused by acquired variants in blood cells precursors, especially myeloid progenitors (1). Because of its recent identification, VEXAS clinical features, complications, outcome, and treatment strategies are not fully established at current. However, it is clearly characterized by prominent inflammation involving almost all organs and tissues with highly increased inflammatory markers. The skin, eyes, lungs, joints, and gastrointestinal system are frequently affected by the disease, with a quite protean range of inflammatory manifestations. Besides these clinical features, which account for a common ground with other "historical" autoinflammatory diseases, hematologic involvement represent the most typical disease manifestation. Indeed, hematological involvement is observed in at least 50% of patients, with myelodysplastic syndrome (MDS) representing the most frequent bone marrow affection. Monoclonal gammopathy with unknown significance (MGUS), macrocytic anemia with normal vitamin B12 and folate levels, leukopenia, and thrombocytopenia are additional hematological features. Noteworthy, marked cytoplasmic vacuolization in hematopoietic precursors are often observed in bone marrow aspirate smears, which represent a good diagnostic clue. Vacuoles are generally identified in erythroid and myeloid precursors (blasts, promyelocytes, and pronormoblasts), but are also observed in eosinophils, monocytes, plasma cells, and megakaryocytes to a lesser degree (2).

At current there is no data about the effective epidemiological burden of VEXAS syndrome, which as to be consider a rare disease based on the current prevalence. Therefore, as with other rare diseases, VEXAS syndrome may benefit from patient registries capable of leading to a better understanding of the disease in a relatively short time. In particular, patient registries are overcoming current research approaches, especially for rare diseases. International registries have the potential to recruit a wide number of patients worldwide and follow enrolled subjects for very long periods of time. The importance of patient registries in the field of rare diseases is shown by the relevance provided by the European Union (EU) to this online tool, making available specific guidelines for high-quality registries (3–5).

Regarding autoinflammatory diseases, the AutoInflammatory Disease Alliance (AIDA) has already developed and launched eight international registries for patients with many rare autoinflammatory diseases (6–8). The AIDA Project has already allowed the construction of an international Network of physicians and researchers interested in putting together information to expand current evidence about monogenic autoinflammatory diseases, Still's disease, Schnitzler's syndrome, Behçet's disease, periodic fever, aphthous stomatitis, pharyngitis, cervical adenitis (PFAPA) syndrome, non-infectious uveitis, non-infectious scleritis, and undifferentiated systemic autoinflammatory diseases (USAIDs). For more details, the AIDA Network may be accessed at the following website: https://aidanetwork.org/en/.

Based on the experience of the AIDA Network in developing registries for rare autoinflammatory diseases, an international patient Registry specifically dedicated to VEXAS syndrome has been developed. This manuscript aims to illustrate the objectives, design, methodology and modalities of diffusion underlying the development and activation of the VEXAS Registry.

MATERIALS AND METHODS

Study Design

The AIDA Registry presented in this work has been created as an international, clinical, physician-driven, population- and electronic-based registry dedicated to patients diagnosed with VEXAS syndrome.

Data collection includes a retrospective phase, for data gathered up to the time of the enrolment in the Registry, and a prospective phase for progressive data available starting from the time of the enrolment. The prospective phase requires the collection of at least one follow-up visit per year. However, prospective data collection should be performed whenever a change in the treatment strategy occurs.

The Registry is designed to collect demographic, genetic, clinical, laboratory and treatment data starting since the disease onset. These data will be essentially derived from the routine follow-up visits performed to guarantee the best standard of care, while no additional information will be required. In the same way, none of the treatment choices and drug adjustments will be influenced by the participation to this Project. Indeed, physicians' clinical judgement based on current evidence represents the only factor capable of determining the therapeutic management of the patient.

The access is open for all Centers dealing with the management, diagnosis, and treatment of VEXAS syndrome. The Centers that would like to participate, may join the AIDA Network by contacting the Promoter or sending an email to the

AIDA Team by writing to support@aidaregistry.org or using a specific form, that may be found at the following page: https://aidanetwork.org/en/aida.

All clinical specialities are included in the AIDA Network; the location and the type of practice setting do not influence the inclusion in this Project. As data inserted in the Registry are usually included in the standard management of VEXAS patients, no costs or financial fees are settled. As an essential prerequisite for the inclusion in this Project, each Center must obtain the approval from the local ethics committee. Also, it is essential to identify a Principal Investigator for the local coordination of the study and at least a Site Investigator, who will manage documentation and take care of data collection. Both the Principal Investigator and the Site Investigator will receive the credentials to enter the Registry and start patients' enrolment after having expressed the formal intention to participate in the VEXAS Registry.

Registry Objectives

The Registry for patients with VEXAS syndrome is primarily aimed at gathering information from the larger number of patients as possible. A large cohort of patients is critical to obtain solid evidence from data analysis and transfer the results into daily clinical practice. A further objective of the Registry is to learn about VEXAS syndrome in detail and in a rapid manner, avoiding the delays that would inevitably result from traditional clinical research, which generally relies on limited study populations available at a single research center.

Additional objectives of this Project are: (I) to fully characterize the wide spectrum of inflammatory manifestations and their frequency; (II) to eventually identify different disease subtypes; (III) to describe mutations that will be found in the *UBA1* gene, to differentiate among pathogenic or likely pathogenic variants from benign polymorphisms; (IV) to search for genotype-phenotype associations; (V) to study the influence of other mutations on genes associated with monogenic autoinflammatory diseases; (VI) to identify any pathognomonic features to facilitate diagnosis; (VII) to develop classification criteria and diagnostic algorithms to be applied in clinical practice to select patients for genetic assessment; (VIII) to identify variables capable of distinguishing VEXAS patients from other mimicking diseases; (IX) to fully understand the possible spectrum of haematologic disorders; (X) to describe hematologic and non-hematologic complications occurred in the long-term; (XI) to better characterize information from bone marrow biopsy and aspirate; (XII) to search for prognostic factors able to select patients with a higher probability to develop complications; (XIII) to recognize predisposing factors and triggers associated with the onset and disease's exacerbations, quantifying and stratifying the severity of the features; (XIV) to describe treatment attempts, taking in to account their efficacy as a whole and the impacts on the different aspect of the disease; (XV) to report the safety profile of single treatment approaches in VEXAS patients; (XVI) identifying the better treatment approach tapered on the patient's features and disease characteristics; (XVII) to carefully study treatment dosages and their changes to develop standardized treatment protocols; (XVIII) to asses any influence of the environmental background and the ethnic origin on the VEXAS syndrome phenotype; (XIX) to assess any impact of the socioeconomic status in terms of access to healthcare and patients' absenteeism due to the disease; (XX) to monitor the cardiovascular risk in such patients; (XXI) to monitor the causes of death in VEXAS syndrome.

Other pioneering studies will be eventually designed according to the unmet needs arising from patients' management over time.

Table 1 summarizes primary and additional objectives of this Registry.

TABLE 1 | Objectives considered for the implementation of the AIDA registry for patients with VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome.

Primary objectives	To collect as much real-world data from a large cohort of patients enrolled with an international basis
	To avoid the time delay associated with the traditional clinical research in obtaining a comprehensive knowledge and awareness about VEXAS syndrome
Additional objectives	To fully characterize the wide spectrum of inflammatory manifestations and their frequency
	To eventually identify different disease subtypes
	To differentiate among pathogenic and likely pathogenic variants from benign polymorphisms that will be found in the *UBA1* gene
	To search for any genotype-phenotype associations
	To study the influence of other mutations on genes associated with monogenic autoinflammatory diseases
	To identify any pathognomonic features able to facilitate diagnosis
	To develop classification criteria and diagnostic algorithms to be applied in clinical practice to select patients for genetic assessment
	To identify variables capable of distinguishing VEXAS patients from other mimicker diseases
	To fully understand the possible spectrum of hematological disorders associated with VEXAS syndrome
	To describe hematologic and non-hematologic complications occurring in the long-term
	To better characterize information from bone marrow biopsy and aspirate
	To search for prognostic factors able to select patients with a higher probability to develop complications
	To recognize predisposing factors and triggers associated with the onset and disease's exacerbations, quantifying and stratifying the severity of the features
	To describe treatment attempts, taking in to account their efficacy as a whole and the impacts on the different aspect of the disease
	To report the safety profile of single treatment approaches in VEXAS patients
	To identify the better treatment approach tapered on the patient's features and disease characteristics
	To create standardized treatment protocols
	To assess any influence of the environmental background and the ethnic origin on the VEXAS syndrome phenotype;
	To assess the socioeconomic influence of the disease
	To monitor the cardiovascular risk in such patients
	To monitor the causes of death in VEXAS syndrome
Ancillary objectives	To design other pioneering studies according to the unmet needs arising from patients' management over time

Inclusion/Exclusion Criteria

Patients carrying a *UBA1* gene somatic mutation and showing an inflammatory phenotype may be included in the Registry.

The patient has to give the written and informed consent after a careful explanation of the Project: the objectives of the Registry, the lack of implications on clinical management and treatment, the opportunity to withdraw the consent at any time, and the laws to comply with to guarantee patients' privacy, anonymity and security of data. Patients have to be ensured about the lack of consequences deriving from her/his will to participate or not to the study.

For patients unable to provide their consent, this should be given by legally authorized representatives, who must observe the study requirements for the entire duration of the study or until the consent withdrawal. In any case, the patient's assent is essential for patients aged ≥12 years.

No exclusion criteria or conditions are previewed to the enrolment.

Online Data Collection

The Research Electronic Data Capture (REDCap) instrument has been used for data gathering and storing. REDCap is an electronic data collector produced at Vanderbilt University Medical Center (VUMC). It is currently located at the Virginia Commonwealth University (Award Number UL1TR002649). The employment of the REDCap platform is free to all the members of the *REDCap consortium*, which may benefit from using the tool in return for technical support. At current, take part in the *REDCap consortium* from the 4 continents over 5,600 worldwide institutions from 144 Countries already (9). To access the Registry, Principal Investigators and Site Investigators have to enter their own username and password. The Registry is available at the webpage https://aidanetwork.org/en/register/vexas. Data are kept on the servers of the University of Siena, Siena, Italy. Privacy is ensured for each Centre's data, with Principal and Site Investigators unable to access data collected in other Centers.

The Registry's browser interface provided for the data entry is entirely supplied in English in order to reduce the language barriers and facilitate the international data collection.

The retrospective assessment requires the collection of clinical and laboratory data referring to the symptoms of the disease at the onset, at the diagnosis, and at the enrollment into the Registry; clinical and laboratory data would be inserted referring to the start of each treatment performed, the 3-, 6- and 12-month visits and at the last assessment. On the other hand, follow-up visits will be added at the visits performed after the inclusion in the AIDA Registry; follow-up assessments should be filled in at least every year and at any change in the treatment strategy, as for the introduction of new drugs and posology changes. Socioeconomic data include variables embedded to assess the impact of VEXAS syndrome on the national health care system (access to primary care physician, specialist visits, laboratory examinations, imaging tests, access to emergency care and hospitalization) and on the working world (absenteeism and presenteeism).

The Investigators will be responsible for the own study data introduced in the online Registry and for the precision of the information accrued; the Principal Investigator is required to check for the accuracy of the data. The online access through personal username and password guarantees the security of the patients' information.

Ethics

In June 2019 the Ethics Committee of the Azienda Ospedaliero-Universitaria Senese, Siena, Italy (Ref. N. 14951) granted the first national regulatory approval for the AIDA Project. After that, Centers experienced with diagnosis, clinical management, and treatment of autoinflammatory diseases have joined the AIDA Network from Europe, Middle East, Africa and America.

Patients' information is kept in accordance with the EU General Data Protection Regulations (GDPR) on the processing of personal data and the protection of privacy (2016/679/EU) (10), or other counterparts.

Regarding the patients' voluntary informed consent, the AIDA registries meet the recommendations from the Declaration of Helsinki. For minor patients aged ≥12 years the assent is also required when the patient is not competent to provide the consent. In these cases, parents/legal guardians have to provide their authorization to allow the patient's participation in the Project.

Consent for processing data for statistical or research purposes may be withdrawn at any time by either patients or Principal Investigators. In these cases, no further information will be captured; moreover, the patient has the right to obtain the complete erasure of all personal data already gathered in the Registry if required and notified to the study Promoter (University of Siena).

No financial remuneration is planned for patients or physicians for the study participation; in addition, there is no evidence of any billing relationships with the national health systems or insurance companies.

Statistical Analysis

Statistical analysis will be based on the specific type and nature of data undergoing computation and will be performed according to the specific objectives of the studies conducted on behalf of the AIDA Network. In any case, the analysis will embrace general principles of descriptive statistics, correlations between groups and comparisons between subgroups. Details about statistics will be provided in the future papers obtained from data collected in the VEXAS Registry.

Principal Investigators and Site Investigators are encouraged to put forward their study proposals during the AIDA meetings. The data collected in a center may be analyzed by satellite centers independently from the other centers on condition that the AIDA Network appears among acknowledgments. On the contrary, the totality of data collected in the Registry will be managed by statistics and physicians involved in the network and selected based on their field of expertise.

RESULTS

The development and activation of this AIDA Registry is a first fundamental result of the AIDA Network. In this regard, an

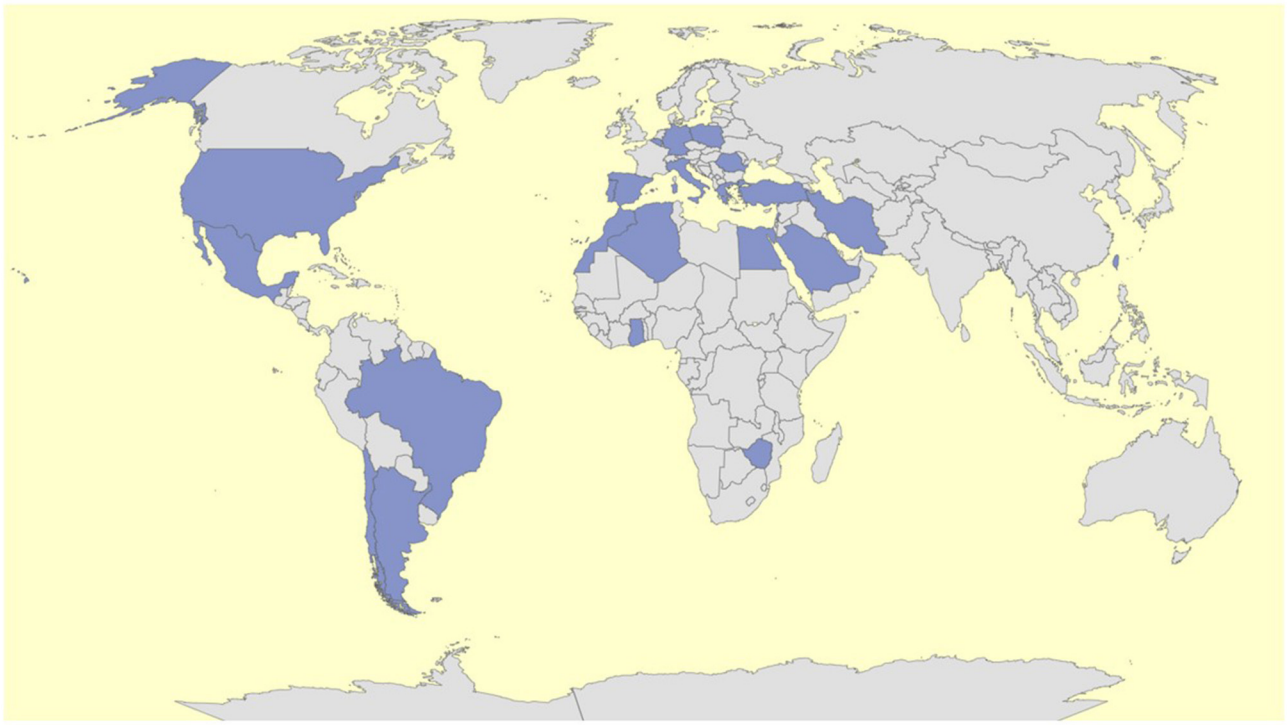

FIGURE 1 | Worldwide distribution of the AIDA network on 22nd of April 2022.

international registry dedicated to VEXAS syndrome is essential to extensively gather real-life data in a quick manner.

To date, 23 nations in 4 continents (Algeria, Argentina, Belgium, Brazil, Chile, Egypt, Germany, Ghana, Greece, Iran, Italy, Lebanon, Morocco, Mexico, Poland, Portugal, Romania, Saudi Arabia, Spain, Taiwan, Turkey, United States, Zimbabwe) have already joined the AIDA Network. The **Figure 1** highlights the current (April 22nd, 2022) worldwide distribution of the AIDA Network.

Overall, 113 Centers around the world have joined the AIDA project for a total of 324 users (114 principal investigators, 205 site investigators, 2 lead investigators, 3 data managers). This Project was registered at ClinicalTrials.gov (ID: NCT05200715).

Registry Development

When choosing the clinical variables constituting the Registry, information useful for a valuable knowledge of VEXAS syndrome was included, in order to quickly obtain data and comprehensively understand this new clinical entity in a relatively short time. For this reason, the registry was developed to comprehensively trace the entire clinical and therapeutic history of the patients enrolled. To date (April 22nd, 2022), the Registry contain 4,952 common data elements (each corresponding to a study variable) organized into 18 instruments. Thirteen of these instruments are specifically built to collect retrospective information, one instrument is dedicated to the prospective phase and 4 instruments should be used both to collect retrospective information and to describe any change starting from the time of the enrolment. **Table 2** provides more detailed information about the instruments included in this Registry, the phases they refer to and the number of fields they include.

Common data elements consist of demographic, clinical, instrumental, histological, laboratory, therapeutic and any other medical variable required to fully describe disease course. Many of these are shared with other AIDA registries dedicated to different autoinflammatory and non-infectious ocular diseases, to facilitate the merging of data among different Registries.

Each variable will require to be answered only in case it is useful according with the patient's clinical picture. This is allowed by a branching mechanism that will drive the opening of the answers only in case it will be necessary to complete a previously provided information. Therefore, only a small number of the 4,952 variables will appear to the investigators.

Patients' Involvement

As for other autoinflammatory diseases, patients and patients' associations play a pivotal role in supporting data collection and the diffusion of the Project. Indeed, patients may stimulate Centers to join the Project, provide their own time for data collection, and supply patient's reported outcomes.

The associations of patients were invited to furnish patients' opinion about how to develop this AIDA Registry since the very beginning of the project. In particular, patients' point of view and impressions were required before creating variables and instruments of the Registry, while concerns, related to

TABLE 2 | Panel of instruments constituting the registry dedicated to subject with VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome; the number of common data elements are also provided along with the phase (i.e., retrospective/prospective) at which they should refer.

Instruments	Fields	Retrospective/prospective phase	No. of mandatory fields
Demographics	10	Retrospective phase	4
Consents	4	Retrospective phase	2
General information about VEXAS onset	10	Retrospective phase	2
VEXAS features up to the enrollment	148	Retrospective phase	3
Concomitant hematological disorders	23	Retrospective/prospective phase	0
Concomitant and associated diseases	19	Retrospective/prospective phase	1
Genetic information	6	Retrospective phase	1
Otherthan*UBA1* gene mutations	8	Retrospective phase	0
Laboratory data	156	Retrospective phase	5
Bone marrow evaluation	6	Retrospective phase	0
Cardiovascular risk	24	Retrospective/prospective phase	2
Past and current treatments	2	Retrospective phase	0
Corticosteroid monotherapy/main therapy–the retrospective phase	256	Retrospective phase	1
Treatment with cDMARD not associated to biotechnological agents–the retrospective phase	647	Retrospective phase	6
Treatment with small molecules not associated to biotechnological agents–the retrospective phase	1,271	Retrospective phase	12
Treatment with biotechnological agents–the retrospective phase	1,245	Retrospective phase	14
Follow-up visits–the prospective phase	1,093	Prospective phase	60
Death of the patient (to open only in case of patient's death)	4	Retrospective/prospective phase	0

the use of sensitive data were solved together. In order to meet patients' expectations, a Registry focused on the different aspects of VEXAS syndrome was developed. In this way, clinical, laboratory, and therapeutic unmet needs will be widely investigated without giving preference to a single field.

The AIPF (*Associazione Italiana Febbri Periodiche*), the ANMAR (*Associazione Nazionale Malati Reumatici*) and the APMARR (*Associazione Nazionale Persone con Malattie Reumatologiche e Rare*) are currently giving their active support. To date, on Italian patients' organizations are included in the project; however, other international patient advocatory groups are about to join AIDA worldwide.

DISCUSSION

VEXAS syndrome is a very recently identified autoinflammatory disorder caused by acquired somatic mutations of *UBA1* gene in blood cells precursors. Despite the genetic origin, the epidemiological burden could be much higher than that characterizing hereditary periodic fevers. In addition to the knowledge gap about the prevalence, all the clinical aspects of the disease should be widely explored, especially in relation to the optimal therapeutic approach to use. As for other autoinflammatory diseases (11), treatment should be based on the specific disease manifestations, the long-term outcome, and complications arising over time. The use of a patient registry can dramatically facilitate these goals, allowing a better knowledge of the disease in a relatively shorter time.

Regardless of the real impact that this disease has in the population, VEXAS is to be considered a rare disease at present. Therefore, as for other autoinflammatory diseases (6–8), we have developed and launched a Registry capable of gathering the few real-life data available worldwide. While waiting for randomized controlled clinical trials, which are likely to take many years for their conduction, a registry dedicated to VEXAS syndrome can lead to the rapid collection of real-life data from a sufficiently large number of patients. This will allow the scientific community to achieve solid results that may be applied on VEXAS patients in daily clinical practice.

Of note, the AIDA Network is intended both to enable a broad population-based data collection and to enhance international collaboration, focusing the research efforts on international projects. In this regard, the first steps will be to reach a full knowledge about VEXAS clinical manifestations and their frequency, pointing out rare and atypical disease expressions. Furthermore, it is essential to describe the *UBA1* mutations really capable of determining VEXAS syndrome, highlighting pathogenic or likely pathogenic variants from benign polymorphisms. Actually, as for other genetic autoinflammatory conditions, low-penetrance variants and genotype-phenotype correlations may be described (12, 13).

It would be useful to search for any pathognomonic element capable to easily direct the diagnosis and genetic examination. In this regard, the presence of vacuoles and their number could be a central diagnostic factor, but their sensitivity and specificity should be confirmed on a wide number of patients (14). Similarly, bone marrow biopsy and aspirate can provide diagnostic or prognostic data that should be clarified.

Another focus of research should be to comprehensively disclose all the possible expressions of long-term hematologic

involvement, revealing any predictive factors and complications. To date, it is well-known that VEXAS patients often present a hematological involvement with myelodysplastic syndrome, monoclonal gammopathy with unknown significance (MGUS), macrocytic anemia, and thrombocytopenia. However, myeloid malignancies are also frequently described in such patients (2, 15). These data must be confirmed and expanded in large cohorts, while a proper long-term follow-up should reveal all the various hematological aspects.

If VEXAS syndrome is only little known as a whole, the lesser-known aspect is the proper therapeutic approach. Many treatments have been tested in VEXAS syndrome, including glucocorticoids, conventional disease-modifying antirheumatic drugs (cDMARDs), azacytidine, biologically targeted agents and janus kinase (JAK) inhibitors. Except for corticosteroids, which are especially useful at high dosage, preliminary data show a significant interindividual variability in the effectiveness of these therapeutic strategies (1, 16). Therefore, identifying the better treatment approach based on the patient's features could allow the optimal treatment in the perspective of a personalized medicine. Similarly, the identification of the best dosages and the assessment of long-term safety profile represent indispensable goals to ensure a correct management.

As for other AIDA registries (6–8), the assessment of the socioeconomic influence of the disease on the national healthcare systems, on patients' social role and job impact represent an intriguing subject of analysis. Other objectives will be identified based on the challenges that clinical practice and scientific research will bring forward in the coming years. The Registry benefits from a remarkable plasticity and it may adapt to changes that will be required according to future acquisitions. In addition, the registry boasts the capability to communicate with other present or future registries dedicated to VEXAS syndrome; this will further enhance research projects through the merging of collected information.

Noteworthy, a new online tool defined as "AIDA for patients" is under development. "AIDA for patients" is an instrument primarily aimed at including patients in the network in terms of diffusion of the project, sharing of research strategies, outreach to physicians in the various centers toward a better and wider enrollment, and involvement of the patients themselves in providing their own data.

Since this disorder has been discovered only in recent times, there are not yet associations specifically dedicated to VEXAS syndrome; for this reason, existing associations of patients with rare rheumatological diseases have been involved.

The AIDA Registry for patients with VEXAS syndrome shows the typical limitations of observational studies. In particular, the completeness and accuracy of information accrued in the Registry accounts for the main issues of the retrospective phase. Furthermore, there is no obligation to consecutively enroll all the patients followed in the AIDA Centers, and this may cause an unintended selection bias. Enrolling patients in the Registry needs much time and attention, especially when the patient's history is remarkably long due to the complex clinical framework and numerous treatments approaches. Therefore, both investigators and patients enrolled have to be sensitized as to provide their time for the study purposes. This is especially true for the retrospective phase, which requires from 1–3 h for a complete data collection. Conversely, the prospective phase does not affect substantially physicians and patients' time, as 10 min are required to fill-in the follow-up page. Beyond these limitations, this Registry represents an unvaluable tool to fully understand the disease in terms of clinical management and treatment. Furthermore, the Registry may be a source for patients' enrolment in future randomized clinical trials.

CONCLUSION

The AIDA international Registry dedicated to patients affected by VEXAS syndrome has been made available for data collection. Joining the AIDA project in reference to the VEXAS Registry will allow the achievement of a comprehensive knowledge about this new disease in a relatively short time. The final goal of this Project will be to conduct observational and prospective studies leading to real-world evidence to be applied in the everyday clinical practice for patients with VEXAS syndrome.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Azienda Ospedaliero-Universitaria Senese, Siena, Italy (Ref. N. 14951). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

AV wrote the first draft of the manuscript, conceived and designed the study, and the registry for VEXAS syndrome. VC, FD, JH-R, MF, SM, AT, ST, and EC actively enrolled patients in the registry for VEXAS syndrome. GR, GL, IA, RP, DY, MC, AMar, TG, FLT, PR, EA, EW-S, ED, PSfi, MGo, GEm, MM, RG, FCi, GC, DA-I, CL, VS, MP, AS, DO-B, RI, EB, FF, PP, AP, GEs, AMai, GS, AI, FS, PSfr, FM, MAle, JM, GH, NA, FLG, AG, AO, SA-M, SE, and SG were the principal investigators of centers actively enrolling in the AIDA registries. IV, MT, AMah, MAlz, AL, FR, FCard, KJ-R, FCr, MD, MGh, CG, JS, ID, CF, HG, AF, AC, MB, and FCaro were included in the authorship as investigators from to the three top contributor centers for any of the other AIDA registries. GT, AR, BF, and MB actively contributed to the launching of the registry dedicated to VEXAS syndrome. AB involved in the technical management of the platform and registries. DR took care of the final revision of the manuscript. LC conceived and designed the study and accounted for AIDA registries coordinator. All authors contributed to the article and approved the submitted version.

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Development and implementation of the AIDA international registry for patients with Schnitzler's syndrome

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Objective: The present paper describes the design, development, and implementation of the AutoInflammatory Disease Alliance (AIDA) International Registry specifically dedicated to patients with Schnitzler's syndrome.

Methods: This is a clinical physician-driven, population- and electronic-based registry implemented for the retrospective and prospective collection of real-life data from patients with Schnitzler's syndrome; the registry is based on the Research Electronic Data Capture (REDCap) tool, which is designed to collect standardized information for clinical research, and has been realized to change over time according to future scientific acquisitions and potentially communicate with other existing or future similar registries.

Results: Since its launch, 113 centers from 23 countries in 4 continents have been involved. Fifty-seven have already obtained the approval from their local Ethics Committees. The platform counts 324 users (114 Principal Investigators, 205 Site Investigators, 2 Lead Investigators, and 3 data managers) at current (April 28th, 2022). The registry collects baseline and follow-up data using 3,924 fields organized into 25 instruments, including patient's demographics, history, clinical manifestations and symptoms, trigger/risk factors, laboratory, instrumental exams, therapies, socioeconomic information, and healthcare access.

Conclusions: This International Registry for patients with Schnitzler's syndrome facilitates standardized data collection, enabling international collaborative projects through data sharing and dissemination of knowledge; in turn, it will shed light into many blind spots characterizing this complex autoinflammatory disorder.

KEYWORDS

autoinflammatory disease, rare disease, international registry, personalized medicine, biotherapies, interleukin-1

Introduction

Despite being individually uncommon, rare diseases affect a significant proportion of the general population if taken collectively: they actually represent a huge burden to society in terms of direct and indirect social, economic and healthcare costs (1). In this context a considerable proportion of inpatient burden, hospital admissions, orphan drug sales and impact on community medicine is connected with the management of rare diseases, especially in the Western countries (2–4). Moreover, clinical trials in the field of rare diseases are difficult to conduct due to the low epidemiologic burden. Therefore, based on conventional recruitment methods, clinical trials are sparse and more likely single arm,

non-randomized and open label studies (5). Taken together, these aspects highlight the substantial difficulties that physicians encounter in everyday clinical practice when dealing with rare diseases. In the context of autoinflammatory diseases, these limitations have generated the urgency to develop an international network capable of gathering together the Centers experienced with these conditions worldwide. In this regard, the AutoInflammatory Disease Alliance (AIDA) network has been developed with the aim to represent an international group of physicians and researchers interested in sharing their experience and information on the clinical, therapeutic and research approach to autoinflammatory diseases. This will facilitate a comprehensive description of disease manifestations, their long-term clinical course, prognostic outcomes and a targeted treatment approach tailored according to the patient's profile in the view of a personalized medicine.

The present paper has been proposed to describe the design, development and deployment of an international disease-specific registry specifically dedicated to Schnitzler's syndrome in the frame of the AIDA network. Schnitzler's syndrome is a very rare condition that has many similarities with the hereditary autoinflammatory diseases (6). Pathogenesis along with disease clinical course and prognosis are still far from being fully defined. Therefore, an international registry oriented to this very rare syndrome constitutes a precious source of data to be translated into valuable and solid evidence capable of significantly widening the current evidence on this disorder.

Materials and methods

Study design

The Registry for Schnitzler's syndrome is classified as a clinical-, physician-driven, population- and electronic-based registry; it was developed along with other autoinflammatory disease-specific registries in the context of AIDA network (7–9).

Participation is open to any Center that deals with Schnitzler's syndrome regardless of location, medical specialty, or type of practice setting. Centers may join the AIDA network and obtain credentials to access the Registry after having officially requested an involvement into the Network to the study promoter. However, obtaining approval from the local Ethics Committee and appointing a Principal Investigator able to coordinate the study locally and at least one Site Investigator responsible for the documentation and data entry should be considered essential pre-requisites. As data collected refer to information routinely collected in the field of the best standard of care, there is neither cost nor financial compensation for the study participation.

Data collection is made up of a retrospective and a prospective phase: the former refers to the information routinely gathered during the past years of active disease up to the inclusion in the registry; the latter includes clinical, therapeutic, and socioeconomic information collected starting from the moment of enrolment. It is advisable to insert the retrospective data with the patient actively participating in the recruitment, in order to obtain as many details as possible, minimizing missing data and any recall bias. Regarding the prospective collection, data have to be updated at least annually or in case of treatment changes, as for additional therapy and/or posology adjustments.

According to its observational nature, the registry includes demographic, genetic, clinical, laboratory, diagnostic and therapeutic data; long-term outcomes and prognostic variables will also be collected if written informed consent will not be withdrawn over time. Neither the clinical management, nor the adherence to the study is influenced by the study participation in any way.

Study objectives

The primary aim of this registry is to bypass the limitations related to the standard research approach and to remedy the poor number of patients available for each Center.

Other objectives consist in the following points: (I) to fully characterize the disease phenotype and its changes during the long-term follow-up; (II) to point out the prognosis of Schnitzler's syndrome in the light of the new therapeutic acquisitions; (III) to identify predictive variables to therapeutic response; (IV) to refine the process of differential diagnosis; (V) to analyze the role of posology adjustments when primary or secondary inefficacy occur; (VI) to study the behavior of Schnitzler's syndrome during pregnancy and post-partum period and possible therapeutic strategies to employ in pregnant or breastfeeding women; (VII) to estimate the socioeconomic impact of Schnitzler's syndrome and the benefits potentially obtained with therapy; (VIII) to comprehensively define hematological complications in the long-term; (IX) to report the cardiovascular complications in patients with Schnitzler's syndrome; (X) to develop recommendations useful for everyday clinical management.

As the enrolling process will expand, it would be possible to design more specific and cutting-edge studies according to future unmet needs.

Ethical/legal aspects

The first national regulatory approval of the AIDA Project was obtained in June 2019 by the Ethics Committee of the Azienda Ospedaliero-Universitaria Senese, Siena, Italy (Ref. No. 14951). Later, national, and international expert centers for the diagnosis, clinical management and treatment of autoinflammatory diseases have approved the project before joining the AIDA network.

Patients' data are kept in accordance with the EU General Data Protection Regulations (GDPR) about the protection and processing of personal data (2016/679/EU) (10).

This project was registered at ClinicalTrials.gov (ID: NCT05200715) and follows the principles of the Declaration of Helsinki.

After having received age-appropriate information sheets, patients (or their parents/legal guardian) have to give their voluntary informed consent; minors aged ≥12 years are also required to provide their assent to be included in the study.

Patients have to properly receive information about aims of the study, terms of data collection and management, rules for data access, and possible withdrawal of the consent to continue data collection. In addition, both patients and Principal Investigators may withdraw their consent for the use of data for statistical analyses at any time. In this case, all gathered data will be deleted soon after the patient and/or Principal Investigator communication to the study promoter.

Patients will not receive any honoraria or other payments for the participation in this project. Also, no relationships to billing of the healthcare system or insurance companies have to be disclosed.

Patients' eligibility

Inclusion criteria for the recruitment into this AIDA Registry consist in the fulfillment of Strasbourg diagnostic criteria for Schnitzler's syndrome (11). The lack of a written informed consent by the patient or her/his parents or legal guardian accounts for the only exclusion criterium considered in this project.

Data collection

Data are collected through the Research Electronic Data Capture (REDCap), a metadata-driven software application and novel metadata-gathering workflow developed at Vanderbilt University Medical Center, routinely used to support translational research projects in the academic research environment (12).

Each Principal and Site Investigator included into the AIDA Project is provided with his/her own password and login identification to access the registry through the REDCap web-interface, insert data on the Instruments of the registry and then review or complete the already inserted information. None of the participating Principal and Site Investigators are allowed to check information uploaded from other Centers.

While the public website (https://aidanetwork.org/en/) may be accessible by anyone who wants to learn more about AIDA network, its objectives and how to participate to the project, the registry website (https://sitbio.med.unisi.it/redcap/redcap_v12.2.7/index.php?pid=28) is hosted on a separate password-protected platform.

Data are stored on a server placed in the University of Siena, Siena, Italy. Ownership of results generated from the analysis of aggregated data will belong to the Promoter.

Statistical analysis

Data collected will be converted into an appropriate format for statistical analysis. To this end, a good and reliable statistical plan is warranted according with the specific objectives that will be pursued. The statistical plan will include general principles related to descriptive statistics as well as inferential statistics.

Statistical analysis will take into consideration missing data before performing computations. Given the real-life context of data collection, a threshold level of missing data is set to 25%.

Results

Current numbers and registry development

Since its launch on November 27th, 2020, the AIDA project has quickly reached a wide geographic coverage: 113 centers have already joined the project around the world (by April 28th, 2022).

To date, 3,924 common data elements (fields) organized into 25 instruments (forms) compose the registry. The full list of instruments and their fields are listed in Table 1. The fields for data collection are organized in such a way as to appear only if patient's clinical history make necessary to answer, according to a branching structure. Therefore, only a part of the 3,924 fields will initially appear to the investigators, and the number of questions to answer in the registry will depend exclusively on patient's clinical complexity. Table 2 provides the full list of the objectives of the registry for the future agenda. Figure 1 shows AIDA network distributions around the world.

Data elements correspond to patient's demographics, medical history, laboratory features, symptoms at onset, symptoms developed over time, comorbidities, cardiovascular risk, work-up exams, pregnancies, long-term clinical outcomes, past and current treatments. On the other hand, longitudinal data are captured through a specific "follow-up" instrument, including disease activity, disease manifestations occurred in the last follow-up period, laboratory exams worn by the patient at the last assessment, any treatment adjustments, clinimetric scores, any hematologic complications, socio-economic details about access to the healthcare system, absenteeism and working capacity.

TABLE 1 List of instruments (to be regarded as "forms") included in the registry dedicated to patients with Schnitzler's syndrome, with the corresponding number of common data elements, time-points at which they should refer to and number of mandatory fields.

Instruments	Fields	Retrospective/prospective phase	No. of mandatory fields
Demographics	9	Retrospective phase	3
Consents	4	Retrospective/prospective phase	1
Diagnostic data and family history	20	Retrospective phase	2
Features of attacks at the time of disease onset	26	Retrospective phase	0
Features of attacks up to the time of diagnosis	44	Retrospective phase	0
Features of attacks from the diagnosis to the enrolment into the registry	44	Retrospective phase	0
Clinical diagnostic scores and criteria	14	Retrospective/prospective phase	0
Laboratory data	17	Retrospective phase	1
Cardiovascular risk	23	Retrospective phase	2
Past and current treatments	1	Retrospective phase	0
NSAIDs monotherapy—the retrospective phase	74	Retrospective phase	1
Corticosteroid monotherapy/main therapy—the retrospective phase	131	Retrospective phase	1
Antihystamines—the retrospective phase	12	Retrospective phase	0
Colchicine treatment—the retrospective phase	89	Retrospective phase	1
Treatment with cDMARDs (not associated to biotechnological agents)—the retrospective phase	387	Retrospective phase	6
Treatment with small molecules not associated to biologic agents—the retrospective phase	756	Retrospective phase	12
Treatment with biologic agents—the retrospective phase	1,022	Retrospective phase	14
Fertility and pregnancy	14	Retrospective/prospective phase	1
Disease course and treatment during pregnancies	66	Retrospective/prospective phase	1
Follow-up visits—the prospective phase	647	Prospective phase	55

TABLE 2 Objectives of the registry dedicated to Schnitzler's syndrome in the platform of AIDA network.

Main objective	To bypass the limitations related to the standard research and to remedy the poor number of patients available for studies
Other objectives	To fully characterize the disease phenotype and its changes during follow-up
	To point out the prognosis of the syndrome
	To identify predictive variables for the therapeutic response
	To refine the process of differential diagnosis
	To analyze the role of posology adjustments in the case of drug inefficacy
	To study the disease course during pregnancy/post-partum period and eventual therapeutic strategies useful in pregnant or breastfeeding women
	To estimate the socioeconomic impact of the syndrome and the benefits obtained with therapy
	To define long-term hematological complications
	To report the cardiovascular complications
	To develop recommendations useful for routine clinical management

Patients' involvement as key stakeholders

In recent years patients have become increasingly aware of their role, which is central in stimulating the research efforts and quality of clinical management. Patient advocacy groups may help by disseminating information, supporting the recruitment of patients, and taking part in regulatory processes. At current, many different associations have already taken part into the AIDA project, as for the Italian Association of Periodic Fevers (A.I.F.P., *Associazione Italiana Febbri Periodiche*), the National Association for Rheumatologic and Rare Diseases (A.P.M.A.R.R., *Associazione Nazionale Persone con Malattie Reumatologiche e Rare*), and the National Rheumatic Diseases Association (A.N.M.A.R., *Associazione Nazionale Malati Reumatici*). The involvement of patients' associations in other countries is actively ongoing

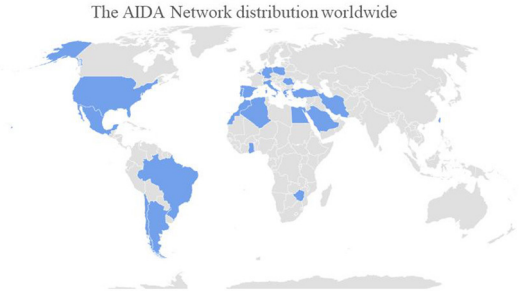

FIGURE 1
Countries involved in the AIDA Network (updated on April 28th, 2022).

to include a higher number of proactive components in the AIDA project.

Discussion

Thanks to the new technologies and online tools for the worldwide sharing of information, recent years have witnessed a rapid proliferation of rare diseases registries, which have completely changed the approach to research and participation in international projects. Indeed, according to Orphanet, a European website aimed at providing information about orphan drugs and rare diseases, there are more than 793 current European registries dedicated to rare diseases (13). Their goals are heterogeneous and range from clinical management to epidemiology and research projects; each of them is supported by a wide variety of information systems, data collection and management tools. In this context, the AIDA network has been developed with the aim of overcoming the current issues in the field of rare autoinflammatory diseases, including the fragmentation of knowledge and research affecting Schnitzler's syndrome. This condition is considered as the paradigm of late-onset acquired autoinflammatory syndromes (6). Despite this, the diagnostic delay often accompanied with several misdiagnosis especially during the initial phases, is already remarkable (roughly 5 years), complicating the disease course with significant morbidity due to the lack of a proper treatment. The advent of IL-1 blocking agents on the other hand has dramatically changed the management of Schnitzler's syndrome (14), which are now considered as a first-line therapy. This leads to a considerable health burden with a notable decrease in the quality of life and an even greater impact on the healthcare system. The low incidence and prevalence of Schnitzler's syndrome not only results in a reduced awareness of this condition—and thus the ability to include it in differential diagnosis—but makes it a clinical and therapeutic conundrum. Therefore, an increased awareness is needed among physicians to improve patients' quality of life and enhance the overall prognosis of this disease, which is still largely dependent on the onset of hematological complications (15).

The development and activation of this international registry represents an invaluable opportunity to widen the knowledge about this unusual disease through the accrual of real-life data, obtaining solid scientific information and final real-world evidence to apply in the everyday medical practice. Its pioneer mission is to create an international network of researchers capable of joining forces for the common purpose to solve the unmet needs that will gradually arise for both patients and physicians.

In this regard, the AIDA network has joined together the different specialties involved in the management of Schnitzler's syndrome, including rheumatologists, dermatologists, immunologists, hematologists, internal medical physicians, and radiologists. These figures may now communicate with each other globally, resulting in the final goal to create an effective strategic approach toward challenges associated with this rare disease.

Among other things, this Registry will clarify the geographical distribution of the disease and any change in clinical expression according to the environmental contexts. Also, interesting areas of research would be to fully describe the range of disease manifestations and their change over time; to improve the diagnostic process in the field of systemic inflammatory diseases; to assess the prognosis in the light of the new treatment strategies; to understand which patients are more responsive to a specific therapy; to disclose the proper therapeutic approach when a first biologic line fails; to evaluate how therapy may improve the impact of the disease from a socioeconomic perspective.

The flexibility of the registry allows a rapid implementation of the tool in case of protocol variations. In this regard, the registry has the ability to change with the aim of also meeting future challenges arising from either new scientific acquisition or everyday clinical practice. In addition, the registry has the ability to communicate with any other present or future registry focused on the same disease.

The AIDA Registry for Schnitzler's syndrome shows the typical shortcomings of observational studies. In particular, entering data requires time and attention, especially when the patient's medical history is long or complex in terms of treatment attempts and number of disease complications; in this case, a high frequency of missing data could affect the research potentialities. Furthermore, investigators are not required to consecutively enroll patients followed in their Centers. This could lead to selection biases. Despite these limitations, this registry has the potential to definitively overcome the issues typically associated with the low epidemiological burden and poor number of patients to enroll in clinical trials. The real-life context of data collected in this registry will lead to the achievement of real-life evidence directly applicable in the care of patients with Schnitzler's syndrome. In conclusion,

the development of the AIDA International Registry for patients with Schnitzler's syndrome will allow the collection of standardized information, enabling international multicentre collaborative research through data sharing and implementation and optimisation of scientific efforts worldwide.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of the Azienda Ospedaliero-Universitaria Senese, Siena, Italy (Ref. No. 14951). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

JS wrote the first draft of the manuscript. AV conceived and designed the study and revised the draft of the manuscript. EW-S, MF, GL, GE, MG, AP, AM, AG, SM, DO-B, RP, KJ-R, CG, FCr, FI, IMa, FR, IMo, KR, VC, and PA were involved in data recruitment in the Registry dedicated to patients with Schnitzler's syndrome. AT, SG, GR, IA, AA-FK, MC, FT, MT, HG, MS, MB, FCa, EC, PRus, PRub, MD, BF, AG, FDC, MM, and CF were included in the authorship as investigators from to the top three contributor centers for any of the other AIDA Registries. AR, DB, and KK were included as leading AIDA experts in the field of Schnitzler's syndrome. AB is the bioengineer involved in the technical management of the platform and registries. DR took care of the final revision of the manuscript. LC conceived and designed the study and accounted for AIDA Registries Co-ordinator. Authorship has been established based on the number of data recruited in the AIDA Registries on April 20th, 2022. All authors contributed to the article and approved the submitted version. '

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Behçet uveitis: Current practice and future perspectives

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Described as early as Hippocrates in his "Third Book of Endemic Diseases," Behçet's Disease (BD), also known as "The Silk Road Disease" following its initial demographics, consists of a triad of recurrent oro-genital ulcers and associated uveitis. Current demographics and rising percentages of patients seen far beyond the Silk Road in Ocular Inflammatory Disease and Uveitis Clinics list BD uveitis as one of the frontliners of non-infectious autoinflammatory eye diseases. Clinical features of BD and juvenile-onset BD are detailed alongside various approaches in classification and suggested algorithms for diagnosis that are outlined in this review. With the ongoing Human Microbiome Project and studies such as the MAMBA study, the role of the human microbiome in BD is highlighted in the pathophysiology of BD to include the current research and literature perspective. Furthermore, with the advancement of recent diagnostic and investigative techniques, especially in the field of Optical Coherence Tomography (OCT), disease-related characteristics are updated to encompass SD, EDI and OCT-angiography characteristics of BD. Having entered the era of biologic therapy, the role of various specific cytokine-blocking biologic drugs, such as TNF-α inhibitors (e.g., adalimumab, infliximab), interferon α-2a inhibitors, IL-6 and IL-1 inhibitors are presented and contrasted alongside the conventional immunosuppressant drugs and the classic old gold standard: corticosteroids (systemic or local). Finally, with the ongoing SARS-CoV-2 pandemic, it was not possible to conclude the review without reviewing the latest evidence-based literature reporting BD morbidity in this era, the observed pattern and treatment recommendations as well as those related to reported post-vaccine complications and emergence of BD.

KEYWORDS

Behçet's disease, uveitis, diagnostic criteria, ocular investigation, immunosuppression, biologics, COVID-19

Introduction

Historically, "The Silk Road Disease", now better known as Behçet's Disease, has been described as early as Hippocrates in his "Third Book of Endemic Diseases" (1–3). However, the clinical trial of recurrent oro-genital ulcers and associated ocular uveitis

remained obscure until the dermatologist Hulusi Behçet defined it as a syndrome, having seen it in three native patients of Middle Eastern origin in 1937 (3). Today, Behçet Disease has extended beyond its localities along the "Ancient Silk Road" to encompass a more global reach and is expanding further north and south (3, 4).

Today, the development of international registries dedicated to specific or rare autoimmune disease entities provides a powerful, structured multidisciplinary tool for data collection, disease identification, epidemiological studies on more current, evidence-based and multi-centric basis. One of these registries is the AIDA International Registry for BD patients, which is considered a successful model and is currently being developed and implemented for other diseases (5).

BD is a multi-system disease. The most frequent clinical features manifest at a mucocutaneous and ocular level. However, cardiovascular, articular, gastrointestinal as well as neurological manifestations frequently accompany or even precede the disease, making diagnosis more difficult (4, 6–12). Given that BD remains a clinically diagnosed entity and its heterogeneous nature of presentation, criteria for BD were developed and continue to be refined and re-evaluated to allow for the ethnic variabilities encountered across various demographic ethnicities (9, 13, 14).

In a recent epidemiologic study by Abdelwareth et al., data for 313 uveitis patients managed at the Uveitis Subspecialty Clinic of Kasr Al Aini, Cairo University Hospital (the largest tertiary referral center in Egypt) between May 2015 and May 2017 was statistically examined. Out of the 313 patients, 75.4% were diagnosed having a specific etiology, with Behçet uveitis at the lead, constituting 29.1% of the clinic's patient profile for that time period (6). Hassan et al. further analyzed the cohort of non-infectious uveitis patients in multiple Egyptian tertiary health care centers (Cairo, Tanta and Benha University Hospitals), identifying BD as the leading diagnostic entity (51.2%) (7).

In this review article, the authors introduce and highlight the latest updates over the past decade, regarding diagnosis and management of Behçet disease and its associated uveitis. However, they will remark on the juvenile-onset BD (Jo-BD), which presents a real challenge due to the difficulty in diagnosis and management of this less common subgroup.

Pathogenesis

HLA-B51 has been confirmed as the principal genetic predisposing factor by Genome-wide Association studies (GWAS). A positive test increases the risk of developing BD by 5.79-fold (10, 11). This genetic predisposition, together with associations discovered by the GWAS to other non-HLA genes (10), in addition to evidence of altered microbiome especially gut in Behçet patients and infectious agents such as Streptococcus sanguinis (isolated from the oral mucosa of patients with Behçet's disease), enter into an interplay, that triggers a sustained immune response. This disrupts a previously intact T-cell homeostatic environment and results in a state of chronic inflammation in these individuals (10, 12–14). The new understanding of these immuno-pathogenic processes have expanded the standard treatment protocols, which now include the more recent biologic therapy, especially TNF-alpha antagonists, which are administered for control of the ongoing and repeated disrupted immune response (12).

The IL-23/IL-17 axis plays an important role in immune mediated pathologies, including uveitis Increased levels of IL-23 trigger the maturation of pathogenic Th17 cells (rather than the homeostatic subtype). These Th17 cells in turn promote the production of proinflammatory cytokines via the JAK/STAT signaling cascade. Furthermore, IL-23 continues to upregulate its receptor expression, thus stabilizing a proinflammatory response environment, aggravating the inflammatory response (15, 16).

The microbiome is defined as the genetic material of all microorganisms (bacteria, fungi, protozoa and/or viruses) living both on the surface and inside the human body. The majority inhabit the large intestine and help regulate important body functions as food digestion, blood coagulation and vitamin production. Consequently, this microbiome is mappable. such as by the Human Microbiome Project (HMP) sponsored by the National Human Genome Research Institute (NHGRI) and part of the National Institutes of Health (NIH) in the United States (17).

The suggested hypothesis is that an alteration or disturbance of a susceptible individual's microbiome by other pathogenic microorganisms can trigger a cascade process altering his/her genetic material which may ultimately translate into the expression of various autoimmune or autoinflammatory diseases, e.g., multiple sclerosis, diabetes, and currently Behçet's disease.

Currently, the MAMBA Study is an ongoing randomized, cross-over, open trial assessing the effect of regional variations and nutritional modification on a patient's gut microbiome and its possible outcome on BD (8).

The underlying pathology of BD is that of a relapsing-remitting vasculitis of vessels of all sizes, affecting multiple organ systems and manifesting in a gamut of heterogeneous clinical signs (8, 9). While defined as a non-infectious auto-inflammatory disease, theories of an underlying infectious agent date back to Hulusi Behçet, in a trial to explain the recurrent pattern and nature of the oral ulcerations. However, all failed to isolate a viral pathogen. Currently, isolating streptococcal strains from the extraocular lesions in BD patients, still suggests a possible association to an infectious triggering agent. However, the theory remains controversial.

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TABLE 1 International criteria for Behçet's disease—point score system: scoring > 4 indicates Behçet's diagnosis (14).

Sign/Symptom	*Points*
Ocular lesions	2
Genital aphthosis	2
Oral aphthosis	2
Skin lesions	1
Neurological symptoms	1
Vascular manifestations	1
+ve Pathergy test	*1*

* Pathergy test is optional and the primary scoring system does not include pathergy testing. However, where pathergy testing is conducted one extra point may be assigned for a positive result.

TABLE 2 A comparison between the Japanese, ISG, and ICBD criteria for diagnosis of BD.

	ICBD Scoring System	*ISG Scoring System*	*Japanese Scoring System*
Oral ulcer	2 points	Mandatory	Major criterion
Genital ulcer	2 points	Minor criterion	Major criterion
Skin region	1 point	Minor criterion	Major criterion
Uveitis	2 points	Minor criterion	Major criterion
Pathergy test	1 point	Minor criterion	Not included
Arthritis	Not included	Not included	Minor criterion
Epididymitis	Not included	Not included	Minor criterion
GIT	Not included	Not included	Minor criterion
Neurological	1 point	Not included	Minor criterion
Vascular	1 point	Not included	Minor criterion

The Japanese criteria require 3 major criteria, or uveitis and 1 major or 2 minor criteria. ISG requires 3 out of 5 components and the ICBD diagnoses BD at ≥ 4 points (24). Adapted from Kirino and Nakajima (24).
Colours highlight corresponding impact of criteria in the different scoring systems (major is similar to a score of 2 or mandatory for example).

Updated diagnostic criteria

Since its description in 1937, 18 sets of diagnostic or classification criteria have been developed for BD (18). The most famous of which was published in 1990 by the International Study Group "ISG" in a collaboration of 7 countries to bring a consensus on one set of criteria (12).

Despite its high specificity, subsequent application and evaluation of the "ISG" criteria in individual countries repeatedly lacked diagnostic sensitivity relative to other criteria that had been proposed and were not included in the classification (18, 19). It also did not allow for variations in the symptoms of BD, incomplete expression, and failed to discriminate BD from the separate entity of inflammatory bowel diseases (18, 20). Thus, the International Team for the Revision of the International Criteria for BD (ITR-ICBD) was formed under the auspices of the Epidemiology Research Group of the International Society for Behçet's Disease (Table 1). The aim of this team was to re-assess the sensitivity and specificity of existing criteria sets, including ISG, on a large cohort of patients from 27 countries, in order to create a new evidence-based scheme with good discriminatory properties regardless of patient ethnicity (14). It is noteworthy that the ICBD performed better in an Egyptian cohort of cases when compared with that of the ISG (21).

Despite the availability of multiple criteria sets for diagnosing the presence or absence of the disease, none currently determine the "probability" of Behçet diagnosis when put in a list of differentials (22).

Another classification is worth noting, the Japanese criteria set, which was defined by the Japanese Ministry of Health in 1987 (23, 24). Despite predating the aforementioned classifications, it clearly shows the role demographic and environmental criteria play on the phenotypic expression of BD (Table 2). Over the past 30 years, some studies suggest that a new phenotype of BD has evolved in Japan and Korea, where the majority of patients are presenting with incomplete Behçet's and milder phenotypes. This was in comparison to the 80s, where BD was identified as the leading cause of non-infectious uveitis in Japanese patients, a statistic that has shifted recently in favor of sarcoidosis as the principal cause (24–27).

The Japanese criteria is of significance, as they take into account the higher incidence of gastrointestinal Behçet's (12%) vs. the markedly lower Mediterranean as well as Western incidence of (1–7%). On the other hand, pathergy is rarely positive in Japanese patients and hence omitted entirely from this classification set (24). A patient diagnosed with intestinal, neurological or vascular BD is classified as a special-BD subtype, and noticeably, these patients advance faster in their disease.

Ocular Behçet's clinical presentations

Just as the main disease, ocular Behçet may present with various pictures and degrees of severity in 50 to 70% of patients. It may initially begin unilaterally. However, it is usually a bilateral disease and the second eye soon follows. The usual age of onset is around 30 years of age and is often more severe in the male patients. Behçet's uveitis is recurrent, non-granulomatous, and extends from the anterior to the posterior pole. It is a progressive sight-threatening disease that may involve parts or the entire uveal tract and may blind up to 25% of patients within a course of 10 years, after which disease progression tends to stabilize (28, 29). Thus, good disease control is essential within this window to save the eye either from the direct ocular manifestations of Behçet's uveitis or its potentially and equally blinding complications (30–32).

Tugal-Tutkun et al. reported anterior uveitis in 11% of cases, posterior uveitis in 28.8%, while panuveitis involvement

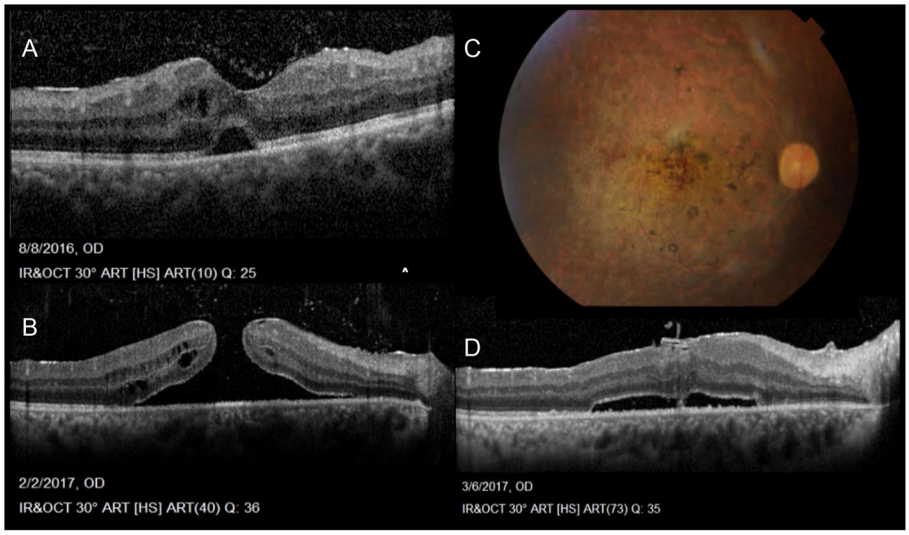

FIGURE 1
Sequelae of Behçet Uveitis: **(A)** Cystoid macular edema, epiretinal membrane, neurosensory detachment and vitreous opacities denoting vitritis **(B)** Progression of the cystoid changes in to a full thickness, macular hole **(C)** Color photos Post vitrectomy sealing of the hole, also showing severely attenuated vessels, pale discs and laser marks **(D)** OCT post PPV showing residual NSD following vitrectomy with peeling of ILM and sealing of the hole (Series courtesy of Dr. Soliman MM, MD).

was seen in 60.2% of their entire cohort of 880 patients (1,567 eyes). Intermediate uveitis in the form of isolated vitritis without anterior or posterior involvement (clinically and angiographically) was also reported more often in early rather than late onset BD (31–33). However, the latest SUN classification criteria published in 2021 does not include isolated vitritis in its diagnostic criteria, rather in association with anterior, posterior or panuveitis (34). On the other hand, vitritis accompanying posterior segment involvement is common and may be so dense, obscuring the fundus view. Retinal vasculitis, predominantly periphlebitis, but also combined with arteritis are a main feature and are often accompanied by vaso-occlusive retinopathy with retinal and vitreous hemorrhages, retinal ischemia, neovascularization and secondary neovascular glaucoma (Figure 2) (35). Papillitis is also seen as part of the vasculitis typical of BD, while neovascularization at the disc is rare and may be secondary to chronic, uncontrolled inflammation but not ischemia (35, 36). All through, macular edema is a leading complication, often a blinding sequelae of posterior uveitis (37). Macular holes have also been reported with BU and associated changes involving the vitreo-macular interface (Figure 1) (35, 38, 39).

Isolated anterior uveitis is rare. Fine dusting of the endothelium accompanies iritis and the typical shifting hypopyon may form. The hypopyon invariably points to involvement of the posterior segment. Throughout an attack, the eye may appear white or show strong ciliary injection (28, 31, 37). Finally, Behçet patients may also present with complications of the disease due to its chronic relapsing

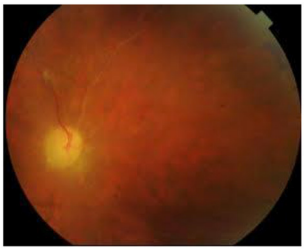

FIGURE 2
Colored fundus photo of Behçet uveitis showing a pale disc and ghost vessels following the occlusive vasculitis (Image courtesy of Dr. Soliman MM, MD).

remittent nature, such as cataract, synechiae and glaucoma as well as the above mentioned posterior segment complications. Untreated, the eye will show the end-stage appearance of an ischemic, thinned out retina, with sheathed ghost vessels and optic atrophy (35, 40) (Figure 2).

In 2020, Tugal-Tutkun et al. published an algorithm for the diagnosis of BD uveitis based on characteristic ocular findings. Their study consisted of 4 steps: (i) survey of expert opinion on characteristic features of ocular involvement in BD; (ii) retrospective clinical data collection and analysis; (iii) prospective clinical data collection; (iv) development of a diagnostic algorithm (41). The variables identified to provide the highest accuracy for the diagnosis of BD uveitis, which constitutes an estimated 15% of cases, included the presence of

superficial retinal infiltrates or related sequelae, RNFL defects, angiographic signs of occlusive retinal vasculitis and diffuse retinal capillary leakage in the absence of granulomatous anterior uveitis or choroiditis in patients with vitritis. The authors postulated that a combination of these ocular findings, rather than individual BU-associated lesions would be more readily recognizable. Accordingly, the presence of all the aforementioned signs (criteria) in a patient would then suggest the highest (92%) probability of a BU diagnosis (42). This algorithm however requires further validation in larger, multicentric studies and larger clinical cohorts.

Pediatric Behçet's disease

Pediatric Behçet is a rare and difficult condition to diagnose. It includes children up to the age of 16 years and its pattern differs from adults in appearance and predominance of principal diagnostic signs (43, 44). Terminology further differentiates between pediatric BD, which fully manifests before the age of 16 years and juvenile-onset BD (JO-BD), which presents with a childhood onset of the disease but does not fulfill the criteria (18). The percentage of JO-BD is reportedly between 4 and 26% of Behçet patients. Not only the paucity, but also the latency of complete disease manifestation and the heterogeneous presentations pose a diagnostic, as well as treatment challenge in the younger age groups (4, 18, 44, 45).

Attempts at improving classification and diagnostic criteria for Behçet's disease are not limited to adults and continue to attempt to bypass regional variabilities of clinical expression, such as the skin pathergy test, which is not applicable to all demographics (14). From 18 classification sets of BD, mainly 2 are in use for adult BD, the ISG and the ICBD classification, while only one, the Pediatric Behçet Disease (PEDBD) consensus, which was published in 2015 addresses pediatric BD separately (Table 3) (18, 46).

Koné-Paut et al., suggested a revised consensus based on a large cohort study of 219 patients from 42 centers located in 12 different countries. The ethnic subgroups were about one third European-Caucasian, one third North African and one third Middle Eastern-Caucasian (46). Their findings were tested regarding confirmed (156 patients) and unconfirmed (63 patients) against the ISG Criteria for BD as well as the ICBD classifications. On the other hand 410 patients with 3 different disease entities distinct from BD were provided from the Eurofever Database as negative controls to test for the validity of the identified diagnostic criteria (12, 14, 46).

Similar to adults, the most common presenting sign and often the first at a mean age of 8 to 9 years is recurrent, widespread multiple or single oral ulcers (44, 47, 48), with Sota et al. deriving similar data from the AIDA Registry network (49). Genital ulcers are comparatively less frequent than in adults, however they are the second most common presenting sign in children and are seen predominantly in females. Unlike their oral counterparts, they are characterized by a tendency to scar. Chronologically, with a longer latent period between the first and second presenting sign compared to adults, oro-genital ulceration is often followed, at a mean age of 10 to 13 years, by skin lesions, neurological symptoms and musculoskeletal manifestations) (18, 45, 46).

TABLE 3 Consensus classification of pediatric Behçet's disease (46).

Item	*Description*	*Value/item*
Recurrent oral aphthosis	≥3 attacks per year	1
Genital ulceration/aphthosis	Typically with scar	1
Skin involvement	Necrotic folliculitis, acneiform lesions, erythema nodosum	1
Ocular involvement	Anterior uveitis, posterior uveitis, retinal vasculitis	1
Neurological signs	With exception of isolated headaches	1
Vascular signs	Venous thrombosis, arterial thrombosis, arterial aneurysm	1

Three of six items are required to classify a patient as having pediatric Behçet's Disease.

Regarding the frequency of ocular involvement, Atmaca et al. and Krause et al., reported a similar ocular involvement rate between adults and children (50, 51). Koné-Paut et al., on the other hand suggested a lower prevalence of ocular involvement in childhood BD. However, the presence of ocular signs, such as anterior and/or posterior uveitis or retinitis have a higher morbidity and carry a worse prognosis compared to adults (46). Uveitis was reportedly more common in boys often running a severe course (47, 52), and according to Koné-Paut et al., bilateral involvement was mostly noted in the European-Caucasian cohort of their series (4, 45, 46).

Ocular investigations in Behçet's disease

The complexity in the diagnosis of BD lies in the fact that there is no specific diagnostic test. Alone, a positive pathergy test or positive typing for HLA-B51 are not diagnostic. Rather, the diagnosis is based on the cumulation of multiple clinical signs that fall within the aforementioned diagnostic criteria (29).

Cases of BU, especially those with posterior segment involvement, often require ocular imaging. Currently, multimodal imaging is heavily relied upon, not only in the diagnosis of this condition, but also in assessment of disease activity, outlining as well and monitoring response to treatment (53).

Color photography

Although not new, fundus photography is a simple, economic but often overlooked tool. It can document the grade of vitreous haze for disease monitoring and can document the transient nature of retinal infiltrates, which is particular to BU (40, 54, 55).

Indocyanine green angiography (ICGA)

Although BD is a systemic vasculitis, vasculitis and inflammatory lesions are mainly documented at the level of the retina (sparing the choroidal vessels). Thus, ICGA may be used to differentiate Behçet's disease from other entities primarily affecting the choroid, while lacking any specific or pathognomonic diagnostic signs for BD itself (56, 57).

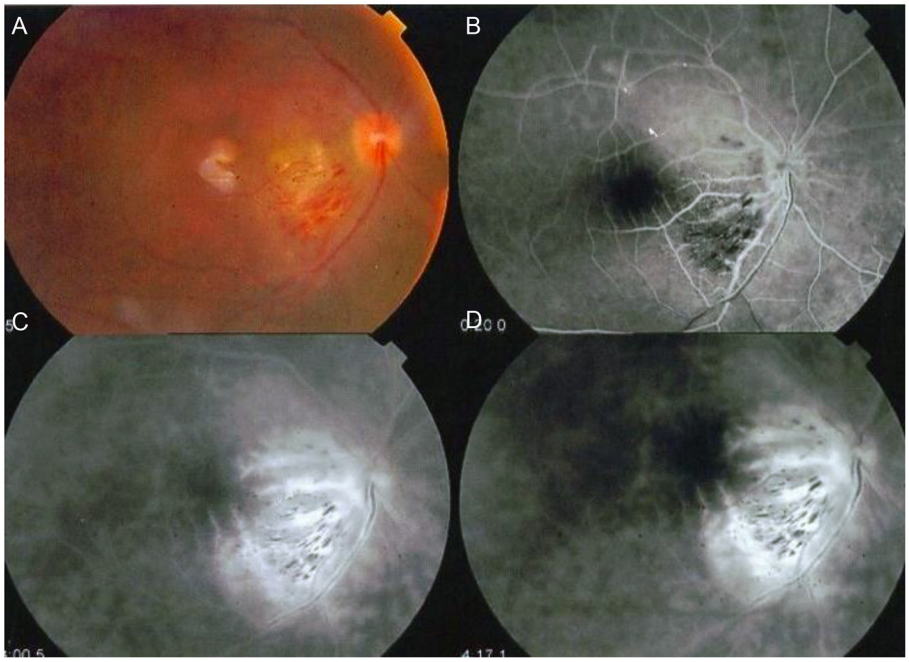

FIGURE 3
FFA of a patient with Behçet s vasculitis. **(A)** Color photo showing macular branch retinal vein occlusion and disc edema. **(B–D)** FFA images showing the macular vein occlusion and widespread vasculitis with characteristic "fern-like configuration" (Images courtesy of Dr. Soliman MM, MD).

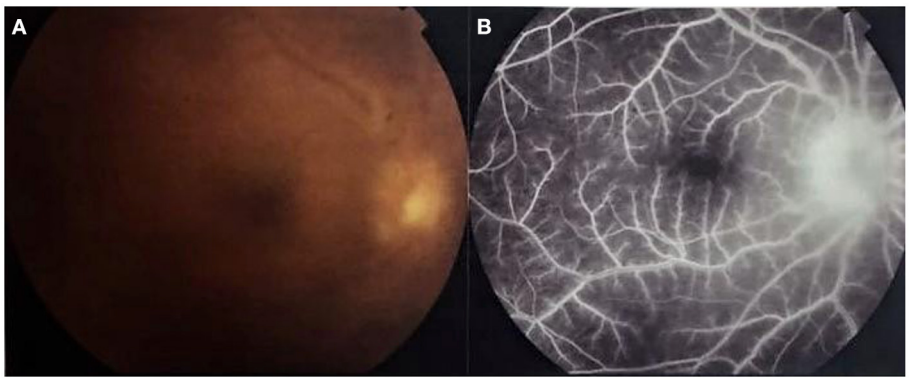

FIGURE 4
Color photo and fundus fluorescein angiography (FFA) of a patient with active Behçet uveitis. **(A)** Color photo showing disc edema, sheathed vessels, blunt macular reflex. **(B)** FFA showing active vasculitis (fern-like configuration typically extending beyond one quadrant) and disc leakage (Images courtesy of Dr. Wassef A, MSc.).

Fundus fluorescein angiography (FFA)

Even though there have been rapid advances in ocular imaging techniques, FFA remains the gold standard investigation for diagnosis and follow-up of the characteristic occlusive vasculitis or active (leaking) vasculitis seen in Behçet's posterior uveitis (55) (Figure 3).

Ozdal et al. reported that the most common FFA findings of posterior segment involvement of ocular BD were vasculitis in 38% of eyes, optic disc edema in 14.8% and macular edema in 11.3% (40). The most characteristic FFA finding in BU is a "fern-like capillary leakage" that indicates activity. Although similar vasculitis may be observed in other uveitic entities, in BD, the leakage often involves more than three quadrants of the fundus (55) (Figure 4).

In a study on 23 eyes with inactive ocular BD, FFA imaging detected uveitic activity in 52.1% of the studied eyes. This was observed in the form of vasculitis (30%), macular edema (17.3%), macular ischemia (8.6%) and peripheral occlusive vasculitis (4.3%) (58). This finding suggests that inflammation remains radiologically active despite clinical uveitic quiescence and may indicate that the current treatment is inadequate (55).

The introduction of the more recent ultra-wide fluorescein angiography (UWFA) has allowed the visualization of vasculitis anterior to the equator in BD, which can cause peripheral leakage, ischemia, and neovascularization, that are otherwise difficult to detect clinically. In a 2014 study, UWFA imaging of 33 eyes unmasked peripheral vasculitis in 28 eyes (84.8%) and peripheral retinal non-perfusion in 22 eyes (66.7%), which were not clinically evident. Subsequently, immune-modulatory treatment was modified based on the UWFA findings in 13 of 20 patients (65%) (59).

Optical coherence tomography

Spectral domain OCT

In eyes with suitable optical media, optical coherence tomography (OCT) provides a rapid and non-invasive means of investigating macular complications, the most frequent being

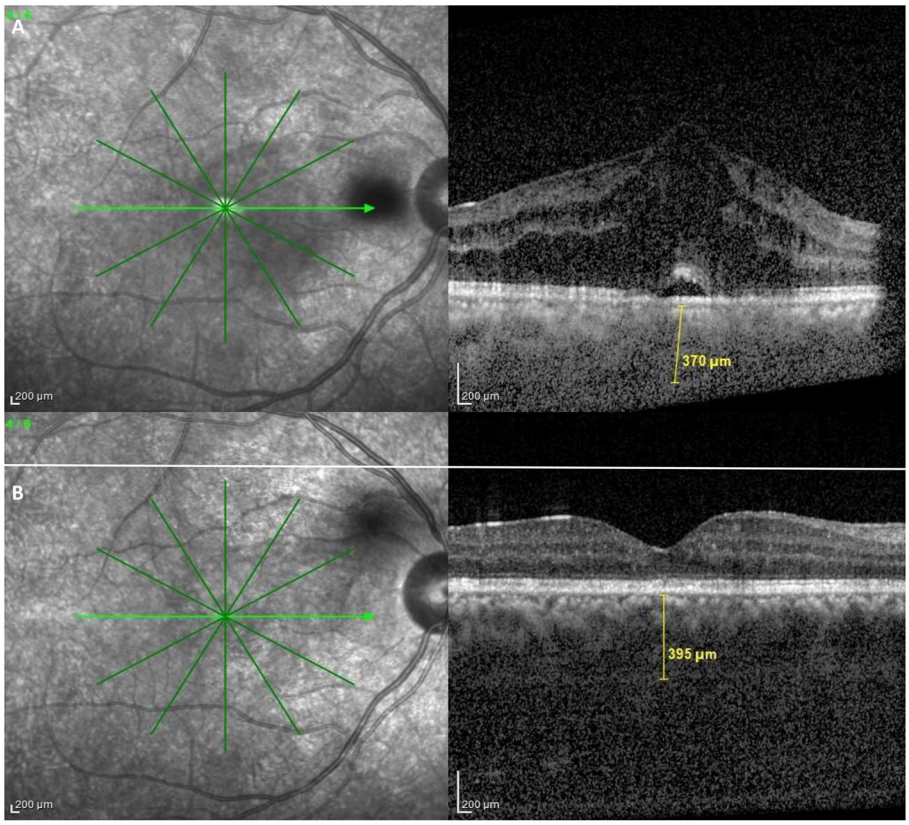

FIGURE 5
OCT findings in Behçet Uveitis. **(A)** OCT of an active BU patient showing center involving cystoid macular edema, neurosensory detachment, epiretinal membrane and increased subfoveal choroidal thickness. **(B)** OCT of an inactive BU patient showing diffuse parafoveal edema, epiretinal membrane and also above average subfoveal choroidal thickness (Images courtesy of Dr. Wassef A, MSc.).

cystoid macular edema, which should be closely monitored by OCT (53).

Other studies have demonstrated that decreased foveal thickness and disruption of the photoreceptor inner and outer segment junction detected by OCT are associated with poor visual function, indicating irreversible damage to the macula (60).

The appearance of retinal infiltrates denotes an activation of intraocular inflammation in the posterior segment. Spectral Domain OCT (SD-OCT) sections through retinal infiltrates typically show focal retinal thickening, increased hyper-reflectivity and back shadowing, which resolve without visible chorioretinal scarring (53). Oray et al., observed localized retinal nerve fiber layer (RNFL) defects as sequelae of superficial retinal infiltrates affecting the posterior pole in patients with BU. They proposed these OCT findings could serve as an early indicator of posterior pole involvement (61).

Recently, OCT has also been used to objectively measure the associated degree of vitreous inflammation in BU, as a tool for monitoring activity. Behçet neuroretinitis often reveals itself with a localized vitreous condensation overlying the infiltrated optic disc. Optically, OCT scans through the optic disc may show a "smoking volcano" picture or a "mushroom-shaped cloud that caps the plume" corresponding to the clinical finding. Thus, OCT allows non-invasive monitoring of the disc infiltration and overlying inflammatory reaction (62, 63).

Enhanced depth OCT

Enhanced Depth Imaging (EDI), the recent addition to most OCT devices, has allowed histologic in-depth examination of the choroid. There are multiple studies investigating choroidal thickness by this EDI mode of SD-OCT in patients with BU.

Kim et al., studied choroidal thickness during active and quiescent BU. They observed choroidal thickening during the active phase. Furthermore, subfoveal choroidal thickness during the quiescent phase remained significantly greater than that of normal subjects (Figure 5). They also found that the degree of reduction in choroidal thickening significantly correlated with an improvement in retinal vascular leakage on FFA (64). In support of these findings, longitudinal follow-up data by Ishikawa et al. also suggested a decrease in choroidal thickness with resolution of intraocular inflammation. However, according to their study, this change did not translate into any significant corresponding visual improvement (65).

OCT angiography

Optical coherence tomography angiography (OCTA) is a novel imaging technique that resolves and displays high-resolution, depth-resolved, en face images of the retinal and choroidal microvasculature by calculating motion contrast in OCT B-scans acquired repeatedly at the same location (66).

In 2016, Khairallah et al., demonstrated that the main changes detected by OCTA were retinal capillary non-perfusion, rarefied, dilated or shunting perifoveal capillary vessels, disorganization of the normal architecture of the capillary network, enlargement of FAZ, and reduction of capillary vessel density (CVD) (Figure 6). They determined that the deep capillary plexus (DCP) was more affected than the superficial capillary plexus (SCP) (67).

Numerous studies have been conducted to assess microvascular changes associated with BD. In an Egyptian study done on 22 eyes with BU during activity and following remission, the authors proposed that OCTA can be used to monitor activity of Behçet's posterior uveitis. The superficial capillary plexus (SCP) density was more sensitive to the activity status. On the other hand, the deep plexus (DCP) and the FAZ area -being areas where damage is more irreversible- were more useful as prognostic indicators (68).

Somkijrungroj et al., proposed that deep capillary affection in BU occurs at an early stage of the disease and proceeds regardless of the activity status of the disease. They suggested that it correlates positively with the number of reported attacks, thus there tends to be a bigger irreversible component of the hypoperfusion in the deep plexus than in the superficial (69). Likewise, Accorinti et al. found that even in inactive stages of the disease, a permanent alteration of the macular microvasculature might be observed and that the duration of a disease-free period was strictly related to OCTA findings, indicating that in inactive uveitis, the vessel density is inversely related to the number of ocular relapses and cannot be restored over time (70).

OCTA may be superior to FFA for visualizing, characterizing, and quantifying perifoveal microvascular alterations in active BU. OCTA images allow clear vessel visualization, due to the absence of dye leakage phenomenon, seen on FFA (67). However, FFA still remains indispensable, as there is no correlation between the presence of peripheral retinal ischemia on FFA and any of the OCTA pathologic features. Thus, FFA remains, currently, the only means for detecting and evaluating peripheral retinal capillary non-perfusion and neovascularization and is better at showing retinal vascular and optic disk leakage, which are definite signs of activity in BU (67).

Possibly, with the advent of the wide-field OCTA imaging, more peripheral retinal data can be obtained that may supplement ultra-wide field FFA imaging and do so in a non-invasive, dye-free technique. Currently the drawback lies in the trade off in resolution for the large acquisition area over a short time (71).

Updates in treatment

Medical management of the BU should be tailored according to the mode of presentation (anterior, posterior or panuveitis), as well as the severity of the attack, as there are no standard rules

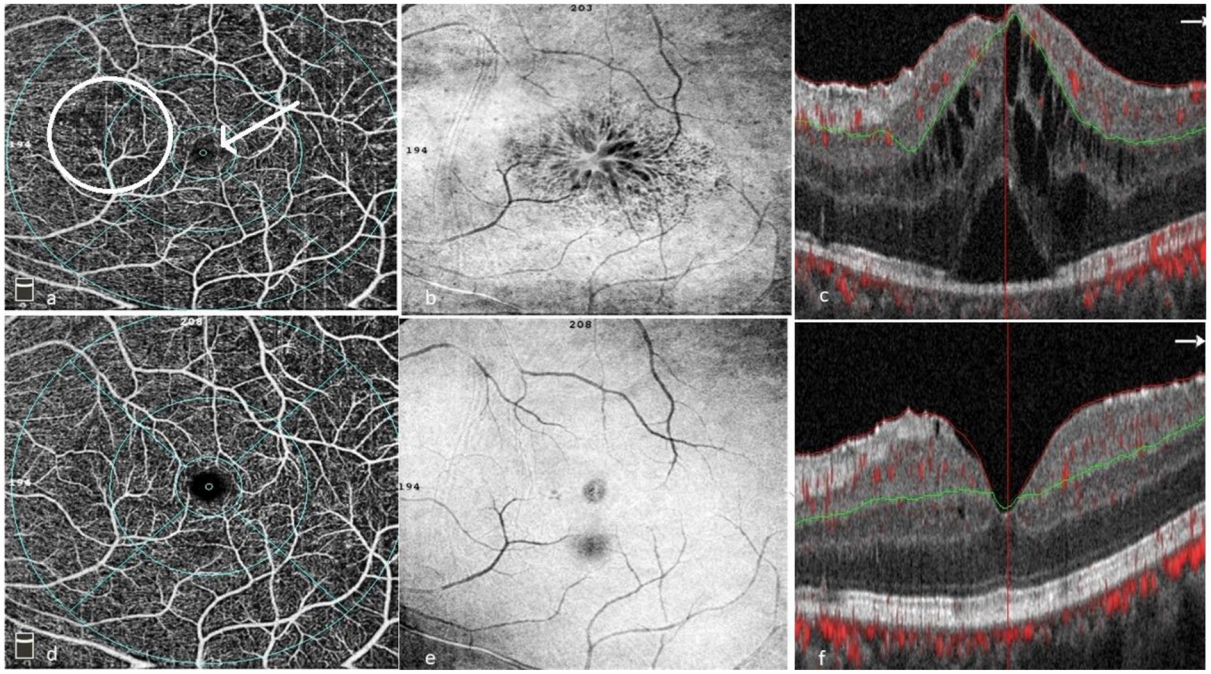

FIGURE 6
Patient with BU pre- **(a–c)** and post treatment **(d–f)**. **(a)** OCTA of the superficial capillary plexus showing areas of capillary drop outs, capillary telangiectasia, disorganization and hyporeflective areas corresponding to the cystoid spaces on SD-OCT. **(b)** En face OCT showing cystoid spaces involving the fovea. **(c)** SD-OCT with center involving cystoid spaces, subfoveal neurosensory detachment and a hyperreflective epiretinal membrane. **(d)** OCTA showing resolution of most capillary changes (telangiectasia, drop outs, and disorganization). **(e)** En face showing resolution of cystoid changes with residual epiretinal membrane. **(f)** SD-OCT showing resolution of cystoid changes and neurosensory detachment with residual diffuse edema and an epiretinal membrane (Images courtesy of Dr. Wassef A, MSc.).

of treatment (72). The European League Against Rheumatism (EULAR) published first guidelines for management of the disease in 2008 (73). Over the past decade, additional numerous studies were published addressing different therapies which lead to the development of updated EULAR guidelines in 2018 (13). The consensus in uveitis management has clearly shifted to being a multidisciplinary collaboration between experienced uveitis specialists and rheumatologists. Another recommendation was the limitation of steroid administration to short-term and acute stage control, to be replaced by DMARDs or biologic therapy according to EULAR and American Academy of Ophthalmologists' guidelines. Furthermore, the American Academy of Ophthalmology recommended bypassing the "classic DMARDs" in favor of anti-TNF-alpha agents in severe, sight-threatening uveitis (13). In this section we review the updates on the different systemic drugs used in the management of BD-associated uveitis.

Steroids

The 2018, the EULAR updated guidelines recommended administering glucocorticoids in posterior segment ocular BD patients, but only in combination with steroid-sparing therapies such as azathioprine (AZA), cyclosporine A (CsA), interferon alpha or monoclonal anti-TNF antibodies. The role of systemic steroids was defined to primarily address an acute episode, to control the attack and prevent extensive tissue damage (13). In cases with severe vitritis, extensive occlusive retinal vasculitis, retinitis and optic neuropathy, high doses of steroids (whether pulse methylprednisolone regimen followed by oral prednisone 1 mg/kg/day, or directly skipping to the latter) are given, bearing in mind steroid-related systemic complications (7). Tapering steroids, in addition to steroid-sparing therapy, are then initiated targeting maintenance of remission (13, 37).

When BD manifests as isolated anterior uveitis, usually topical steroids and cycloplegics are sufficient to control the disease (74), yet a manifestation in the form of an aggressive attack with hypopyon necessitates systemic steroids, especially when associated with poor prognostic factors, such as young age and male gender (13, 32).

Regional steroids, in the form of sub-Tenon Triamcinolone acetonide (TAA) injections are also effective in controlling active ocular disease and are often used in conjunction with other systemic treatment regimens in severe cases. Adjunct intravitreal steroid administration has also been reported to

control ocular inflammation and macular edema in ocular Behçet, administered either as TAA intravitreal injections or, more recently, in the form of fluocinolone acetonide or dexamethasone implants, especially in cases with refractory CME. Success was reported both anatomically as well as visually and may require the management of complications such as the temporary rise of intraocular pressure and/or cataract formation. These complications were reportedly higher with fluocinolone acetonide vs. dexamethasone implants (75–77).

Steroid-sparing immunosuppressants

This drug class is used to allow for steroids withdrawal while controlling the disease activity and reducing or preventing relapses. The choice of the drug(s) as well as the doses should be done in collaboration with an expert rheumatologist for drug monitoring.

Currently, immunosuppressant therapy for BD uveitis can be grossly divided into conventional treatment AZA and the biologic agents such as TNF-alpha inhibitors and Interferon alpha-2a (78–80).

Conventional treatment (CT)

Randomized controlled trials (RCT) have proven that the antimetabolite AZA and T-cell inhibitor CsA to be effective in the treatment of posterior uveitis in BD as well as in successfully decreasing the frequency of relapses (81–84). These evidence-based results maintained their validity and thus the updated 2018 EULAR guidelines recommended the use of these two drugs in the initial therapy of posterior uveitis. On the other hand, mycophenolate mofetil and cyclophosphamide were not included in the latest EULAR guidelines update (13). Once control of inflammation on low-dose maintenance steroids (≤5–7.5 mg/day) is achieved for several months, a progressive tapering of the immunosuppressant dose is begun. Generally reducing the dose by 10% every 2 to 3 months until discontinuation, which may be achieved after 18 to 24 months of treatment. However, a longer duration of immunosuppressant medication is often necessary.

Azathioprine (AZA) is one of the two most commonly used conventional treatment drugs in the control of systemic BD, and specifically in Behçet's uveitis. It requires 2–3 months to achieve full effect. During this period, control of the active disease should be achieved with steroids. The dose of AZA usually used is 2.5 mg/kg/day with a maximum of 3 mg/kg/day and has proven efficacious in BD uveitis, improving the visual acuity, reducing relapses and halting progression into severe disease (14).

In spite of necessary regular monitoring of blood picture and liver enzymes, AZA is generally considered a well-tolerated drug. A trial of tapering and withdrawal can be initiated after a period of remission and may extend beyond 18–24 months (79, 80).

Cyclosporine A (CsA) is the second most commonly used conventional drug and is usually started at 2–5 mg/kg/day in two divided doses which can be increased gradually until good control is achieved in addition to the low oral steroids dose. Similar to AZA, CsA has proven to be effective in improving visual acuity and reducing severity of the attacks with fewer recurrences (84). The main side effects of CsA are nephrotoxicity and hypertension (85). Due to its neurotoxicity, it is contraindicated in cases with neuro-Behçet's (86). After disease control is achieved, the drug is to be tapered very gradually over a long period like AZA to prevent rebound inflammation. The concomitant use of AZA and CsA, whether as first or second-line therapy, has shown efficacy in controlling ocular BD with periodic monitoring of systemic side effects (14, 73).

Biologics

While still some of the most commonly used CT drugs have been associated with refractory BU cases or treatment side effects. Their use as first-line therapies has decreased since the emergence of biologics. Due to their potent and fast effects, biologics are now used alone or in combination therapy in refractory ocular Behçet's cases or sometimes even as first line treatment in severe sight-threatening attacks (13).

Tumor necrosis-alpha (TNF-alpha) inhibitors

In BD, TNF-alpha production by macrophages, CD4+ and CD8+ T-cells, and Natural Killer cells is increased (87, 88). The reduction of circulating TNF-alpha by blocking agents has resulted in dramatic improvement in disease activity as demonstrated in many trials especially in those with severe pan- or posterior uveitis.

Anti-TNF-alpha drugs used are recombinant monoclonal antibodies directed against TNF-alpha. Pre-treatment protocol with biologics necessitates the exclusion of tuberculosis and hepatitis B or C as well as occult malignancies before starting therapy due to possible flare-ups of these diseases by the drugs. Multiple effective and inter-changeable agents are currently present, should one drug option fail (89). Usually an additional dose of an immunosuppressant is necessary with some of the TNF-alpha blockers to prevent anti-chimeric, or anti-human, antibody production, which decreases the drug's efficacy resulting in secondary failure (90–92).

Adalimumab (ADA) is a fully human monoclonal antibody directed against TNF-alpha. It is one of the few drugs that has been tested in RCTs against a placebo, in both active and quiescent non-infectious uveitis (VISUAL I and VISUAL II

studies, respectively) (93, 94), in which Ocular BD represented 7% of the uveitic cases enrolled. Due to its superiority over placebo in improving central retinal thickness and control of disease activity (but not in terms of macular edema), the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) approved ADA for non-infectious non-anterior uveitis in 2016. Adalimumab is administered via a subcutaneous injection at an adult dose of 40 mg every 2 weeks.

Numerous uncontrolled studies, such as the data presented by Fabiani et al. and Urruticoechea-Arana et al. also showed significant results regarding efficacy of ADA in improving BD uveitis (95–97). Not only was it superior to placebo in the control of disease activity but also a higher percentage of patients on ADA were able to withdraw oral steroids (94).

Adalimumab has also been tried in the pediatric BD subgroup where early initiation of the drug in two children succeeded in control of the disease activity with tapering of topical and systemic steroids and hence avoiding complications (98).

Humira is the reference adalimumab drug investigated in all of the above trials. Several biosimilars-adalimumab (bio-ADA) are still under investigation regarding their efficacy in ocular BD. A very recent study by Soheilian et al. reported the significantly positive results achieved by bio-ADA in improving visual acuity, decreasing vitreous haze and improving anterior chamber activity in 48 patients with refractory BU on conventional treatment (99). Sota et al. report good results in controlling retinal vasculitis and disease activity while preserving visual acuity (100, 101).

Infliximab (IFX) is another TNF-alpha blocker in the form of a chimeric monoclonal antibody. It is usually reserved for refractory cases or used as a first-liner in case of severe posterior uveitis with higher risk of tissue damage or visual loss. Infliximab is administered at a dose of 3 to 5 mg/kg in a slow intravenous infusion over 2–3 h. Loading regimen includes repeating the dose at the 2nd week, then the 6th week, then every 6–8 weeks for maintenance of disease control (102).

Many trials have demonstrated the rapid, profound effect infliximab had on BD uveitis. The drug has resulted in rapid remission of the disease and improved visual acuity. It also reduced the number and severity of attacks in comparison with other immunosuppressants during the first 6 months of treatment, as well as long-term therapy (103–107). Early administration within the first 36 vs. 72 months seemed to favor a protective value in visual outcome and disease control (108).

Similar to ADA, IFX is usually taken with another immunosuppressant drug to guard against anti-chimeric antibodies and might be associated with reactivation of tuberculosis and Hepatitis B or C diseases. Numerous adverse effects have been reported with IFX such as allergic reactions, induced lupus, aggravation of multiple sclerosis, optic neuritis and pulmonary embolism that might necessitate cessation of the drug (103, 104).

Several comparative studies between ADA and IFX have been conducted (109). Prominently, a multicenter study on 177 patients compared ADA with IFX as first line biologic in cases with refractory BD uveitis, and found that both groups had significantly better control in terms of disease activity but the ADA group had higher percentage of patients with better BCVA and higher drug retention rate with fewer drug related reactions (110).

Regarding the biosimilar IFX (bio-IFX), few contradicting reports exist as to its efficacy in the management of ocular BD. While bio-IFX was found to be disappointing in 3 patients with ocular and neuro-BD and resulted in recurrence of activity after switching from reference drug to biosimilars (111), another study reported the success of bio-IFX in achieving remission in 4 out of 6 patients with BD involving uveitis, nervous system, vascular and joint involvement (112).

Golimumab is another totally humanized anti-TNF alpha antibody that appears to have promising efficacy, notably in refractory BD cases (113, 114). Additional studies are necessary to better evaluate the efficacy and safety profile.

Interferon alpha-2a

Interferon alpha is a cytokine produced in nature in response to a viral infection or tumor with variable antiviral, antiproliferative, antiangiogenic and immunomodulatory effects. In medical practice, interferon alpha-2a is generally indicated as second-line therapy in resistant cases, or as a first-line treatment in very severe posterior uveitis or in cases of intolerance to conventional immunosuppressive medications. Studies have revealed that it improved visual acuity, resolved macular edema, significantly reduced the rate of relapses, and sometimes allowed for steroids to be completely withdrawn (115, 116).

There is no standardized consensus regarding initial dosing up to reaching the maintenance dose, fulfilling remission and quiescence for a minimum of 6 to 9 months. However, upon commencement of therapy, oral steroids should be lowered to a maintenance dose of 10 mg/day (117, 118). The main side effects of interferon are a flu-like syndrome, psoriasis, epilepsy, depression, leukopenia and autoimmune manifestations (119).

Interleukin-6 (IL-6) antagonists

Tocilizumab (TCZ)

During the past few years, there has been several reports demonstrating the efficacy of TCZ, an interleukin-6 inhibitor, in the control of BD uveitis cases refractory

to conventional treatment and TNF-alpha blockers (120–122). The drug was able to achieve complete remission in some of the ocular Behçet cases, although it was not successful in systemic control of the disease in the same patients (123, 124) and may be considered in selected patients with refractory uveitic macular oedema (STOP-Uveitis Study) (125). The SATURN and SARIL-NIU trials focused on sarilumab, a newer IL-6 antagonist, in non-infectious uveitis. However, sarilumab has not yet been established in managing BU (126).

Interleukin-1 (IL-1) antagonists

Anakinra (ANA) and canakinumab (CAN)

Both ANA & CAN are currently under investigation in the treatment of BU. A retrospective Italian multicentric study in 2017 stated these two IL-1 antagonists were successful in managing intraocular inflammation in a small cohort of Behçet patients (127, 128), a result further endorsed in another study, that reports a better BD patient response to IL-1 therapy in those with BD uveitis vs. BD without ocular involvement (129). The rationale for IL-1 inhibition and its reported success is based on the possible role played by IL-1β expressed by retinal dendritic cells, macrophages and neutrophils as a mediator of the local inflammatory process (130).

Interleukin-17A (IL-17A) antagonists

The SHIELD trial was conducted to assess the efficacy of secukinumab in BD uveitis. The trial failed to meet its primary objective vs. placebo in uveitis recurrences, however, it significantly reduced the requirement for concomitant immunosuppressive treatment (125).

Janus kinase inhibitors (JAKi)

Several studies have recently reported success with JAK inhibitors in the treatment of non-infectious autoimmune uveitis refractory to conventional DMARDs and anti-TNFα agents, suggesting they could be an alternative to the aforementioned (131, 132). Some have also reported steroid-sparing success. JAKi have already been approved in several rheumatological, gastrointestinal and dermatological autoimmune diseases. They act by inhibiting JAK-transmembrane protein phosphorylation, thus blocking or downregulating the cytokine expression cascade prior to its initiation (133). Zou et al. report successful results with tofacitinib BD patients with refractory BD uveitis, meriting a larger prospective controlled trial (133).

Moving the systemic to the local environment

Given their systemic success and the booming era of anti-VEGF drugs, it was inevitable, that trials would soon follow, testing anti-VEGFs on one hand (in controlling the CME element of the inflammation), but more prominently the introduction of intravitreal injections of Infliximab initially, followed by Adalimumab (134–138). The rationale was to concentrate the treatment on site as well as to evade systemic side effects (134).

While Hamza et al. considered IFX IV injections a potential and safe, yet temporary option to consider for Behçet posterior uveitis with its drawback being a short study design of 18 weeks duration (138). A recent Egyptian study assessed the efficacy of 9 doses of monthly intravitreal IFX as an adjunct to systemic treatment, in 22 eyes of 16 patients with active posterior uveitis. Only 7 eyes achieved success (35%), in the remaining 13 (65%) failure was due to inability to control the inflammation or due to severe flaring of inflammation. The authors concluded that IV IFX for active posterior uveitis in Behçet's disease was associated with a high complication rate, failure to control inflammation in most eyes and could not be considered a substitute to systemic therapy (139).

In conclusion, so far studies are small and results remain inconclusive, while the desired favorable outcome seemed only temporary. Safety profiles, the issue of possible acquired immunogenicity, need for repeated injections and open questions regarding clinical benefit and quality of life remain topics for more extensive research (134).

Behçet's uveitis and Covid-19

BD patients may be candidates for immunosuppression and hence more liable to contract serious infections compared to healthy individuals. A fine, critical balance is needed in BD patients with Covid-19 in an attempt to decrease mortality from the infection as well as avoid disease activity relapse. According to current expert recommendations, there is no reason to discontinue topical treatments, colchicine, and non-steroidal anti-inflammatory drugs. There may be a rationale to consider lowering systemic steroids to the lowest possible dose necessary. In cases with COVID-19 symptoms, immunosuppressive and biological agents can be temporarily stopped, but the decision should be tailored according to the patients' needs. Considering their potential beneficial effects on the course of COVID-19; colchicine, pentoxifylline, and dapsone can be considered as safe treatment options where indicated in BD. However, their role needs further evaluation (140). A retrospective analysis conducted by Bolletta et al. showed that despite immunosuppression (or some patients having stopped treatment) along with Covid-19 infection in Behçet patients, few

of their cohort required hospitalization, none was admitted to the ICU and eventually about one third had exacerbation in at least one of their BD-related symptoms (141).

Although BD patients are recommended to receive SARS-CoV-2 vaccine, there have been reports of post-vaccination emergence or reactivation of BD and possible ocular inflammatory flare ups (142, 143).

Conclusion

BD maintains a somewhat elusive nature to clinicians due to its heterogeneous presentations and its mimicry of other inflammatory diseases, as well as its ability to progress rapidly—and sometimes unexpectedly. This is mirrored in the multitude of classifications constantly developed and modified in an attempt to truly define this disease. A new tool expected to aid in classification, defining and identifying epidemiology, demographics, microbiome and genetic profiles of BD, and management data through real-life data collection are international and national registry programs, such as the AIDA Registry for BD. Management of BD and uveitis have seen a plethora of updates, especially pertaining to medical treatment and the entry of new investigative tools to aid in diagnosis, prognosis as well as disease monitoring and therapeutic response. The target remains to rapidly control the ocular inflammation and reduce the frequency and severity of relapses utilizing a combination of conventional therapies as well as the more recently biologic agents as defined by the latest EULAR guidelines.

Author contributions

SA, MS, and GR: conceptualization, critical revision, and editing of the article. SA, RA, RE, LH, and MR: writing original draft. All authors reviewed and agreed on the final version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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The Autoinflammatory Diseases Alliance Registry of monogenic autoinflammatory diseases

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Objective: The present manuscript aims to describe an international, electronic-based, user-friendly and interoperable patient registry for

monogenic autoinflammatory diseases (mAIDs), developed in the contest of the Autoinflammatory Diseases Alliance (AIDA) Network.

Methods: This is an electronic platform, based on the Research Electronic Data Capture (REDCap) tool, used for real-world data collection of demographics, clinical, laboratory, instrumental and socioeconomic data of mAIDs patients. The instrument has flexibility, may change over time based on new scientific acquisitions, and communicate potentially with other similar registries; security, data quality and data governance are corner stones of the platform.

Results: AIDA project will share knowledge and expertise on mAIDs. Since its start, 118 centers from 24 countries and 4 continents have joined the AIDA project. Fifty-nine centers have already obtained the approval from their local Ethics Committees. Currently, the platform counts 337 users (122 Principal Investigators, 210 Site Investigators, 2 Lead Investigators, and 3 data managers). The Registry collects baseline and follow-up data using 3,748 fields organized into 21 instruments, which include demographics, patient history, symptoms, trigger/risk factors, therapies, and healthcare information for mAIDs patients.

Conclusions: The AIDA mAIDs Registry, acts both as a research tool for future collaborative real-life studies on mAIDs and as a service to connect all the figures called to participate. On this basis, the registry is expected to play a pivotal role in generating new scientific evidence on this group of rare diseases, substantially improving the management of patients, and optimizing the impact on the healthcare system. NCT 05200715 available at https://clinicaltrials.gov.

KEYWORDS

autoinflammatory diseases, international registry, personalized medicine, precision medicine, rare diseases

Introduction

Monogenic autoinflammatory diseases (mAIDs) are a group of rare inborn errors of immunity caused by mutations in genes linked to the innate immune pathways. Constitutive overactivation of these pathways leads to increased release of monocyte- and neutrophil-derived cytokines, such as interleukin-1β, tumor necrosis factor α and type 1 interferon, which results clinically in periodic fevers and a variety of unprovoked inflammatory symptoms affecting any organ or system (1). Since the candidate gene for familial Mediterranean fever (FMF) was identified in 1997, the spectrum of mAIDs has rapidly broadened especially after the remarkable advances in molecular techniques and the extensive use of next-generation sequencing (NGS): this has led to the description of more than 50 new rare diseases in the last 10 years (2, 3). Given the heterogeneity and low prevalence of mAIDs, transnational collaboration is critical in order to collect an adequate volume of data and perform groundbreaking high-impact research. To this end, the Autoinflammatory Diseases Alliance (AIDA) Network was established in 2019 to provide an international collaborative framework for scientific research and education on rare autoinflammatory diseases (https://aidanetwork.org/en/).

In the field of rare diseases, patient registries are recognized at the international level as invaluable tools that support clinical research and orientate clinical trial design, improving both the management of patients and the overall healthcare system. According to the definition provided by the Agency for Healthcare Research and Quality, a registry is "*an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes*" (4). In this respect, it is now acknowledged that a circular flow of quality actions—governance, data source identification, standardization of data, FAIRness (findable, accessible, interoperable, and reusable) of information technology (IT) infrastructures, data/information quality check, training, and audits—are seminal to create tools of significant clinical impact (5). Furthermore, clinical registries are increasingly perceived as a *service* facilitating learning networks and establishing virtuous collaborations among the scientific community, industry, regulative agencies, patients, and their support networks (6). Indeed, one of the primary aims of the European Reference Networks is "*to reinforce research and epidemiological surveillance like registries*" (7). Also, the development of the European Platform on Rare Disease Registration (EU RD), providing common services and tools to rare disease registries operating across Europe, accounts for a strategic objective of the European Commission

(EC). Through the EPIRARE project ("Building Consensus and Synergies for the EU Registration of Rare Disease Patients", www.epirare.eu) the EC seeks to harmonize registry data to ensure interoperability, standardization, and data comparability (8). In the field of rare diseases, the AIDA Network has already worked to develop different registries dedicated to specific autoinflammatory diseases and ocular inflammatory disorders (9–11).

The present manuscript aims to describe an international, electronic-based, user-friendly and interoperable patient registry for mAIDs, the Autoinflammatory Diseases Alliance Registry of Monogenic Autoinflammatory Diseases (AIDA mAIDs), developed in the context of the AIDA Network program (ClinicalTrials.gov, Identifier: NCT05200715).

Methods

To be as comprehensive as possible, the authors adopted the registry description template questionnaire developed by Kodra et al. (12).

Registry organization

The AIDA mAIDs registry was launched on June 25, 2020 in the context of the AIDA Network program. English is the official language of the platform.

The University of Siena is the promoter of the AIDA Project. The promoter center is responsible for the registry governance and the coordination of the AIDA Network program. The role of registry/data manager is held by the personnel of the biomedical engineering department of the University of Siena, also in charge of the IT personnel of the AIDA project. The medical staff involved in the conceptual design and development of the registry and clinical advice to enrolling centers, includes physicians with expertise in rheumatology, pediatric rheumatology, ophthalmology, immunology, gastroenterology, and medical genetics. Methodologic, statistical, ethical, legal, and social issues (ELSI) and administrative support are provided by the University of Siena.

Type of registry

The AIDA mAIDs is an electronic-based, non-population based, physician-driven, clinical/genetic research registry (5).

Objectives

The overarching scope of the AIDA registry for mAIDs is declined into the following general aims: (i) to share knowledge and expertise on mAIDs by linking key referral centers for these rare diseases at an international level; (ii) to raise awareness among physicians and the general population about mAIDs, improving early diagnosis; (iii) to promote future multicenter studies based on a critical volume of data from patients with mAIDs.

The AIDA mAIDs-based studies will pursue the following specific objectives:

- to depict the clinical phenotype of newly identified mAIDs and broaden the phenotypic spectrum of well-established nosological entities;
- to describe genotype-phenotype correlations;
- to describe clinical manifestations based on patients' ethnicity;
- to identify age- and gender-related factors that may affect disease onset and progression;
- to outline the long-term prognosis for these diseases and identify potential prognostic factors for negative outcomes;
- to evaluate response to different therapeutic strategies and safety of drugs;
- to recognize the possible impact of mAIDs on fertility and course of pregnancy;
- to estimate the socio-economic burden of mAIDs.

Further objectives may be added over time thanks to the flexible modular infrastructure of the registry.

List of diseases under registration

All hereditary autoinflammatory diseases (monogenic forms) will be included in the registry. As new diseases are identified in this group, the registry shall be updated accordingly given its flexible framework. The list of genes/diseases currently included in the registry is given in Table 1. However, it is also possible to enroll patients carrying mutations in genes associated with mAIDs not yet included in the list.

Inclusion and exclusion criteria

Patients will be enrolled on the AIDA registry if they meet all the following criteria:

1. Subjects diagnosed and/or treated at the AIDA network partner centers (the full list is available at https://aidanetwork.org/en/clinical-sites).
2. Diagnosis of mAIDs based on one of the following scenarios:

TABLE 1 List of genes/diseases covered by the Autoinflammatory Diseases Alliance Registry of monogenic autoinflammatory diseases.

Gene	Inheritance	Disease	ORPHA number
ADA2 (HGNC:1839)	AR	ADA2 deficiency vasculitis	ORPHA:404553
AP1S3 (HGNC:18971)	AD	Generalized pustular psoriasis	ORPHA:247353
CARD14 (HGNC:16446)	AD	Pityriasis rubra pilaris	ORPHA:2897
IL1RN (HGNC:6000)	AR	DIRA	ORPHA:210115
IL36RN (HGNC:15561)	AR	DITRA	ORPHA:404546
LACC1 (HGNC:26789)	AR	LACC1 deficiency	–
LPIN2 (HGNC:14450)	AR	Majeed syndrome	ORPHA:77297
MEFV (HGNC:6998)	AR	FMF	ORPHA:342
	AD	PAAND	–
MVK (HGNC:7530)	AR	MKD	ORPHA:343
NLRC4 (HGNC:16412)	AD	AIFEC	ORPHA:436166
NLRP3 (HGNC:16400)	AD	CAPS-FCAS 1	ORPHA: 47045
NLRP3 (HGNC:16400)	AD	CAPS-MWS	ORPHA:575
NLRP3 (HGNC:16400)	AD	CAPS-NOMID	ORPHA:1451
NLRP12 (HGNC:22938)	AD	FCAS 2	ORPHA:247868
NOD2 (HGNC:5331)	AD	Blau syndrome	ORPHA:90340
OTULIN (HGNC:25118)	AR	ORAS	ORPHA:500062
PLCG2 (HGNC:9066)	AD	APLAID	ORPHA:324530
PLCG2 (HGNC:9066)	AD	PLAID	ORPHA:300359
POMP (HGNC:20330) PSMA3 (HGNC:9532) PSMB4 (HGNC:9541) PSMB8 (HGNC:9545) PSMB9 (HGNC:9546) PSMG2 (HGNC:24929)	AR	PRAAS	ORPHA:324977
PSTPIP1 (HGNC:9580)	AD	PAID	ORPHA:69126
RBCK1/ HOIL1 (HGNC:15864)	AR	HOIL1 deficiency	ORPHA:329173
SH3BP2 (HGNC:10825)	AD/AR	Cherubism	ORPHA:184
SLC29A3 (HGNC:23096)	AR	H syndrome	ORPHA:168569
TMEM173 (HGNC:27962)	AD	SAVI	ORPHA:425120
TNFAIP3 (HGNC:11896)	AD	Hereditary pediatric Behçet-like disease	ORPHA:476102
TNFRSF1A (HGNC:11916)	AD	TRAPS	ORPHA: 32960
Others	–	Hereditary periodic fever syndrome	ORPHA:324924

AD, autosomal dominant; ADA, adenosine deaminase; AIFEC, periodic fever infantile enterocolitis autoinflammatory syndrome; APLAID, autoinflammation, PLCG2-associated antibody deficiency and immune dysregulation; AR, autosomal recessive; CAPS, cryopyrin-associated periodic syndromes; DIRA, sterile multifocal osteomyelitis with periostitis and pustulosis; DITRA, deficiency of interleukin-36 receptor antagonist; FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; IL, interleukin; LACC1, laccase domain containing 1; MKD, mevalonate kinase deficiency; MWS, Muckle Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease; ORAS, OTULIN-related autoinflammatory syndrome; PAAND, pyrin-associated autoinflammation with neutrophilic dermatosis; PAID, PSTPIP1-associated inflammatory diseases; PLAID, PLCG2-associated antibody deficiency and immune dysregulation; PRAAS, proteasome-associated autoinflammatory syndrome; SAVI, STING-associated vasculopathy with onset in infancy; TRAPS, tumor necrosis factor receptor-associated periodic syndrome.

a) the presence of a confirmatory[1] genotype AND at least 1 among the clinical items included in the Eurofever classification criteria for cryopyrin-associated periodic syndromes (CAPS), FMF, tumor necrosis factor receptor-associated periodic syndrome (TRAPS) or mevalonate kinase deficiency (MKD) (14);

1 According to Gattorno et al., the genotype is considered confirmatory if 1 pathogenic/likely pathogenic mutation (for CAPS and TRAPS) or 2 pathogenic/likely pathogenic mutations (for FMF and MKD) in the causative genes are detected; the genotype is considered not confirmatory if (1) trans compound heterozygous for 1 pathogenic *MEFV* variant and 1 variant of uncertain significance (VUS), or biallelic VUS, or heterozygous for 1 pathogenic *MEFV* variant is detected, or if (2) 1 VUS in *MVK* or *TNFRSF1A* genes are detected. The pathogenicity of gene variants shall be based on the Infevers classification (10, 13).

b) the presence of a not confirmatory (see text footnote 1) genotype AND at least 2 among the clinical items included in the Eurofever classification criteria for CAPS, FMF or TRAPS;
c) fulfillment of the Tel Hashomer or the Yalcinkaya criteria for FMF, irrespectively of the genotype (13, 15);
d) fulfillment of the Kuemmerle-Deschner criteria for CAPS, irrespectively of the genotype (16);
e) the presence of a clinical picture consistent with MKD or adenosine deaminase (ADA)2 deficiency AND a positive biomarker test for DADA2 (ADA2 enzyme activity) or MKD (MVK enzyme activity or mevalonic aciduria) AND an inconclusive genotype[2] (17);
f) the presence of a clinical picture consistent with Blau syndrome, pyogenic arthritis-pyoderma gangrenosum-acne (PAPA) syndrome, A20 haploinsufficiency, ADA2 deficiency or pyrin-associated autoinflammation with neutrophilic dermatosis (PAAND) syndrome AND the detection of a confirmatory or consistent genotype (see text footnote 2) (17);
g) the presence of a clinical picture consistent with any monogenic autoinflammatory disease covered by the registry other than FMF, MKD, TRAPS, CAPS, Blau syndrome, PAPA syndrome, A20 haploinsufficiency, DADA2 and PAAND syndrome (Table 1) AND a confirmative genotype according to the expert clinician and genetic counseling of the reference center.

3. Willing of the subject (and/or his/her parents or legal guardian where applicable according to the national regulatory frameworks) to join the project.

Subjects carrying benign variants, likely benign variants (based on the INFEVERS classification) or no variants in genes known to be responsible for mAIDs, except for the scenarios described in 2c and 2d, are excluded from the registry (18). Specific scenarios other than those described above should be discussed with the AIDA medical staff to be considered as eligible.

Data sources and data flow

The data sources for the registry are extracted from (i) hospital clinical charts, (ii) laboratory reports, (iii) genetic laboratory reports, (iv) instrumental exams reports, (v) patient reported outcomes. The registry system is designed to capture both retrospective and longitudinal data.

To minimize recall bias for self- or proxy-reported information in the retrospective section, participants are notified before sensitive information is asked and they are allowed to provide secondary sources of information to update or validate previously collected data. As for the prospective section of the registry, a streamlined approach through real-time ad-hoc updates to the records during routine follow-up visits is suggested. Recruiting centers are advised to enter at least one follow-up record per year or when therapeutic changes are made.

The system includes mandatory and non-mandatory fields. However, it allows editing and completing any previously unanswered fields at the user's convenience. User-friendly data collecting tools are in place, such as automatic calculation fields, calendar fields, branching logics, electronic joint count homunculus and integrated Online Mendelian Inheritance in Man (OMIM), HUGO Gene Nomenclature Committee (HGNC) and International Classification of Diseases (ICD) 10 databases. Direct explanations or Internet addresses referring to external resources useful to the interpretation of specific fields are provided when required [i.e., INFEVERS classification of gene variants (18), diagnostic/classification criteria, clinimetric scores, laboratory reference values]. Complex branching logics allow the registry system to unfold following the patient's clinical history, making data collection straightforward. Each field includes a free text area for comments and queries.

Population under surveillance of the registry

The target population includes subjects affected by mAIDs. No specific demographic, geographic, clinical, or genetic determinants are foreseen.

Geographic coverage

The AIDA mAIDs registry is a non-population-based registry. The geographic coverage is the catchment area of the clinical centers affiliated to the AIDA Network. The countries with at least one AIDA partner center are shown in Figure 1 (updated to June 20th, 2022). Moreover, the updated geographic coverage of the registry can be found at https://aidanetwork.org/en/clinical-sites.

2 According to Shinar et al., the genotype is considered confirmatory when 1 (likely) pathogenic variant in *NOD2*, *PSTPIP1*, *TNFAIP3* genes or 1 pathogenic dominant variant in *MEFV* gene or 2 (likely) pathogenic variants in *ADA2* gene are detected; the genotype is considered consistent when 1 novel likely pathogenic variant in *NOD2*, *PSTPIP1*, *TNFAIP3* genes or 2 (likely) pathogenic not phased variants in *ADA2* gene or 1 (likely) pathogenic and 1 rare/novel VUS variants in *ADA2* gene are detected; the genotype is considered inconclusive when 1 (likely) pathogenic or 2 rare VUS in *ADA2* or *MVK* are detected (15).

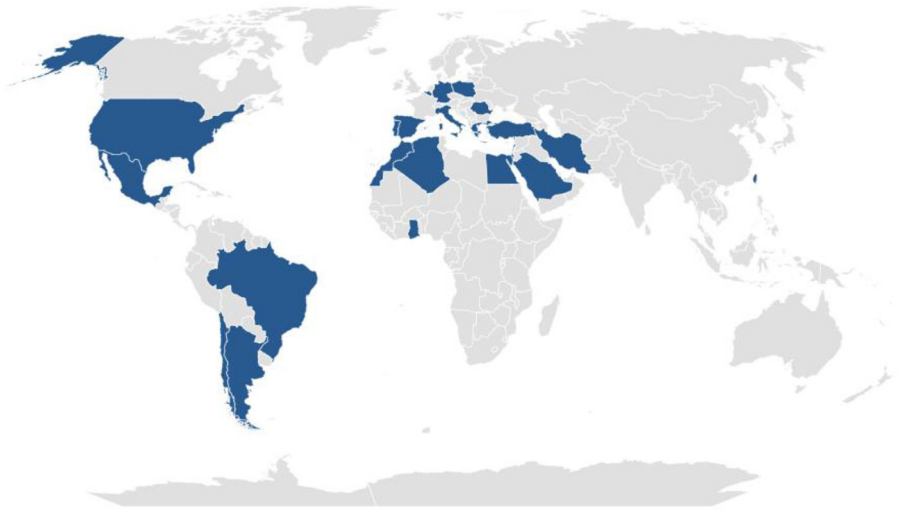

FIGURE 1
Current geographical coverage of the Autoinflammatory Diseases Alliance (AIDA) Registry of Monogenic Autoinflammatory Diseases. Countries highlighted in violet are those with at least one AIDA partner center (updated to June 20th, 2022).

Specification of the information to report

The instruments constituting the registry investigate the following sets of variables:

- demographics
- consents
- diagnostic data and family history
- general genetic information:
  - gene mutations
- features of inflammatory attacks:
  - at disease onset
  - between disease onset and diagnosis
  - between diagnosis and the time of enrolment
- clinical diagnostic and classification criteria
- laboratory data
- cardiovascular risk
- past and current treatments:
  - treatment with corticosteroids as main therapy
  - treatment with colchicine
  - treatment with conventional disease-modifying anti-rheumatic drugs
  - treatment with small molecules
  - treatment with biotechnological agents
- fertility and pregnancy
  - disease course and treatment during pregnancies
- follow-up visits: clinical manifestations and treatment
- Death of the patient (to open ONLY in case of patient's death)

The following *common data elements (CDE)* are included in the registry, according to the EPIRARE set of CDE for the European RDR platform (19): patient consent, patient sex, patient date of birth, patient country of birth, diagnosis (standardized according to the OMIM classification), patient country of residence, ID treatment center, other cases in the family (if Yes: degree of kinship), case parents are consanguineous (Yes/No), genetic features of the patient (gene-HGNC Gene Symbol, variant description in HGVS format, variant description in other formats), date of symptom onset, date of final diagnosis, current drug treatment, hospitalizations, patient vital status (and date of death), comorbidity (standardized according to the ICD10 format).

Registry regulatory status

The ELSI and privacy expertise are provided by the University of Siena. The AIDA project has been firstly approved by the Tuscany Region Ethics Committee - South-East (C.E.A.V.S.E.) area on 24/06/2019 (Ref. N. 14951). The

last amendment to the protocol was approved on 02/05/2022. The approval of the protocol should be provided by local Ethics Committee for each of the Centers joining AIDA, whenever required by local regulations. The approval is essential for data collection, but does not affect the participation to the other branches of the AIDA project, such as AIDA Academy or AIDA for patients.

The registry has been developed in accordance with the World Medical Association (WMA) Helsinki declaration 2013 (20) and with ELSI principles and rules, including international and local data protection regulations. The registry conforms to the General Data Protection Regulation (GDPR) (21) ensuring compliance with legal requirements regarding the processing of personal data.

To be eligible for inclusion in the AIDA registry for mAIDs, patients (or their parents/legal guardians) have to provide written opt-in consent. Patients receive from the investigator appropriate information about registry objectives, the type of information collected, how data will be used, the governance and data access rules for third parties and how to withdraw consent at any time.

Collaborative framework status

The AIDA registry for mAIDs was developed as a specific action of the AIDA Network program (https://aidanetwork.org/en/). Established in 2019, the program aims to move beyond the isolation of reference centers for rare autoinflammatory diseases and autoimmune ocular diseases, facilitating the collection and exchange of clinical data, conduction of multicenter studies and dissemination of scientific knowledge at an international level.

The registry management function and high-level decision making are responsibility of the AIDA Network program governance, chaired by the principal investigator of the AIDA promoter center.

The AIDA registry stakeholders include clinicians, patients, family, and patient organizations (to date, the Italian associations AIFP-Italian Association of Periodic Fevers, ANMAR-National Association of Patients with Rheumatic Diseases, and APMARR-Association of People with Rare Rheumatic Diseases), researchers, the European Reference Network (ERN) RITA.

Inspired by the FAIR guiding principles for scientific data management and stewardship, the AIDA mAIDs registry is included in the European Rare Disease Registry Infrastructure directory (ERDRI.dor, available at https://eu-rd-platform.jrc.ec.europa.eu/erdridor/home) and is committed to promote the interoperability with the other ERN RITA registries and potentially with the other ERNs, within the context of the MeRITA (Metadata registry for the ERN RITA) project (22, 23).

Informatics infrastructure

The AIDA registry for mAIDs is hosted by a virtual server in the platform of the Laboratory of Bioengineering of the University of Siena, which is located in the Data Center of the Azienda Ospedaliero-Universitaria Senese at the Santa Maria alle Scotte hospital in Siena (Italy).

The registry service is based on REDCap (Research Electronic Data Capture, https://projectredcap.org) a secure web application designed to support data capture for research studies. REDCap provides (i) an intuitive interface for validated data capture; (ii) audit trails for tracking data manipulation and export procedures; (iii) automated export procedures for seamless data downloads to common statistical packages; and (iv) procedures for data integration and interoperability with external sources (24, 25). REDCap requires a typical web infrastructure including one or more secure web servers running a standard software stack (LAMP) that can be deployed "on-premise" (i.e., on the local institution's hardware servers or virtualized servers) or on various cloud-based infrastructures. REDCap can integrate new software modules to extend functionality, such as data query workflow, support direct data capture from patients *via* user-facing surveys and patient pseudonymization. Even though it is not open source, REDCap software is licensed at no-cost for academic, non-profit, and government institutions.

The AIDA Network program developed a standard scheme to build a federated infrastructure of interoperable systems for registry services between partner sites to securely share data and collaborate on research goals. This scheme takes advantage of the portability of project metadata across REDCap installations and on a set of standard operating procedures with rapid turnaround times to: (i) assess, deploy and manage multiple aligned REDCap framework instances and project registries; (ii) efficiently share and deploy standard resources, such as medical data models and ontologies, that already exist or that are newly released by international framework initiatives (such as ERDRI-JRC and ERNs), integrating them into the network of project registries and data collection instruments; (iii) ensure compliance with privacy and security requirements throughout the project partners; and, (iv) guarantee global sharing and FAIR access to data.

Data management procedure/quality control

The principal investigators of each site are responsible for the validation of data of the corresponding records. They will be also responsible for the accuracy of the information accrued, with the Principal Investigator required to supervise the goodness of overall data. Each Principal Investigator may

analyze data gathered in his/her center. Site opening visits are scheduled virtually for each new partner center in order to train the investigators in the correct use of the registry. Further assistance from the AIDA team may be asked by the investigators by email (support@aidanetwork.org). The REDCap system allows quality data control at the moment of the data entry by users. In addition, internal data quality audits are periodically performed by the registry staff at the time of sample data extraction or when significant sources of error are identified. The quality control at the time of data extraction is aimed at the control of duplicate records from different investigator sites or logical inconsistencies and range errors on individual data batches sent by each site. When range errors or logical inconsistencies are found, a query is sent to the correspondent principal investigator in order to check the data source. When duplicate records are identified, the record management is dependent on the type of duplication and objective of analysis.

Security standards and procedures

Data are accessed through secure channels and there are procedures ensuring traceability of their processing, including login authorization procedures and history logs. Confidentiality is ensured on an operational level by pseudonymization and double codification if data are shared, in accordance with the GDPR rules. Full on-site and off-site encrypted data and system back-ups are programmed periodically.

Results

The AIDA mAIDs registry is running since June 2020.

The registry is composed of 21 instruments and 3,748 fields. By data lock in June 2022, the network counts 118 partner centers and 24 countries in 4 continents and is open to new membership applications. The protocol has been already approved by the local Ethics Committees of 59 partner centers; the remaining EC submissions performed in the last few weeks are in progress or, in a few cases, are not required by local regulations.

At last evaluation (June 20th, 2022), 418 subjects (M:F = 195:212, transsexual $n = 1$, missing $n = 10$) from 35 centers in 11 countries have been enrolled in the registry. Enrolling countries listed in alphabetical order are the following: Algeria, Belgium, Brazil, Egypt, Greece, Iran, Italy, Poland, Romania, Spain, Turkey. Patients' country of birth are Algeria ($n = 23$), Armenia ($n = 1$), Belgium ($n = 4$), Brazil ($n = 1$), China ($n = 1$), Egypt ($n = 58$), Greece ($n = 6$), Iran ($n = 3$), Italy ($n = 195$), Lebanon ($n = 1$), Morocco ($n = 2$), Palestine ($n = 1$), Poland ($n = 27$), Romania ($n = 4$), Spain ($n = 2$), Turkey ($n = 78$), Ukraine ($n = 1$), missing ($n = 10$). Mean age at the time of enrolment is 33.9 ± 16.7 years (range 0–75.9). A positive family history for the same mAID is recorded for 162 subjects (40.9%). Proband's parents are consanguineous in 40 cases (10.2%).

Discussion

The AIDA mAIDs registry is a powerful infrastructure embedded in the solid collaborative framework of the AIDA program. The registry enables the collection, sharing and valorization of a critical volume of data on mAIDs. Collecting data on autoinflammatory diseases is hampered by the well-known obstacles that rare disease research has to deal with, including the limited number of patients, isolation of research centers, and difficulty in obtaining the correct diagnosis in non-specialized clinical settings. Launched in June 2020, this AIDA registry received favorable attention on the European stage, showing increasing attractiveness, including 118 partner centers from 24 countries in a relatively short time.

According to the results of a survey conducted among the ERN RITA members in 2018, there are twenty-two registries collecting data on monogenic and/or multifactorial autoinflammatory diseases in Europe, with different scopes and geographic coverage: five of them (Eurofever, Infevers, Blau Cohort Study, Pediatric Behçet's Disease Registry, and ImmunAID) are transnational and devoted exclusively to AIDs (in two cases to a single specific disorder); four other registries (ESID, JIR-cohort, Brainworks Study, European Society for Blood and Marrow Transplantation Registry) are transnational and include both autoinflammatory diseases and primary immunodeficiencies and/or autoimmune diseases. The remaining registries collect regional or national data about rare immune diseases, including autoinflammatory diseases, with variable specificity (23). Therefore, it is of the greatest relevance to adopt a standardized scheme and provide a detailed description of the instrument when developing a new registry, in order to ensure adequate quality, efficient interoperability, and long-term sustainability. The AIDA Registry has been developed in such a way to potentially communicate with the existing registries in order to analyze the current clinical and scientific issues from different perspectives. In this regard, the AIDA registry for patients with monogenic autoinflammatory disease is already included within the context of the MeRITA.

In the scene of European registries for mAIDs, the AIDA registry stands out for its disease-specificity, richness in details, flexibility, complex branching logics allowing smart and time-saving data collection, and wide geographic and demographic coverage. With specific regard to the latter, the choice of including subjects of any age naturally follows from the well-established evidence that mAIDs may start from the very first hours of life to late adulthood, and also that adults with pediatric-onset disease may obtain the correct diagnosis with a delay of several decades. The inclusion of adult patients

along with children is an asset to this registry, allowing the design of comparative and longitudinal studies, research focused on childhood-to-adult transition and adult-specific issues not yet explored, such as pregnancy, fertility, adult vaccination, comorbidities, long-term disease-related damage, adult-specific outcome measures and PROMs, workability and further socio-economic issues. With this respect, the AIDA actions will be aligned to the research agenda set by the EULAR/ACR points to consider for diagnosis, management and monitoring of the IL-1 mediated AIDs and autoinflammatory type I interferonopathies (26, 27), also in the context of possible future collaborations at the international level.

The registry has been conceived as a flexible and modular tool able to capture the evolving landscape of this field of research. Whensoever new theoretical or practical knowledge is generated, the system enables agile updating of data collection tools. As an example, new modules may be added to include newly identified genes, new treatments that become available or to address to future unmet needs with new research objectives. Moreover, direct queries to the investigators can address specific gaps in the data collection. The AIDA mAIDs registry is inspired by the principles of FAIRness and is committed to adopt the instruments that the EC suggests for the development of registry platforms. Data are standardized by the use of shared libraries such as the ICD-10 and the OMIM classification; the EPIRARE set of CDE for the European RDR platform has been employed when possible (19). The registry has been already registered on the ERDRI directory (https://eu-rd-platform.jrc.ec.europa.eu/erdridor/) and will adopt the new SPIDER tool in the future, with the aim of facilitating the pseudonymization, linkage and transfer of encrypted pseudonymized data among European rare disease registries.

On the other hand, the registry platform supports data capture *via* user-facing surveys and the MyCap application (https://projectmycap.org/), which leverages REDCap, ResearchKit, and ResearchStack tools to capture patient reported outcomes *via* mobile devices. Later, the tool synchronizes the results back to the registry project. The integration of data from the "*AIDA for patients*" action into the AIDA mAIDs registry highlights the huge potentiality of this instrument. Actually, data obtained through the surveys proposed by "*AIDA for patients*" will complement the registry with patient-reported data about quality of life, fatigue, the socio-economic burden of the disease, psychological health, experience of the healthcare pathway and beliefs about medicines. This will allow four-hands studies with the active participation of both patients and their physicians. With this regard, a pilot project co-designed with the patient's association S.I.M.B.A. (*Associazione Italiana Sindrome e Malattia di Behçet*) has been already launched by the "*AIDA for patients*" action for Italian patients with Behçet's disease. A similar experience may be reproduced also in the context of mAIDs and other multifactorial AIDs, with the collaboration of local patient associations (https://aidanetwork.org/en/magazine/aida-for-patients-is-ready-for-launch).

As for the long-term sustainability of the registry, it seems relevant to highlight the lively interest raising from a growing number of international partners both in and outside European borders. Moreover, the AIDA Network program strategic communication and dissemination activities (website, magazine, web events) are equally important to the registry promotion. The program also includes the provision of high-level specialized education in the field of AID, through web-based seminars, face-to-face meetings, and a permanent education archive in collaboration with a renowned international faculty (*AIDA Academy action*). Of note, the program is endorsed by a growing number of patient associations, whose active involvement enhances a multiplier effect, by giving resonance to both AIDA Network program and AIDA mAIDs registry.

Furthermore, the AIDA mAIDs registry has been designed for the implementation of top-down and bottom-up research initiatives. Each Principal Investigator and Site Investigator may provide their study proposals during dedicated meetings. In particular, each Principal Investigator may analyze data collected in their own center for clinical and administrative use. On the contrary, the whole data will be managed by statistics and physicians involved in the network, selected by the Promoter on a case-by-case basis according to their field of expertise. Aggregated CDE are also used for periodic AIDA progress reports and are ready to be shared at the national and European level in the context of the ERNs as publicly indexed metadata and for clinical benchmarking.

In conclusion, we provide a new powerful instrument, the AIDA mAIDs registry, acting both as a research tool for future collaborative real-life studies on mAIDs and as a service to connect all the figures called to participate. These include international researchers, non-specialized clinicians, patients and their representatives, regulatory agencies as well as institutions at the national and supranational level. On this basis, the registry is expected to play a pivotal role in generating new scientific evidence on this group of rare diseases, substantially improving the management of patients and optimizing their impact on the healthcare system.

Ethics statement

The studies involving human participants were reviewed and approved by Tuscany Region Ethics Committee - South-East (C.E.A.V.S.E.) area on 24/06/2019 (Ref. N. 14951). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

CG wrote the first draft of the manuscript. AV conceived and designed the study and revised the draft of the manuscript. DR revised the draft of the manuscript. LC conceived and designed the study and accounts for AIDA Registries Coordinator. AB is the bioengineer involved in the technical management of the platform and registries. AT, GR, EA, EW-S, DA-I, GC, LI, MCM, MC, FLT, GL, EV, AP, AS, AI, PPS, AM, MF, BO, DO-B, PP, GE, FS, FCa, MP, JH-R, RP, MA, RNu, AO, ED, PS, PR, FLG, HK, JS, MAH, GM, KJ-R, RS-H, MR, FR, FCi, FI, FD, MF, KL, TG, FF, VSa, DY, VC, MTH, RD, AK, and GK were involved in data recruitment in the Registry dedicated to patients with mAIDs. MT, IA, AL, VM, LD, LB, SGe, FCr, VP, AA-MAM, RNa, MD, CBC, SGr, MM, ID, VSp, HAMG, IV, AR, AF, MAM, BF, GT, and CF were included in the authorship as investigators from the top contributor centers for any of the other seven AIDA Registries. ML was included as leading AIDA expert in the field of mAIDs. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Vasculitis and familial Mediterranean fever: Description of 22 French adults from the juvenile inflammatory rheumatism cohort

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Objective: The frequency of vasculitis may be increased in patients with Familial Mediterranean Fever (FMF), according to several studies. Our aim was to assess the characteristics of French adult patients with both diseases.

Methods: Patients with vasculitis were selected from patients followed for FMF in the French JIR-cohort.

Results: Twenty-two patients were included [polyarteritis nodosa (PAN) n = 10, IgA vasculitis n = 8, unclassified vasculitis n = 2, granulomatosis with polyangiitis n = 1, and microscopic polyangiitis n = 1]. Pathogenic mutations in exon 10 were found in all 21 patients (96%) for which *MEFV* testing results

were available, and 18 (82%) had two pathogenic mutations. Histology showed vasculitis in 59% of patients. Most patients with FMF-associated PAN were HBV-negative and had an inactive FMF before PAN onset, and 40% had a peri-renal or central nervous system bleeding. Most patients with FMF-associated IgA vasculitis had an active FMF before vasculitis onset, and 25% had digestive bleeding. Both patients with unclassified vasculitis had ischemic and/or hemorrhagic complications.

Conclusion: This study confirms the predominance of PAN and IgA vasculitis in patients with FMF and the high frequency of bleeding in FMF-associated PAN. FMF should be considered in case of persistent symptoms and/or inflammatory syndrome despite vasculitis treatment in Mediterranean patients.

KEYWORDS

vasculitis, familial Mediterranean fever, polyarteritis nodosa, IgA vasculitis, pyrin, anti-neutrophil cytoplasmic antibody-associated vasculitis, Behçet syndrome

Introduction

Familial Mediterranean fever (FMF) is the most common monogenic auto inflammatory disease, mainly affecting people from Mediterranean countries and associated with mutations in the *MEFV* gene (1). *MEFV* encodes pyrin, a protein expressed in neutrophils and monocytes and playing an important role in the innate immune response, resulting in the production of interleukin (IL)-1beta (2). Numerous reports suggest a higher frequency of vasculitis in patients with FMF compared to the general population (3–6). These frequencies could reach 2.7–7% for IgA vasculitis (3–5), 0.9–1.4% for polyarteritis nodosa (PAN) (4, 5), and 0.4% for Behçet disease (6). Moreover, the clinical characteristics of these vasculitis may differ between patients with FMF and the general population. Particularly, patients with FMF and PAN seem to have a higher incidence of peri-renal hematoma (7). Most studies arised from Turkey or the Middle East and data regarding European patients with vasculitis and FMF are lacking. In this nationwide French retrospective study, we report the main characteristics and outcomes of adult patients with FMF and vasculitis from the JIR-cohort.

Methods

Patients with vasculitis diagnosed according to international criteria (8–11) were identified among patients aged >18 years in the French JIR-cohort with FMF (12). The Juvenile Inflammatory Rheumatism (JIR) cohort is an international multicenter prospective data repository for patients with systemic inflammatory or rheumatological disease[1] (13). The following data were collected: Socio-demographic (age, sex, and ethnicity), background (family history, and comorbidities), FMF characteristics (diagnostic criteria, age at symptoms onset and at diagnosis, clinical manifestations, age at the start of colchicine treatment, C Reactive Protein (CRP) levels during flares and follow-up, FMF control before the onset of vasculitis, treatments, and dose of colchicine at vasculitis diagnosis), *MEFV* gene testing results (14, 15), vasculitis characteristics (age at diagnosis, clinical manifestations, histological results, results of arteriography and/or CT or MRI angiography, treatment, and follow-up). FMF control was judged on the presence of flares, and monitoring of CRP ± SAA, when available. Data are described as median (first quartile—third quartile) for continuous variables and number (%) for categorical variables. This observational study was based on data extracted from the JIR-cohort, established by the National Commission on Informatics and Liberty (CNIL, authorization number N0: 914677). Patients consented to be included in the JIR-cohort and were informed that data collected in medical records might be used for research studies in accordance with privacy rules.

Results

Among 406 patients with FMF in the French JIR-cohort, 22 had vasculitis and were included (82% men). Most patients had a PAN (n = 10, 46%) or an IgA vasculitis (n = 8, 36%). The characteristics of FMF and of vasculitis in patients with PAN or IgA vasculitis are described in **Table 1**. Other patients had ANCA-associated vasculitis (n = 2 and 9%) or an unclassified vasculitis (n = 2 and 9%). The median ages at FMF and vasculitis diagnosis were 11.5 (7–22) and 22 (16.5–36.5) years, respectively. At least one episode of

1 https://www.jircohorte.org/jircohort

bleeding (renal, central nervous system, and pulmonary) or thrombosis complicated the vasculitis of 8 (36%) and 2 (9%) patients, respectively.

TABLE 1 Main characteristics of patients with FMF-associated PAN and IgA vasculitis.

	PAN (n = 10)	IgA vasculitis (n = 8)
Men	10 (100)	5 (63)
FMF characteristics		
Age at onset/diagnosis (years)	5 (–9)/12 (10–34)	7 (4–12)/9 (5–15)
MEFV* pathogenic variants		
M694V/M694V	7 (70)	6/7 (86)
M694V/V726A	1 (10)	–
I692del/I692del	1 (10)	–
M694V/—	1 (10)	–
M694I/—	–	1/7 (14)
Clinical manifestations**		
Fever	8/9 (89)	8 (100)
Abdominal pain	7/9 (78)	7 (88)
Thoracic pain	2/9 (22)	7 (88)
Arthralgia/arthritis	7/9 (78)	6 (75)
Myalgia	1/9 (11)	3 (38)
Pseudo erysipela	–	3 (38)
Testicular involvement	1/9 (11)	1 (13)
Onset before vasculitis	10 (100)	6 (75)
Colchicine/FMF control[$] before vasculitis	10 (100)/7 (70)	4 (67)/1 (17)
Vasculitis characteristics		
Age at diagnosis (years)	36 (22.5–41.75)	13.5 (7.75–19.5)
Clinical manifestations[$]		
Cutaneous involvement	9 (90)	6/6 (100)
Renal involvement	3 (30)	5/6 (83)
Muscular involvement	7 (70)	2/6 (33)
Fever	6 (60)	1/6 (17)
Abdominal pain	6 (60)	3/6 (50)
Arthralgia/arthritis	5 (50)	3/6 (50)
Other[@]	2 (20)	1/6 (17)
Renal artery/cerebral aneurysms	3 (30)/1 (10)	–
Digestive bleeding	–	2/6 (33)
Histology compatible with the vasculitis[#]	8/8 (100)	3/3 (100)
Treatment		
Corticosteroids	6 (60)	3 (38)
Intravenous pulse cyclophosphamide	3 (30)	–
Other[†]	7 (70)	–

FMF, familial Mediterranean Fever; PAN, polyarteritis nodosa. Data are described as median (first quartile—third quartile) for continuous variables and number (%) for categorical variables.

*Data available for seven patients with IgA vasculitis.

**Data available for nine patients with PAN.

[$]Data available for six patients with IgA vasculitis.

[@]PAN: Weight loss, hypertension, and multineuritis (n = 1); weight loss, hypertension, oral aphthae, and testicular involvement (n = 1). IgA vasculitis: Weight loss (n = 1).

[#]Histology was available for eight patients with PAN and three patients with IgA vasculitis.

[†]Anakinra (n = 3), mycophenolate mofetil (n = 1), azathioprine (n = 1), plasma exchanges (n = 1), and non-steroidal anti-inflammatory drugs (n = 1).

Polyarteritis nodosa and familial Mediterranean fever (n = 10)

Symptoms of FMF appeared during youth in most cases, with a median age at diagnosis of 11.5 (10–34) years. Three patients had a family history of FMF. FMF and AA amyloidosis were diagnosed concomitantly in one patient. *MEFV* testing results were available for all patients; 9/10 had two pathogenic mutations. All patients had ethnicities at risk of FMF (Jewish, n = 6; Turkish, n = 2; Arab, n = 1; and Armenian, n = 1). In all patients, FMF preceded vasculitis and low-dose colchicine was prescribed [median dose 1 (1–1) mg/day]. FMF was controlled in 8/10 patients at vasculitis onset.

Most patients had an HBV-negative PAN (n = 9/10), with a median age at diagnosis of 36 (22.5–41.75) years. PAN was introduced by cutaneous signs (n = 6/10), peri-renal hematomas (n = 3/10), or multineuritis (n = 1/10). The main clinical manifestations of PAN were cutaneous (n = 9/10) or muscular involvement (n = 7/10), fever (n = 6/10), abdominal pain (n = 6/10), and arthralgia (n = 5/10). Cutaneous manifestations included subcutaneous nodules (n = 5/10, **Figure 1**), asymptomatic erythematous papules of the limbs (n = 3/10), purpura (n = 2/10), a pigmented livedo (n = 1/10), and an infiltrated, migrating, erythematous, pruritic annular rash (n = 1/10). No patient was tested for ADA2 deficiency. Histology was available for 8/10 patients and was compatible with PAN (**Figure 1**). Renal artery aneurysms were identified in 3/10 patients, and 4/10 patients had at least one episode of bleeding. Corticosteroids were administered to 6/10 patients. Notably, 3/10 patients with predominantly cutaneous involvement received anakinra, an IL-1-receptor antagonist, resulting in a rapid resolution of the clinical manifestations of PAN for all three patients, with resolution of the biological inflammatory syndrome for two patients. Treatment of PAN led to partial remission for all three patients with PAN introduced by a peri-renal hematoma. Despite treatment, these three patients had occasional flare-ups of febrile abdominal or joint pain, with an episode of purpura in one patient and an episode of erythema nodosum in another, but no patient had recurrent bleeding over a follow-up period of 3, 9, and 17 years. Follow-up was rarely longer than 1 year for the other patients. At last follow-up, 8/10 patients were taking colchicine at a median dose of 1 (1–2) mg/day, and 7/10 patients had a controlled FMF.

IgA vasculitis and familial Mediterranean fever (n = 8)

The median age at FMF diagnosis was 9 (4.5–15) years. *MEFV* testing results were available for 7/8 patients: Six had two pathogenic mutations, and One had a single pathogenic mutation. One patient's ethnicity was unknown; the others belonged to an ethnic group at risk of FMF (Jewish, n = 6 and

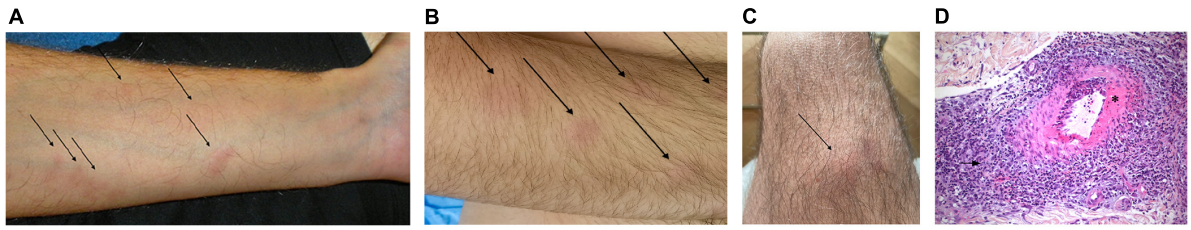

FIGURE 1
Picture of lesion and pathology slide in patients with PAN and FMF **(A–C)** subcutaneous nodules. **(D)** Skin biopsy (Hematoxylin, eosin, and saffron staining; magnification × 200): Deep dermal small artery vasculitis with intimal fibrinoid necrosis (*) and perivascular massive polymorphous inflammation of the adventice (arrow).

Arab, *n* = 1). Five patients had a family history of FMF, while two and one patients had a family history of AA amyloidosis and Behçet disease, respectively. In 6/8 patients, the onset of FMF preceded that of vasculitis by a median interval of 4 (3–7) years. Only 4/6 patients were prescribed colchicine before vasculitis onset [median dose 2 (1.75–2) mg/day], and FMF was controlled in only 1/6 patients.

The median age at IgA vasculitis diagnosis was 13.5 (7.75–19.5) years. Most patients had a single episode (*n* = 5/8, 63%). Three patients had two (*n* = 1/8, 13%) or three (*n* = 2/8, 25%) episodes of vasculitis. Clinical manifestations of IgA vasculitis were available for 6/8 patients. The main ones were purpura (*n* = 6/6), renal involvement (*n* = 5/6, 83%), abdominal pain (*n* = 3/6, 50%), arthritis (*n* = 2/6, 33%), and muscular involvement (*n* = 2/6, 33%; pain *n* = 1 and myositis *n* = 1). For two patients, the vasculitis was complicated by digestive bleeding. Histology was rarely available (*n* = 3/8) and showed vasculitis (*n* = 3/3) and IgA deposits (*n* = 2/3). Three patients were treated with corticosteroids.

The median follow-up time after diagnosis of IgA vasculitis was 12.5 (0–26.5) years. At last follow-up, all patients were taking colchicine, at a median dose of 1.5 (1–2) mg/day, and half of the patients had an active FMF.

Unclassified vasculitis and familial Mediterranean fever (*n* = 2)

One patient had a controlled FMF since his childhood, with two pathogenic mutations of *MEFV* (M694V/R761H). He developed a systemic vasculitis with a thrombosis of the superior mesenteric vein at age 36. Another patient presented with symptoms of FMF at age 13, with a homozygous M694V mutation. In the same year, he developed a vasculitis of vessels of all sizes. Despite treatments, he presented over the years several ischemic (stroke *n* = 1) or bleeding (bilateral peri-renal hematomas *n* = 1, testicular bleeding *n* = 1, and intra-alveolar hemorrhage *n* = 1) episodes, leading to his death at age 29. Both patients had two pathogenic mutations of *MEFV*.

ANCA-associated vasculitis and familial Mediterranean fever (*n* = 2)

One patient had a FMF since the age of seven, with a heterozygous M694V mutation. He presented at age 17 with a constrictive pericarditis, arthromyalgia, an axonal sensory neuropathy on electromyography, erythema nodosum, a skin biopsy showing arteritis with thrombosis, and positive ANCA without specificity; the patient did not present renal involvement. He received corticotherapy and azathioprine. Few years later, he developed two unexplained episodes of stroke. The late positivity of MPO-ANCA antibodies at age 27 led to the diagnosis of ANCA-associated vasculitis. Persistence of fluctuating arthromyalgia, infiltrated papules with thrombosing and inflammatory vasculitis on biopsy, positive MPO-ANCA antibodies (maximum 33 IU/mL) and elevated CRP levels up to 35 mg/L led to the introduction of rituximab. Given the persistence of cutaneous-articular signs, elevated CRP levels, treatment with anakinra was initiated and resulted in resolution of the clinical manifestations.

Another patient had recurrent sinusitis with an alveolar hemorrhage and positive ANCA (type not specified), leading to the diagnosis of granulomatosis with polyangiitis. She was treated with oral corticosteroids and intravenous pulse cyclophosphamide. The persistence of a biological inflammatory syndrome despite treatment with intravenous pulse cyclophosphamide, then methotrexate, then mycophenolate mofetil, led to the diagnosis of FMF with a homozygous M694V mutation, which symptoms had occurred during childhood.

Discussion

We describe the main clinical and genetical characteristics of 22 French adult patients with both FMF and vasculitis. The most frequent vasculitis were PAN (46%) and IgA vasculitis (36%), similar to previous reports from Mediterranean countries (4, 5, 7, 16). Despite possible overlaps between vasculitis and FMF clinical manifestations, all patients fulfilled the Tel Hashomer

FMF criteria (12). A recent review pointed the paucity of genetic data for described patients with FMF and vasculitis (7). In this study, pathogenic mutations in exon 10 were found in all 21 patients for which *MEFV* testing results were available, and 18 had two pathogenic mutations (15).

Polyarteritis nodosa was the most frequent vasculitis. FMF preceded PAN in all cases and was mostly controlled with low-dose colchicine treatment. Age at diagnosis of PAN (median, 36 years) was midway between patients with PAN and FMF described in a recent review (7), and those with idiopathic PAN (17). The prevalence of peri-renal hematoma in FMF-associated PAN could reach 50% (7, 18, 19) in the literature. Along this line, they affected 30% of our patients, and introduced the disease in all cases. Moreover, cutaneous manifestations were particularly frequent and heralded the disease in 60% of cases. Note, only one patient had livedo, unlike the classic cutaneous manifestations of PAN. Other findings were consistent with a literature review describing less weight loss, peripheral neuropathy, cardiac involvement, and more abdominal pain in patients with FMF-associated PAN (7). However, the proportions of joint and CNS signs were closer to that in idiopathic PAN (17). Overall, all these signs should raise the suspicion of PAN in a patient with FMF, and clinicians should be vigilant for the high risk of peri-renal bleeding. In this study, treatment of PAN was standard, except for three patients who received anakinra, a recombinant IL-1-receptor antagonist, resulting in resolution of clinical signs. Its efficacy suggests that IL1 may play a role in the pathophysiological mechanisms associated with vasculitis in these patients.

IgA vasculitis was the second most identified vasculitis in our cohort. FMF symptoms preceded vasculitis in 75% of patients; their FMF was mostly uncontrolled despite high colchicine levels, indicating active disease. These results may suggest a link between active FMF, an ongoing inflammatory state, and the triggering of IgA vasculitis (7). As such, clinicians should consider IgA vasculitis when they see purpura suggestive of small- or medium-vessel vasculitis in a patient with FMF. Our patients were older at the time of diagnosis of their vasculitis, had more renal and muscular involvement, and less fever, than has been described in IgA vasculitis associated or not with FMF (7). The prevalence of renal involvement in our series (83%) was close to that described by Audemard Verger et al. (70%) in their review of adult patients with IgA vasculitis (20). Abbara et al. reported an increased rate of intussusception (9%) in FMF-associated IgA vasculitis, which we did not observe in our cohort (7). However, 33% of patients presented digestive bleeding, which may be related to undiagnosed intussusception. Moreover, a low rate of IgA deposits was reported in FMF-associated IgA vasculitis (23%) (7). In this study, when histology was available, IgA deposits were present in 67% of cases, a rate like that described in patients with IgA vasculitis in the general population.

We described two patients with ANCA-associated vasculitis. In both patients, the diagnosis and management of FMF and vasculitis were challenging, given the overlap of FMF and vasculitis signs. Thus, although the association of FMF and ANCA-associated vasculitis could be fortuitous, we invite clinicians to evoke FMF in case of persistent compatible symptoms and/or unexplained chronic biological inflammatory syndrome, especially if the patient is of Mediterranean origin.

Few patients with FMF and unclassified vasculitis have been described so far (7). Almost half of them developed ischemic or bleeding complications. In this study, we described two patients with unclassified vasculitis; both developed such complications.

Behçet disease (BD) was proposed to be more prevalent in patients with FMF in a study by Schwartz et al. (6). BD shares clinical characteristics with FMF (21, 22). *MEFV* has been evaluated in several studies as a potential pathogenic gene of BD. There are contradictory results as some studies have shown an association of BD and FMF genes, whereas others did not (23–26). We did not identify any patient with both diseases, which could be due to the retrospective nature of the study, the absence of association between both diseases, or the low incidence of Behçet disease in France. In their literature review, Abbara et al. did not find a higher prevalence of BD in patients with FMF (7).

Besides vasculitis, patients with FMF could have an increased prevalence of various immune-mediated conditions, including spondyloarthritis (27, 28), psoriasis (29), hidradenitis suppurativa (30, 31), juvenile idiopathic arthritis (32, 33), multiple sclerosis (34), and inflammatory bowel disease (35, 36). The pathogenic mechanism of these associations remains unknown, particularly the role of *MEFV* mutations (37–42).

Conclusion

In conclusion, this multicenter retrospective study confirms the predominant coexistence of IgA vasculitis and PAN with FMF in French multi-ethnic patients. The presence of a high frequency of bleeding in patients with FMF and PAN, IgA vasculitis, and unclassified vasculitis is intriguing. Whether FMF increases the frequency of bleeding, or whether those vasculitis are FMF-related and represent a severe form of FMF, especially in patients with two pathogenic mutations, is unknown.

Data availability statement

The original contributions presented in this study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

This observational study was based on data extracted from the JIR-cohort, an international multicenter data repository established by the National Commission on Informatics and Liberty (CNIL, authorization number N°: 914677). Patients consented to be included in the JIR-cohort and were informed that data collected in medical records might be used for research study in accordance with privacy rules.

Author contributions

SA wrote the first draft of the manuscript, collected the data, and performed the statistical analysis. SA, SG-L, GG, CB, OF, JB-M, and DS contributed to the conception and design of the study. SG-L and GG supervised the study. All authors contributed to the manuscript revision, read, and approved the submitted version.

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Conflict of interest

SG-L and GG received honoraria as speakers or occasional consultants for the SOBI and Novartis laboratories (5000 euros).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Canakinumab as first-line biological therapy in Still's disease and differences between the systemic and the chronic-articular courses: Real-life experience from the international AIDA registry

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Objective: Interleukin (IL)-1 inhibitors are largely employed in patients with Still's disease; in cases with refractory arthritis, IL-6 inhibitors have shown to be effective on articular inflammatory involvement. The aim of the present study is to assess any difference in the effectiveness of the IL-1β antagonist canakinumab prescribed as first-line biologic agent between the systemic and the chronic-articular Still's disease.

Methods: Data were drawn from the retrospective phase of the AutoInflammatory Disease Alliance (AIDA) international registry dedicated to Still's disease. Patients with Still's disease classified according to internationally accepted criteria (Yamaguchi criteria and/or Fautrel criteria) and treated with canakinumab as first-line biologic agent were enrolled.

Results: A total of 26 patients (17 females, 9 males; 18 patients developing Still's disease after the age of 16 years) were enrolled; 16 (61.5%) patients suffered from the systemic pattern of the disease; 10 (38.5%) patients suffered from the chronic-articular type. No differences were observed between the systemic and the chronic-articular Still's disease in the frequency of complete response, of flares after the start of canakinumab (p = 0.701) and in the persistence in therapy (p = 0.62). No statistical differences were observed between the two groups after 3 months, 12 months and at the last assessment in the decrease of: the systemic activity score (p = 0.06, p = 0.17, p = 0.17, respectively); the disease activity score on 28 joints (p = 0.54, p = 0.77, p = 0.98, respectively); the glucocorticoid dosage (p = 0.15, p = 0.50, and p = 0.50, respectively); the use of concomitant disease modifying anti-rheumatic drugs (p = 0.10, p = 1.00, and p = 1.00, respectively). No statistically significant differences were observed in the decrease of erythrocyte sedimentation rate (p = 0.34), C reactive protein (p = 0.48), and serum ferritin levels (p = 0.34) after the start of canakinumab.

Conclusion: Canakinumab used for Still's disease has been effective in controlling both clinical and laboratory manifestations disregarding the type of disease course when used as first-line biotechnological agent. These excellent results might have been further enhanced by the early start of IL-1 inhibition.

KEYWORDS

AOSD, adult onset Still's disease, sJIA, systemic juvenile idiopathic arthritis, autoinflammatory diseases, biological therapy, interleukin-1

Introduction

Still's disease is a systemic polygenic autoinflammatory condition mainly characterized by fever, maculopapular skin rash, arthritis, arthralgia, serositis, and hepato-splenomegaly. Still's disease may be a life-threatening condition when patients develop the macrophage activation syndrome or other severe affections including pulmonary arterial hypertension, lung fibrosis, and disseminated intravascular coagulation. In patients with no concomitant macrophage activation syndrome, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), and ferritin serum levels are generally increased during disease activity (1).

Abbreviations: AIDA, AutoInflammatory Disease Alliance; AOSD, adult onset Still's disease; cDMARDs, conventional disease modifying anti-rheumatic drugs; CRP, C reactive protein; DAS28, disease activity score based on 28 joints; ESR, erythrocyte sedimentation rate; IL, interleukin;

In the past decades, Still's disease had been distinguished into systemic juvenile idiopathic arthritis (sJIA) for patients experiencing disease onset before the age of 16 and adult-onset Still's disease (AOSD) for patients with a later disease onset. However, based on similar pathogenesis, overlapping clinical manifestations and organ involvement, sJIA and AOSD are currently considered to represent a disease continuum of the same clinical entity arising in different ages (2, 3).

According to the clinical course, Still's disease may be distinguished into a "systemic" type and a "chronic-articular" type. The former includes patients mainly suffering from daily spiking fevers and systemic inflammation with skin, serosal and lymph node involvement; the latter includes patients with a prominent articular affection and less pronounced systemic inflammatory features. Still's disease can be distinguished into a monocyclic and polycyclic type, but this distinction has no relevance with respect to a prognostic stratification (4).

Diagnosis of Still's disease is primarily clinical and requires the exclusion of infections, neoplasms, autoimmune disorders and other autoinflammatory diseases. Different sets of criteria are currently available for diagnostic and classification purposes, with Yamaguchi's criteria and Fautrel's criteria being the most frequently employed in adults and the International League of Associations for Rheumatology (ILAR) criteria and/or the Pediatric Rheumatology INternational Trials Organization (PRINTO) criteria used in the pediatric setting (5–8).

Waiting for new clinimetric tools to measure disease severity and activity (9), the systemic Pouchot's score modified by Rau et al. at current (10); this is also useful in identifying patients at higher risk of death (11). The articular involvement may be assessed using the disease activity score based on 28 joints (DAS28) in adult patients or the juvenile arthritis disease activity score based on 27 joints (JADAS27) in pediatric patients (12, 13).

Treatment with biotechnological anti-interleukin (IL)-1 agents is recommended in patients with active disease especially in cases refractory to glucocorticoids and conventional disease modifying anti-rheumatic drugs (cDMARDs), avoiding a long-term glucocorticoids exposure (14–18). Agents blocking IL-6 are also recommended and may represent a valuable option in patients refractory to other treatment choices, as for joint involvement in Still's disease (14–16). Randomized control trials and real-world studies describe the efficacy of anti-IL-1 inhibition on the articular inflammatory involvement, with a significant decrease in the number of tender joints, swollen joints, DAS28 and JADAS27 (19–21). On the other hand, other evidence suggests that articular involvement responds to IL-1 inhibitors less quickly, especially in patients with a longer time between disease onset and the start of anti-IL-1 agents (21, 22).

With this background, the present study was performed to assess any difference in the effectiveness of canakinumab prescribed as first-line biologic agent between the systemic and the chronic-articular Still's disease.

Materials and methods

This study has been performed based on data collected in the retrospective phase of the international Registry on Still's disease promoted by the AutoInflammatory Disease Alliance (AIDA) Network (23).

The objective of this paper is to investigate the role of the anti-IL-1β canakinumab administered in patients with Still's disease as first-line biologic agent, looking for any difference in the therapeutic outcome between patients with the systemic type and patients with the chronic-articular type, disregarding age at disease onset.

The endpoints of the study are represented by the lack of statistically significant differences between patients with the systemic type and those with the chronic-articular type in terms of: frequency of complete response, frequency of partial response, frequency of flares during treatment, decrease in the systemic Pouchot and Rau score, DAS28, number of tender joints, number of swollen joints, physician global assessment (PhGA) of arthritis, patient's global assessment (PGA) of arthritis, glucocorticoid sparing, cDMARDs sparing, decrease in laboratory markers ESR, CRP, and serum ferritin levels. Clinical outcomes were assessed at the 3-, 6-, and 12-month visits and at the last follow-up evaluation while on treatment with canakinumab. Laboratory outcomes were analyzed at the baseline and at the 3-month assessment.

Patients were retrospectively collected from the AIDA Registry according to the following features required by this study: diagnosis of Still's disease classified according to Yamaguchi and/or Fautrel criteria (5, 6) in adult patients and to the ILAR criteria and/or the PRINTO criteria in patients aged less than 16 years (7, 8); signed consent/assent to participate to the AIDA Registry and studies; treatment with canakinumab as first line biologic agent. **Figure 1** corresponds to the study flow diagram explaining the selection of the patients enrolled in the present study among all patients recruited in the AIDA Registry dedicated to Still's disease. Patients were followed in 12 rheumatologic, immunologic or pediatric Centers joining the AIDA Network.

Complete response was defined as the complete resolution of all disease-related clinical manifestations with decrease of all laboratory inflammatory parameters within normal values. Partial response was defined as persistence of clinical manifestations with remarkable decrease in their severity and inflammatory laboratory parameters normalized or only

ILAR, International League of Associations for Rheumatology; IQR, interquartile range; JADAS, juvenile arthritis disease activity score based on 27 joints; NSAIDs, non-steroidal anti-inflammatory drugs; PGA, patient's global assessment; PhGA, physician global assessment; PRINTO, Pediatric Rheumatology INternational Trials Organization; SD, standard deviation; sJIA, systemic juvenile idiopathic arthritis.

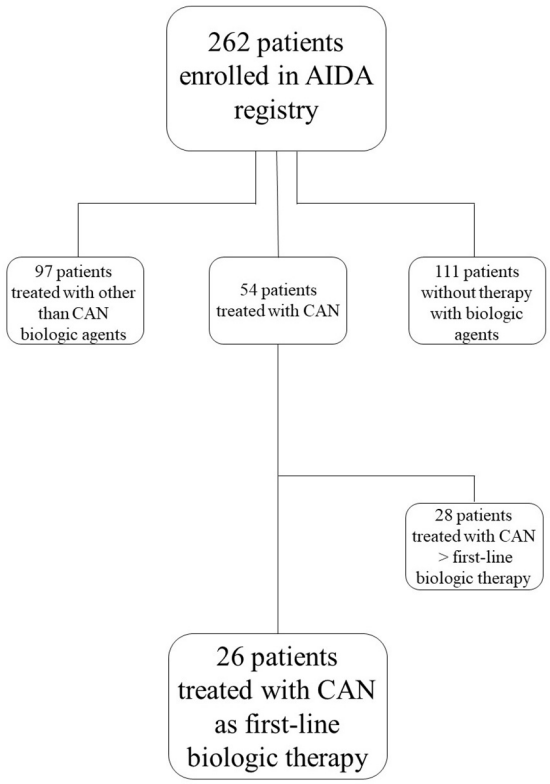

FIGURE 1
Study flow diagram illustrating the process leading to the selection of patients included in the present study among all patients recruited in the international AutoInflammatory Disease Alliance (AIDA) Registry dedicated to Still's disease. AIDA, AutoInflammatory Disease Alliance; CAM, canakinumab.

slightly increased. Poor response included patients not meeting the definitions of complete and partial response. A relapse was defined as reappearance of Still's disease related clinical manifestations leading to treatment change, the addition of a cDMARD or the increase of glucocorticoid dosages.

DAS28 values were calculated based on the CRP values. Glucocorticoids dosages were expressed as prednisone or equivalent (mg/day).

The modified Pouchot score was calculated on both pediatric-onset and adult-onset patients, based on the retrospective evaluation of disease manifestations recorded at the start of canakinumab and at the following time-points. Conversely, DAS28 was only calculated in adult patients, as articular involvement in pediatric patients is assessed with the JADAS27 score in the clinical practice.

The study has been approved by the Ethics Committee of Azienda Ospedaliero Universitaria Senese, Siena, Italy (AIDA Project; Ref. N. 14951) as part of the AIDA Program. The study protocol conformed to the tenets of the Declaration of Helsinki; informed consent was obtained from all patients at the time of the recruitment into the AIDA Registry for Still's disease.

Descriptive statistics included mean, standard deviation (SD), median and interquartile range (IQR) values according to the data distribution at the Shapiro–Wilk test. For qualitative data, comparisons were performed using 4×2, 3×2, and 2×2 contingency tables applying Fisher exact test with Freeman-Halton extension. For quantitative data, Kruskal–Wallis test of ANOVA test were used for global assessments, whilst Student t-test or Mann-Whitney U test were used for pairwise comparisons, as required. Significance level was set at 95% (p-value < 0.05); all tests performed were two-sided. The SPSS software, version 24, was used for statistical computations.

Results

Twenty-six patients (17 females, 9 males) treated with canakinumab as first-line biologic agent were enrolled. The mean age at disease onset was 31.88 ± 17.66 years; the mean age at diagnosis was 32.68 ± 17.61 years.

The 18 patients developing Still's disease after the age of 16 years fulfilled Yamaguchi criteria; 14/18 (77.8%) of these patients fulfilled also Fautrel criteria. The ILAR criteria and PRINTO provisional criteria were fulfilled in 6/8 (75%) and 7/8 (87.5%) pediatric cases, respectively. Canakinumab was started in patients aged less than 16 years in 3 cases.

Sixteen (61.5%) patients suffered from the systemic pattern of disease; 10 (38.5%) patients suffered from the chronic-articular type. The median time from disease onset at the start of canakinumab was 12.5 (IQR = 43.25) months, 9.5 (IQR = 23.0) months among patients with chronic-articular pattern and 30 (IQR = 56) months among patients with the systemic pattern ($p = 0.17$).

Table 1 shows treatment approaches attempted prior to canakinumab administration and those combined with canakinumab at the start of the treatment.

The following schedules of canakinumab administration were employed: 150 mg every 4 weeks in 8 (31%) patients; 300 mg every 4 weeks in 9 (34.6%) patients; 240 mg every 4 weeks in one (4%) patient; 4 mg/Kg/4 weeks in the 8 (31%) pediatric patients. In 5 (19.2%) patients the schedule was changed over time: in 2 cases the posology was increased from 150 mg/4 weeks to 300 mg every/4 weeks and from 150 mg/8 weeks to 150 mg/4 weeks because of inadequate response to the previous posology; 3 patients underwent a decrease in the frequency of administrations from 150 mg/4 weeks to 150 mg/5 weeks, from 4 mg/Kg every 4 weeks to 4 mg/Kg every 7 weeks, and from 240 mg/4 week to 240 mg every 4 months after a long-lasting disease remission. No statistically significant differences existed between groups ($p = 0.10$).

The mean duration of canakinumab treatment was 24.54 ± 17.91 months (range 3–86 months), with no differences between the systemic and the chronic-articular forms of the

TABLE 1 Summary of treatment approaches performed in the study group prior to and concomitantly with the start of canakinumab.

Treatments preceding canakinumab	Systemic group(16 patients)	Chronic-articular group(10 patients)	*p*-value
NSAIDs alone	8 (50%)	7 (70%)	0.325
Systemic glucocorticoids	13 (81.3%)	6 (60%)	0.422
cDMARDs	10 (62.5%)	3 (30%)	0.114
Methotrexate	8 (50%)	2 (20%)	0.134
Colchicine	2 (12.5%)	0 (0%)	0.254
Hydroxychloroquine	1 (6.25%)	1 (10%)	1.000
Cyclosporine	1 (6.25%)	0 (0%)	0.429
Sulfasalazine	1 (6.25%)	0 (0%)	0.429
Treatments at the start of canakinumab			
cDMARDs	9 (56.25%)	5 (50%)	0.760
Methotrexate 15 mg/week	4 (25%)	1 (10%)	0.355
Methotrexate 12.5 mg/week	0 (0%)	1 (10%)	0.206
Methotrexate 7.5 mg/week	1 (6.25%)	1 (10%)	1.000
Hydroxychloroquine 400 mg/day	1 (6.25%)	1 (10%)	1.000
Colchicine 1 mg/day	2 (12.5)	0 (0.0)	0.254
Cyclosporine 200 mg/day	1 (6.25%)	0 (0%)	0.429
Mesalazine 2,400 mg/day	0 (0%)	1 (10%)	0.206

cDMARDs, conventional disease modifying anti-rheumatic drugs; NSAIDS, non-steroidal anti-inflammatory drugs.

disease (25.75 ± 18.9 versus 22.6 ± 17.0 months, respectively, $p = 0.62$); Figure 2 graphically represents the persistence in canakinumab treatment of the two patients' groups as a Kaplan–Meier plot. Twenty-four out of the total 26 patients (92.3%) had a minimum follow-up time of 6 months, and 20 (77%) of at least 12 months, as also reported in Figure 3A. The chronic-articular disease pattern affected 3 out of the 6 patients not reaching a 12-month follow-up period.

Treatment effectiveness

Complete response was observed in 18/26 (69.2%) cases at 3-month assessment, 21/24 (87.5%) cases at 6-month assessment, 19/20 cases at 12-month evaluation and 25/26 (92.3%) cases at the last assessment.

As a whole, 16 disease flares were observed in 9 patients during the follow-up period (638 months of observation), corresponding to 0.012 flares/patient/year; 6/9 patients with flares were characterized by a systemic disease course and 3/9 patients showed a chronic disease course, with no differences between groups ($p = 0.701$).

Treatment discontinuation was observed in 4 (12.5%) patients due to long-term remission (2 patients with the systemic Still's disease), in one patient with the chronic-articular type due to lack of efficacy and in 1 case owing to a scheduled pregnancy. Figure 3B shows the distribution of patients with no complete response according to the clinical course.

Figure 4 shows the frequency of clinical manifestations at the start of canakinumab and at the 3-, 6-, and 12 month and last visit.

Clinimetric changes during treatment

The median Pouchot score was 3.0 (IQR = 4.0) at the start of the treatment, 0.0 (IQR = 1) at the 3-month assessment, 0.0 (IQR = 1) at the 6-month assessment, and 0.0 (IQR = 0.0) at the last visit ($p < 0.0001$). No statistical differences were observed in the decrease of Pouchot score at the 3-month visit, the 12 month-visit and at the last assessment according with the disease course ($p = 0.06$, $p = 0.17$, $p = 0.17$, respectively). Figure 5 describes the amount of the Pouchot score at the different time-points.

Arthritis was described in 14 (53.8%) patients, 5 with the chronic-articular course and 9 with the systemic course ($p = 0.76$). Two patients were affected by monoarthritis, 8 patients with oligoarthritis, and 4 patients with polyarthritis, with no statistically significant difference according to disease course ($p = 0.56$). Figures 6A, B provide details about the total number of tender and swollen joints recorded at the different time points while on canakinumab treatment. No statistically significant differences were observed in the number of tender and swollen joints according to the type of disease course, at each time-point.

The mean DAS28 among patients with active arthritis at the start of canakinumab was 3.65 ± 1.15 at the start of canakinumab, 2.09 ± 0.91 after 3 months, 2.14 ± 1.14 at the 6-month visit, 1.4 ± 0.3 at the 12-month visit, 1.33 ± 0.75 at the last assessment ($p = 0.026$). No statistical differences were observed in the decrease of DAS28 at the 3-month visit, the 12 month-visit and at the last assessment according to the different disease patterns ($p = 0.54$, $p = 0.77$, $p = 0.98$, respectively).

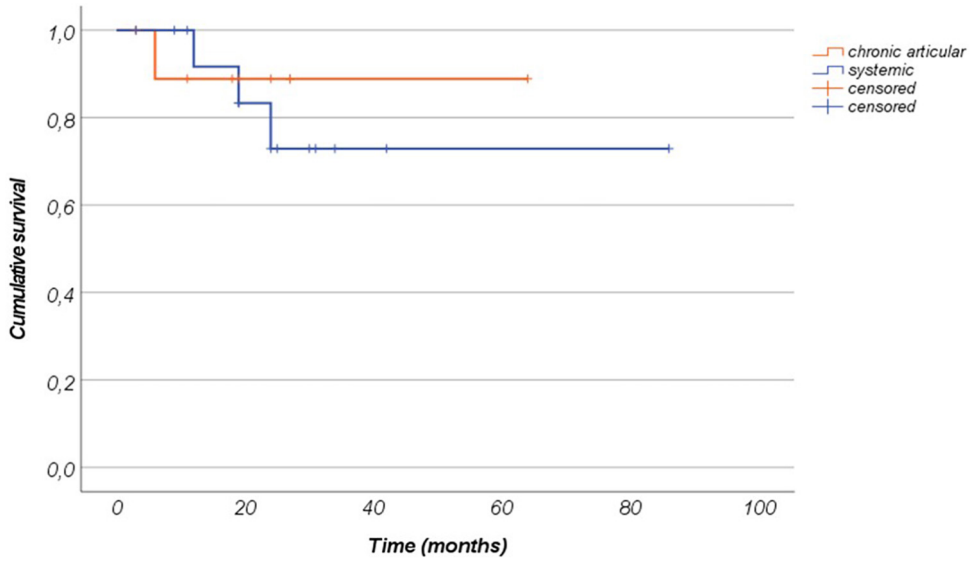

FIGURE 2
Canakinumab retention represented as a Kaplan–Meier plot among patients with the systemic form of Still's disease and patients with the chronic-articular type. Time 0" corresponds to the start of canakinumab and the "event" corresponds to the treatment discontinuation.

Figure 6C shows the mean DAS28 in the two study groups in different timepoints; Figure 7 highlights the overall decrease of the DAS28 in the whole group of patients.

The median PhGA was 40/100 (IQR = 60.5/100) at the start of treatment, 0/100 (IQR = 12.5/100) after 3 months, 0.5/100 (IQR = 11.25/100) at the 6-month assessment, 0/100 (IQR = 0/100) at the 12-month assessment, and 0/100 (IQR = 0/100) at the last assessment. The decrease of PhGA was statistically significant ($p < 0.00001$). No differences were observed in the decrease of PhGA between the systemic and the chronic-articular types at 3-month, 12-month, and last assessments ($p = 0.48$, $p = 0.50$, $p = 0.69$, respectively).

The PGA was 40/100 (IQR = 50/100) at the start of canakinumab, 10/100 (IQR = 19.5/100) after 3 months, 8.5/100 (IQR = 16.25/100) at the 6-month visit; 1/100 (IQR = 10/100) at the 12-month visit, and 0/100 (IQR = 10/100) at the last assessment. The decrease in the PGA was statistically significant ($p = 0.004$). No differences were observed in the decrease of PGA between the systemic and the chronic-articular types at 3-month, 12-month, and last assessments ($p = 0.18$, $p = 0.95$, $p = 0.98$, respectively).

Glucocorticoid and cDMARDs sparing effect

The frequency of patients administered glucocorticoids was 20/26 at the start of treatment, 15/26 after 3 months, 7/24 at 12-month visit and 6/26 at the last assessment ($p = 0.0002$). No statistically significant differences were observed at the 3-month, 6-month, and at the last-assessment according to the different disease patterns ($p = 0.68$, $p = 1.0$, and $p = 1.0$, respectively).

The median glucocorticoids dosage (prednisone or equivalent) was 25 (IQR = 42) mg/day at the start, 5 (IQR = 7.5) mg/day after 3 months, 5 (IQR = 2.5) mg/day at the 6-month assessment, 2.5 (IQR = 2.5) mg/day at the 12-month visit and 2.5 (IQR = 2.5) mg/day at the last assessment ($p < 0.00004$). The overall reduction in glucocorticoid dosage from the start of canakinumab to the last follow-up visit was 93%. No differences were observed in the decrease of glucocorticoid dosage according with the different disease patterns at the 3-month assessment ($p = 0.15$, $p = 0.50$, and $p = 0.50$, respectively). Figure 8A represents the decrease in the number of patients requiring glucocorticoids at the different timepoints of the study and Figure 8B describes the daily glucocorticoids administered in patients already needing combination with steroids.

The cDMARDs were initially used with canakinumab in 14/26 patients; one patient started canakinumab together with methotrexate due to high disease activity. The number of patients administered cDMARDs decreased to 7/26 at 3-months and 6-month assessments, 6/24 at 12-month visit, 5/26 at the last follow-up; the number of patients treated with cDMARDs was significantly reduced at the last assessment if compared to the start of the treatment ($p = 0.044$). No statistically significant differences were observed in the frequency of cDMARDs use according with the different disease patterns pattern ($p = 0.10$, $p = 1.00$, and $p = 1.00$, respectively).

The cumulative methotrexate dosage used in all patients enrolled was 102.5 mg/week at the start of canakinumab (median value: 15 mg/week), 65 mg/week at the 3-month visit

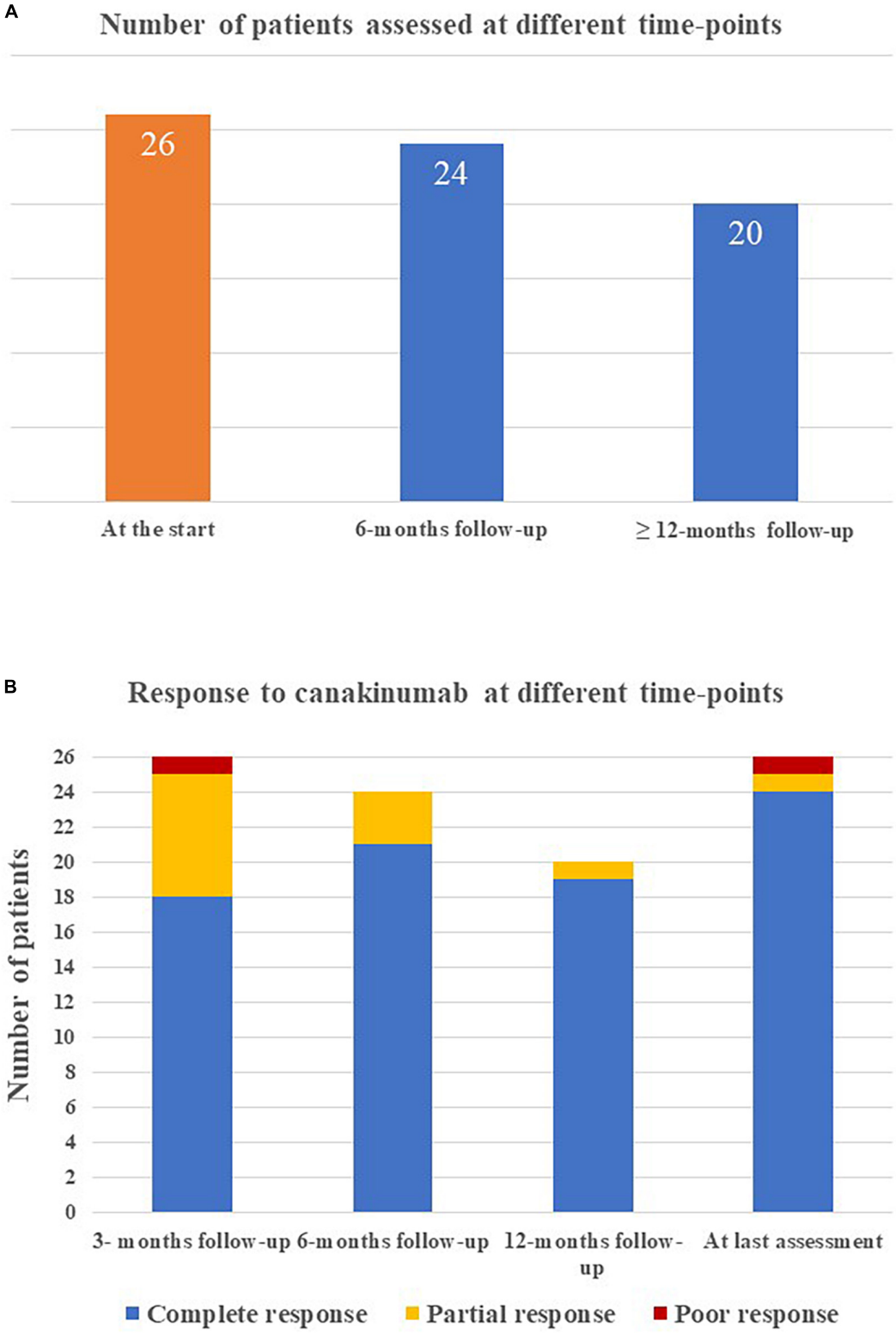

FIGURE 3
Graphical representation of **(A)** the number of patients reaching the different time-points during follow-up while on canakinumab treatment; **(B)** the frequency of complete response, partial response, and poor response in the whole group of patients enrolled at the different tume-points.

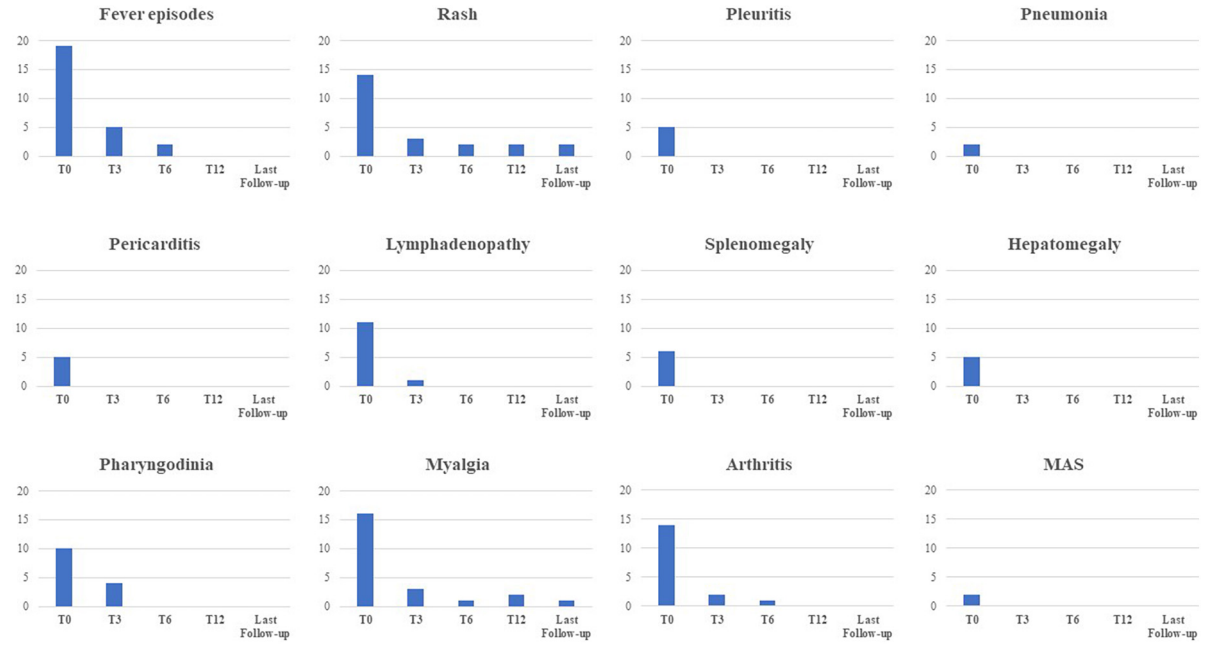

FIGURE 4
Frequency of the main clinical manifestations related to Still's disease at the start of canakinumab and at the following time-points. MAS, macrophage activation syndrome.

(median value: 15 mg/week), 60 mg/week at the 6-month visit (median value: 11.25 mg/week), 35 mg/week at the 12-month visit (median value: 12.5 mg/week), and 30 mg/week at the last assessment (median value: 7.5 mg/week). The overall reduction in methotrexate dosage from the start of canakinumab to the last follow-up visit was statistically significant (p = 0.023) and corresponded to 70.7%.

Figure 8C provides the number of patients administered methotrexate at the start of treatment and at the following visits.

Changes in laboratory inflammatory markers

At the start of treatment, 24/26 patients showed an increase in the ferritin serum levels; 2 of them with systemic pattern presented a ferritin serum value higher than 3,000 mg/dl. At the 3-month assessment, all patients but one had normal serum ferritin levels; this patient showed normal levels at the 6-month assessment. At 6- and 12-month assessments and at the last follow-up visit none had abnormal ferritin serum levels.

The median serum ferritin value was 712 (IQR = 1705) ng/ml at the start of treatment, 95.2 (IQR = 181) ng/ml after 3 months, 75.6 (IQR = 99.75) ng/ml at the 6-month visit, 91.95 (IQR = 149) at the 12-month visit and 63 (IQR = 95) ng/ml at the last assessment. The decrease in the serum ferritin levels was statistically significant (p = 0.0002). No statistically significant differences were observed in the decrease of serum ferritin levels at the 3-month assessment between patients with systemic Still's disease compared with patients with the chronic-articular type (p = 0.34).

The median ESR value was 50.5 (IQR = 25.75) mm/h at the start of canakinumab, 8 (IQR = 13) mm/h after 3 months, 6 (IQR = 12) mm/h at the 6-month visit, 5 (IQR = 7) mm/h at the 12-month visit, and 5 (IQR = 8) mm/h at the last assessment. The decrease of ESR values was statistically significant during the study period ($p < 0.0001$). No differences were observed in the decrease of ESR values at the 3-month assessment based on the disease pattern (p = 0.34).

The median CRP value was 7.16 (IQR = 64.2) mg/dl at the start of canakinumab, 0.28 (IQR = 2.57) mg/dl after 3 months, 0.43 (IQR = 1.4) mg/dl at the 6-month assessment, 0.4 (IQR = 0.85) mg/dl at the 12-month assessment, and 0.36 (IQR = 0.81) mg/dl at the last follow-up visit. The decrease in CRP values was statistically significant ($p < 0.00001$). No differences were observed in the decrease of CRP values at the 3-month assessment according to the different disease patterns (p = 0.48).

Inflammatory markers normalized in all but three patients at the 3-month assessment; no statistical differences were observed in the persistence of increased inflammatory markers between the systemic and the chronic-articular forms of the disease (p = 0.99).

Figure 9 illustrates the median ESR, CRP and ferritin serum values collected in the whole cohort of patients at the different time-points.

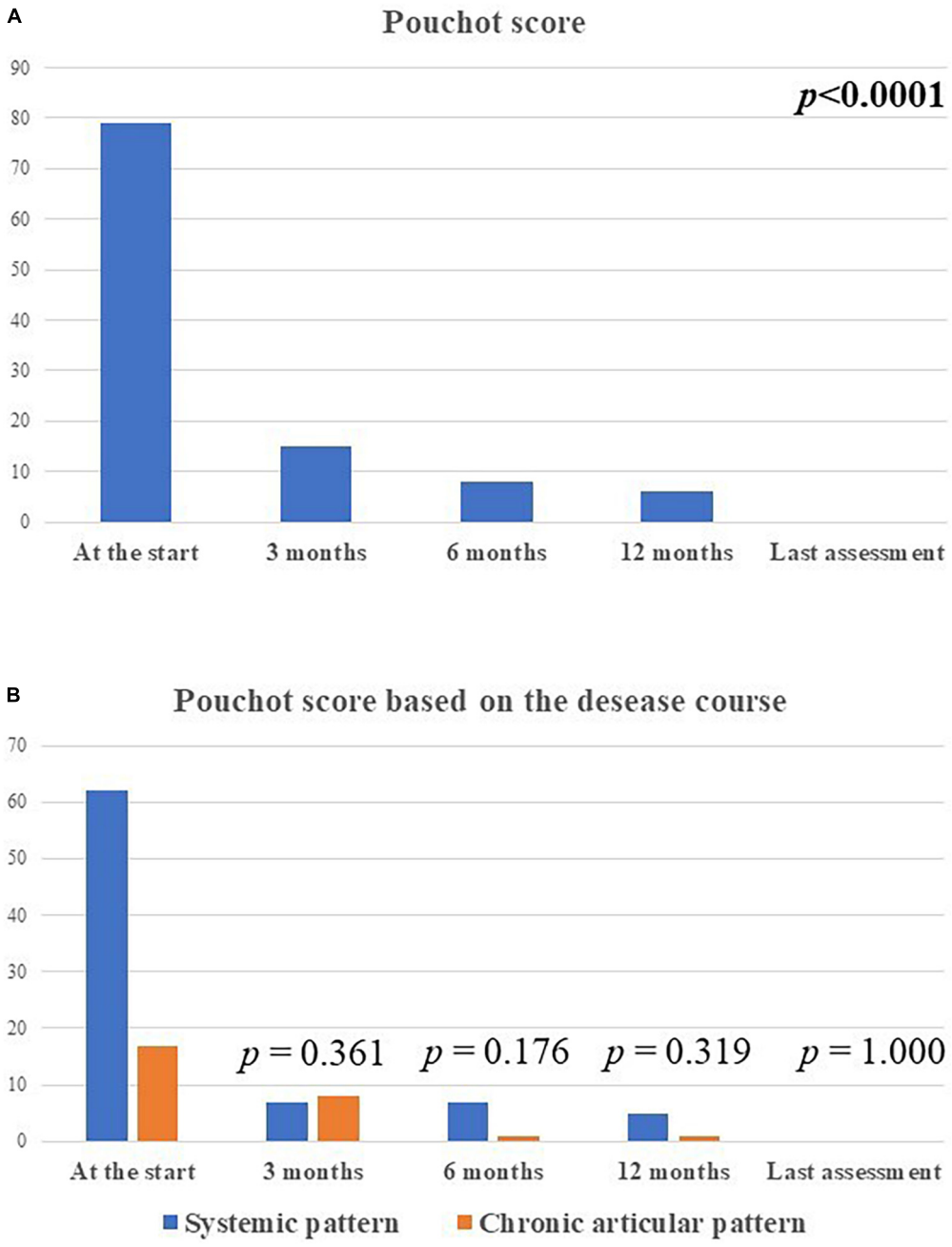

FIGURE 5
The total amount of the modified Pouchot score in the whole group of patients enrolled **(A)** and according with the disease course **(B)** at the different time-points. The total amount of the systemic modified Pouchot score was higher among patients with the systemic Still's disease in relation with the higher systemic involvement in this patients compared to the chronic-articular type.

Regarding other laboratory markers, an increase in transaminases was observed in 10 patients (8 with the systemic pattern) at the start of canakinumab; no patients had abnormal liver function enzymes at the following timepoints. Leukocytosis higher than 15,000 white blood cells/mm^3 was observed in 11 patients (9 with the systemic pattern) at the start of canakinumab and in no patients at the following timepoints.

Safety profile

The following four adverse events were reported during the follow-up period: episodes of dizziness and giddiness in one patient; occurrence of external otitis in one patient; heartburn associated with gastroesophageal regurgitation in one patient; a relapse of concomitant ulcerative colitis in one patient.

FIGURE 6
Detailed information about the treatment outcome relating to joints involvement among the 14 patients with arthritis. In particular, the total number of tender joints **(A)** and swollen joints **(B)** in all patients enrolled, distinguished according with Still's disease course, has been provided. The DAS28 values have also been detailed in the two types of Still's disease **(C)**. *P*-values refer to the differences between the two subgroups of patients in the number of tender joints, swollen joints and DAS28 values at each time-point. The red horizontal line in panel **(C)** indicates the DAS28 threshold below which arthritis may be considered in remission. DAS28, disease activity score based on 28 joints.

Discussion

Inhibition of IL-1 or IL-6 has clearly demonstrated to be effective in controlling clinical and laboratory inflammatory manifestations of Still's disease, with a strong glucocorticoid sparing effect and a tolerable safety profile (21, 24, 25). Despite the lack of internationally shared treatment guidelines, the current approach supports the use of IL-1 inhibitors in patients with Still's disease (14, 16), while IL-6 antagonists may represent an effective treatment choice in refractory cases with persistent inflammatory joint involvement (15, 17). Different cytokine imbalances identified based on the different patterns of the disease (systemic versus chronic-articular) could suggest different molecular targets when establishing a personalized treatment approach in Still's disease (26, 27). Looking at literature, this could partially explain why the frequency of non-responders to IL-1 inhibition has been found higher among patients with chronic-articular Still's disease. Also, the systemic form of the disease and the absence of arthritis (or a lower number of arthritic joints) have been associated with a substantial response to IL-1 inhibition; conversely, the chronic-articular form and the presence of arthritis have been associated to a substantial response to IL-6 inhibition (15). Despite these premises, in our study the frequency of complete response to canakinumab was remarkably high disregarding the disease course. In particular, no statistically significant differences were observed when considering the overall frequency of complete response (with full control of clinical and laboratory manifestations), the retention in canakinumab therapy, the decrease of articular disease, and the glucocorticoid and cDMARD sparing effects. In the same way, the systemic Pouchot score, reflecting the typical Still's disease manifestations, decreased in a significant way in the overall group and disregarding the type of Still's disease.

Noteworthy, despite IL-1 inhibition has been supposed to be less suitable in patients with a prominent joint involvement (18, 19, 28, 29), articular items have proved to be responsive in the overall group, disregarding the type of disease course. Looking at literature, polyarticular involvement was observed to be a negative predictor for clinical response to IL-1 inhibition, especially when considering the persistence of arthritis (19, 28). Actually, the presence of polyarthritis could be associated to a loss of systemic inflammatory activity in favor of an autoimmune phenotype (29). In our cohort of patients, polyarticular forms are equally distributed in the two study subgroups. Therefore, the present study adds to previous experiences supporting the efficacy of canakinumab on DAS28 decrease (20, 30) and also highlights the absence of substantial differences between the systemic form and the chronic-articular form in the response of joint inflammation. In particular, DAS28 values, the number of tender and swollen joints, the PhGA and PGA proved to be overlapping in the two groups during the whole study period. However, we also point out the slower response of joint items in patients with the chronic-articular course: as observed in **Figure 6**, the number of arthritic joints and DAS28 values were significantly higher in the chronic-articular group at the 3-month assessment. Similarly, articular disease remission (DAS28 < 2.6) was reached by the systemic group as soon as the 3-month assessment, while the chronic-articular group reached disease remission starting from the 6-month visit. Despite this slower effect in the chronic-articular group, the control on joint inflammatory

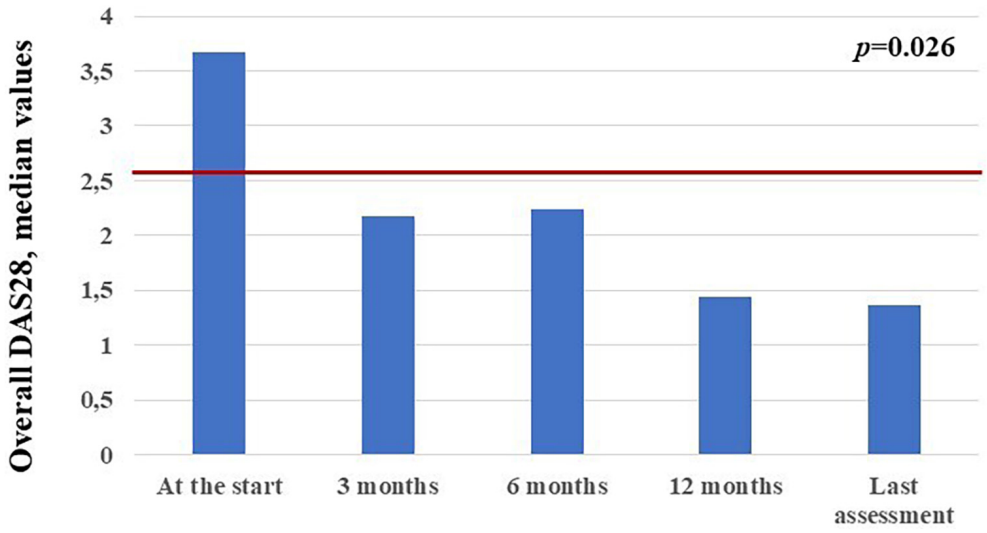

FIGURE 7
Median DAS28 values observed in the 14 patients with arthritis at the different time points. The red horizontal line indicates the DAS28 threshold below which arthritis may be considered in remission.

manifestations resulted to be overlapping with those observed in the systemic group in the subsequent follow-up. At further support of this, no significant differences were observed in the decrease of DAS28 between groups, straightening the superimposable response of joint involvement disregarding disease pattern. This should induce physicians to wait for the 6-month assessment before suspending canakinumab due to the only persistence of joint inflammation in chronic-articular disease.

The remarkable results in both types of Still's course could be explained by the early canakinumab introduction. In this regard, the concept of a "window of opportunity," namely, as the period of time after the disease onset during which starting IL-1 inhibition may be more effective, has been proposed for patients with Still's disease, at least for patients with pediatric onset (19, 31–33). Saccomanno et al. identified a disease duration $\leq$ 3.9 years as cut-off beneath which patients with sJIA were more likely completely responsive to the IL-1 receptor antagonist anakinra (33). Horneff et al. also observed that patients treated with IL-1 inhibitors within 12 months from disease onset achieved clinical remission more frequently than patients starting the treatment thereafter (34). A further experience assessing any window of opportunity in 141 AOSD patients treated with anakinra identified a good effectiveness disregarding the time between disease onset and the start of IL-1 inhibition. Nevertheless, a faster effectiveness of anakinra in articular manifestations was observed in patients undergoing an early IL-1 inhibition (22). These results flanked those provided by Cavalli et al. about the dramatic clinical improvement on arthritis in patients with Still's disease undergoing canakinumab as a first-line treatment (35). Supported by these several evidences, we can speculate that the excellent results obtained with joint indexes in both systemic and chronic-articular still's disease could be related to the early canakinumab administration. This topic should be addressed by future targeted studies.

Beyond the effectiveness on clinical manifestations, canakinumab allowed a complete control of laboratory inflammatory parameters irrespective of the type of disease course, thus confirming a previous similar finding (28). We evaluated this endpoint only between the time at canakinumab introduction and the 3-month assessment. Actually, laboratory inflammatory markers usually reduce dramatically in the first months of canakinumab treatment, remaining substantially reduced thereafter. For this reason, the evaluation of canakinumab effectiveness on laboratory features between groups was more sensible and reasonable during this time.

The excellent results on clinical and laboratory manifestations were obtained despite the significant sparing of glucocorticoids both in terms of patients requiring daily steroids and in terms of daily dosage among patients still needing this concomitant treatment. In the same way a slow but steady reduction was observed in the frequency of use and in the weekly methotrexate dosage. This is a central point highlighting the possibility to decrease the immunosuppressant load in patients with Still's disease, which is essential to reduce adverse events, previously described more frequent in patients administered with IL-1 antagonists and a concomitant cDMARD (36).

We have meshed together adult-onset and pediatric Still's disease, as they have been identified as the same disease

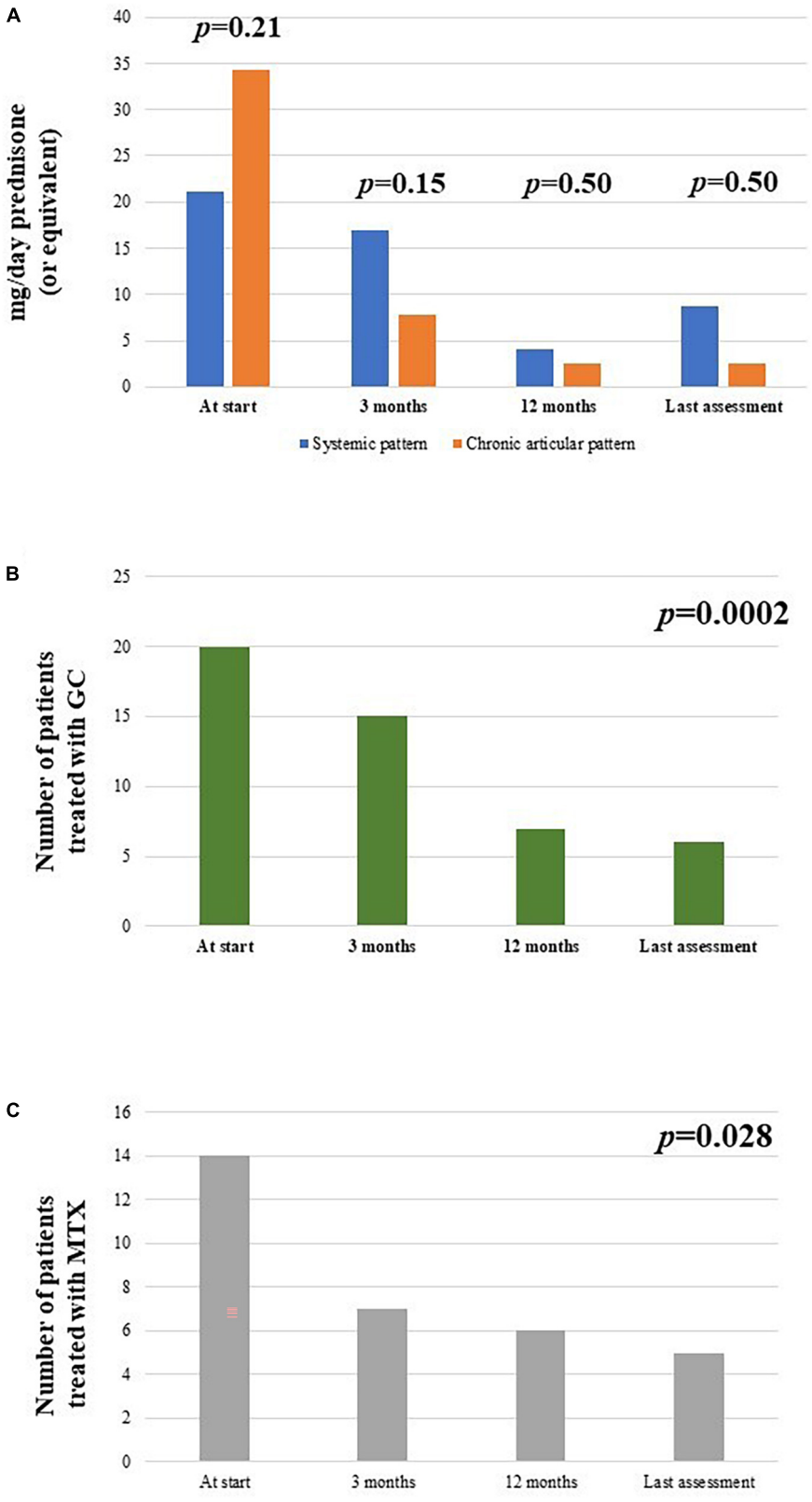

FIGURE 8
Description of **(A)** the median glucocorticoid (prednisone or equivalent) intake as mg/day at the start of canakinumab and at each follow-up visit, distinguishing according to the different disease pattern (systemic versus chronic-articular); **(B)** the total number of patients administered glucocorticoids (GC) at the different timepoints; **(C)** the total number of patients administered methotrexate (MTX) at the different timepoints.

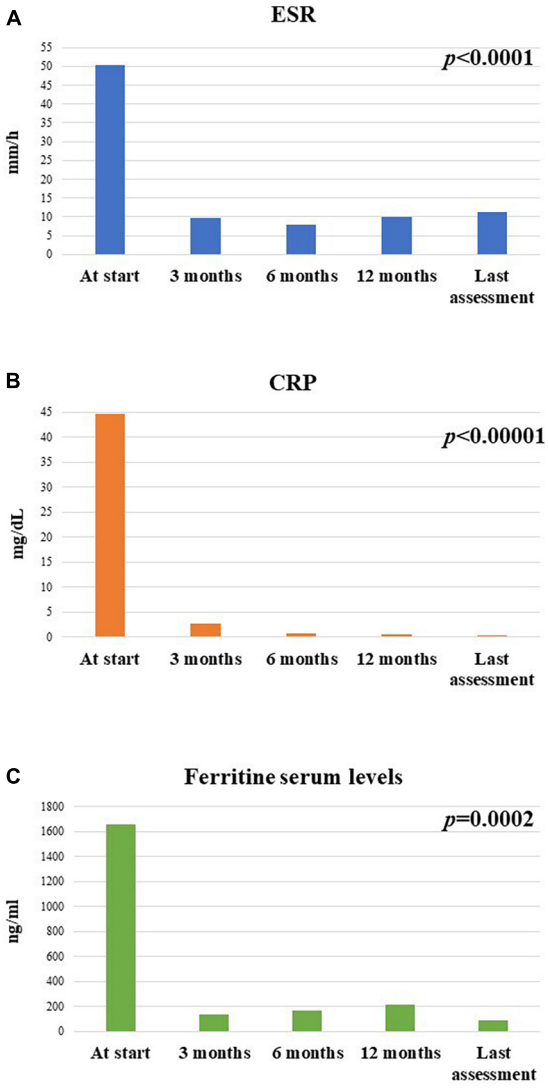

FIGURE 9
Mean **(A)** erythrocyte sedimentation rate (ESR), **(B)** C-reactive protein (CRP), and **(C)** ferritin serum levels at the different timepoints in the group of 26 patients enrolled in the study.

arising in different ages (2, 3). At support of this, a recent Bayesian and population model-based analysis has pointed out a similarity of clinical outcomes in patients with sJIA and AOSD treated with canakinumab (37). Other clinical experiences have also supported the concept of a continuum of Still's disease irrespective of the age at disease onset, with no differences in canakinumab response between sJIA and AOSD regarding the frequency of complete response and the relapse rates (38, 39). On this basis, we also performed a unique data analysis disregarding the age at disease onset.

The limits of this study consist of those that typically affect retrospective studies. Despite being drawn from an international registry (23), the number of patients involved in this study remains not particularly large. This is related to the rarity of Still's disease and the reduced propensity to use canakinumab as first-line biotechnological agent because of healthcare spending issues. Nevertheless, this is a real-world study performed on a small slice of hard-to-enroll patients to address an already unmet need for everyday clinical practice.

In conclusion, canakinumab used for Still's disease has proved to be effective in controlling both clinical and laboratory manifestations disregarding the type of disease course when used as first-line biotechnological agent. Canakinumab could show a slower efficacy on joint manifestations in chronic-articular Still's disease; however, articular disease control is equally obtained in both groups in the long term and the initial persistence of isolated arthritis should not induce the treatment withdrawal in chronic-articular patients. These excellent results might have been further enhanced by the early start of IL-1 inhibition and should draw attention to the concept of window of opportunity, especially in chronic-articular Still's disease. Targeted studies should be conducted in the near future to better clarify this concept.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The study has been approved by the Ethics Committee of Azienda Ospedaliero Universitaria Senese, Siena, Italy (AIDA Project; Ref. N. 14951) as part of the AIDA Program. Written informed consent/assent was obtained from all patients at the time of the recruitment into the AIDA Registry for Still's disease. Written informed consent from the patients or legal guardian/next of kin was obtained to participate in this study, in accordance with the National and European legislation and the institutional requirements.

Author contributions

AV and VC wrote the first draft of the manuscript and conceived and designed the study. AV, VC, MM, GL, GE, JS, FL, PR, EB, GC, IM, CG, FC, LD, CC, RG, AB, KL, BF, FI, and LC were included based on the number of AOSD patients treated with canakinumab recruited in the AIDA Registries by 1st September 2022. CF, AT, GR, IA, PS, EW-S, and RP were included in the authorship as investigators from the top contributor centers for any of the other eight AIDA Registries.

AB was the bioengineer involved in the technical management of the platform and registries. LC took care of the final revision of the manuscript and accounted for AIDA Registries Coordinator. All authors contributed to the article and approved the submitted version.

Conflict of interest

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Axial spondyloarthritis in patients with recurrent fever attacks: data from the AIDA network registry for undifferentiated autoInflammatory diseases (USAIDs)

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Background: Despite the recent advances in the field of autoinflammatory diseases, most patients with recurrent fever episodes do not have any defined diagnosis. The present study aims at describing a cohort of patients suffering from apparently unexplained recurrent fever, in whom non-radiographic axial spondylarthritis (SpA) represented the unique diagnosis identified after a complete clinical and radiologic assessment.

Materials and methods: Patients' data were obtained from the international registry on Undifferentiated Systemic AutoInflammatory Diseases (USAIDs) developed by the AutoInflammatory Disease Alliance (AIDA) network.

Results: A total of 54 patients with recurrent fever episodes were also affected by non-radiographic axial SpA according to the international classification criteria. SpA was diagnosed after the start of fever episodes in all cases; the mean age at the diagnosis of axial SpA was 39.9±14.8years with a diagnostic delay of 9.3years. The highest body temperature reached during flares was 42°C, with a mean temperature of 38.8±1.1°C. The most frequent manifestations associated to fever were: arthralgia in 33 (61.1%) cases, myalgia in 24 (44.4%) cases, arthritis in 22 (40.7%) cases, headache in 15 (27.8%) cases, diarrhea in 14 (25.9%) cases, abdominal pain in 13 (24.1%) cases, and skin rash in 12 (22.1%) cases. Twenty-four (44.4%) patients have taken daily or on-demand non-steroidal anti-inflammatory drugs (NSAIDs) and 31 (57.4%) patients have been treated with daily or on demand oral glucocorticoids. Colchicine was used in 28 (51.8%) patients, while other conventional disease modifying anti-rheumatic drugs (cDMARDs) were employed in 28 (51.8%) patients. Forty (74.1%) patients underwent anti-tumor necrosis factor (TNF) agents and 11 (20.4%) were treated with interleukin (IL)-1 inhibitors. The response to TNF inhibitors on recurrent fever episodes appeared more effective than that observed with anti-IL-1 agents; colchicine and other cDMARDs were more useful when combined with biotechnological agents.

Conclusion: Signs and symptoms referring to axial SpA should be inquired in patients with apparently unexplained recurrent fever episodes. The specific treatment for axial SpA may lead to a remarkable improvement in the severity and/or frequency of fever episodes in patients with unexplained fevers and concomitant axial SpA.

KEYWORDS

arthritis, autoinflammatory diseases, diagnosis, outcome, SpA, treatment

1. Introduction

Fever is an active, yet unspecific response of the innate immune system aimed at neutralizing the harmful cause leading to cytokines release. In addition to infectious and neoplastic diseases, recurrent fever episodes may associate to autoimmune or autoinflammatory disorders, such as hereditary periodic fever syndromes, Still's disease, Schnitzler syndrome, or PFAPA (Periodic Fever, Aphthous stomatitis, Pharyngitis and cervical Adenitis) syndrome (1, 2). In addition to fever, autoinflammatory diseases manifest with a protean spectrum of inflammatory manifestations especially involving joints, the eye, the skin, and serosal membranes (3, 4).

Patients suffering from recurrent fever episodes need an accurate differential diagnosis including all possible causes of inflammation. This process is usually not straightforward and requires careful evaluation of the clinical history and manifestations, followed by a full history-driven laboratory and radiological workup (2). Among the large number of systemic diseases capable of manifesting with systemic inflammation and fever, arthritic conditions should also be considered (5, 6). In this perspective, the presence of fever has been also reported in patients with spondylarthritis (SpA), while Byun et al. have recently shown that fever may account for the initial disease manifestation in various SpA subtypes (7).

Axial SpA is the second most prevalent form of chronic inflammatory arthritis, with an estimated prevalence of 0.5%–1.5% in the Caucasian population (8, 9). It is characterized by inflammation of the spine and sacroiliac joints, with or without peripheral articular involvement. Extra-articular sites may be also involved by inflammation, with the eye, the gut, and the skin especially interested (10). The role of innate immunity in the development of axial SpA has been recently put under the magnifying glass and an autoinflammatory pathogenesis of the disease has consequently been supposed. In this regard, the role of the NLRP3 inflammasome, an intracellular multiprotein

complex primarily involved in many autoinflammatory disorders, has been increasingly implicated in patients with SpA. Special interest has been raised by the identification of a specific pattern of SpA associated with gene mutations capable of inducing inflammasome dysfunction (11, 12). Among others, mutations affecting the *MEFV* gene, which is responsible for familial Mediterranean fever (FMF) and encodes the protein pyrin, an essential regulator of the NLRP3 inflammasome, have been associated to an increased frequency of SpA, disregarding the HLA-B27 haplotype (13, 14).

Based on this preliminary evidence, we inquired the presence of inflammatory low back pain and/or axial SpA signs at physical examination among patients with recurrent fever episodes. Tehus, the present study aims at describing a cohort of patients suffering from apparently unexplained recurrent fever, in whom axial SpA was diagnosed according to the Assessment of SpondyloArthritis international Society (ASAS) criteria during the diagnostic workup (15).

2. Materials and methods

The patients were consecutively identified and enrolled from April 2021 to November 2022. Data were collected in the International AIDA (AutoInflammatory Disease Alliance) network registry for Undifferentiated Systemic AutoInflammatory Diseases (USAIDs) (16). This registry represents an observational study collecting data obtained from patients managed and treated according to the best standard of care, based on patients' history, and tailored on clinical and laboratory manifestations.

All patients were newly diagnosed with non-radiographic axial SpA during the diagnostic workflow related to undiagnosed fever (at least one febrile episode was evaluated and confirmed by physicians). ASAS criteria (imaging arm) were fulfilled in all cases (15). In particular, all subjects referred inflammatory low back pain and other extra-articular affections ascribable to SpA. A subsequent magnetic resonance imaging of sacroiliac joints confirmed the presence of radiologic signs of axial SpA (15). Enteropathic SpA patients were diagnosed when an inflammatory bowel disease coexisted with arthritis. Reactive SpA was excluded, as no patients presented gastrointestinal and/or urinary infections in the 6 months prior of the onset of symptoms. Patients <16 year-old were also included.

Disease duration was defined as the time between the onset of articular symptoms and the diagnosis of axial SpA. Infections, autoimmune and neoplastic diseases were excluded in all patients after a complete laboratory and instrumental assessment. Next generation sequencing was performed to search for any genetic variant linked to the currently known monogenic autoinflammatory diseases. Among others, *NLRP3*, *TNFRSF1A*, *MEFV*, *MVK* and *NOD2* genes were investigated in all cases. Patients did not have to fulfil any criteria for genetically determined FMF or any multifactorial autoinflammatory diseases, including PFAPA syndrome, Behçet's disease, Schnitzler syndrome, Castleman disease, Still's disease (17–27). Laboratory findings, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and human leukocyte antigen (HLA)-B27 test, were collected at the time of diagnosis and at the last assessment.

The objective of this paper is to describe a large cohort of patients diagnosed with axial SpA during the diagnostic process related to otherwise unexplained recurrent fever episodes.

The aim of this paper is to assess the demographic, clinical, laboratory and therapeutic features of patients with axial SpA and recurrent fever episodes. In particular, clinical manifestations accompanying fever and response to different treatment approaches were investigated.

Regarding treatment outcomes, *complete response* was defined as the resolution of all disease-related clinical manifestations, with decrease to normal values of all laboratory inflammatory parameters. *Partial response* was defined as persistence of clinical manifestations with remarkable decrease in their severity, as reported by patients, with inflammatory laboratory parameters normalized or only slightly increased. *Failure* was meant as persistence of fever-associated clinical manifestations and/or no decrease of laboratory inflammatory markers. When available, axial SpA clinical activity was assessed with Bath Ankylosing Spondylitis Funcional Index (BASFI) and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) among patients treated with TNF inhibitors (28, 29). The terms *adverse event* referred to any untoward medical occurrence observed after the exposure to each treatment taken by the patients due to ax-SpA and not necessarily caused by the treatment.

All patients or parents or legal guardian signed the informed consent to participate to this project. The study has been approved by the Ethics Committee of Azienda Ospedaliero Universitaria Senese, Siena, Italy (AIDA Project; Ref. N. 14'951) as part of the AIDA Program. The study protocol conformed to the tenets of the Declaration of Helsinki.

Regarding statistical computations, descriptive statistics included mean, standard deviation (SD), mode, range, median and interquartile range (IQR), as required. Data distribution was evaluated by the Shapiro–Wilk test. Pairwise computations of quantitative data were performed with student *t*-test or Wilcoxon test, according to data distribution; pairwise computations of qualitative data were performed by Fisher exact test with 2×2 contingency tables. Significance level was set at 95% (p-value <0.05); p-values were two-tailed. Statistical analysis was performed through the Stata 17/MP2 software.

3. Results

A total of 54 patients affected by non-radiographic axial SpA referred to our outclinic services because of recurrent fever episodes, between April 2021 and November 2022. None of the patients suffered from reactive axial SpA; all patients fulfilled the ASAS criteria (15).

3.1. Demographic features

The enrolled patients were aged 41.8 ± 13.3 years (median: 41.3 years; mode: 50 50.5 54.4 years; range: 20.3–68.4 years), and were mainly females (n = 36, 66.7%). All patients were Caucasian. Recurrent fever episodes firstly occurred during childhood or adolescence (<16 years) in 14 (25.9%) patients, with a mean age at

TABLE 1 List of comorbidities observed in the cohort of patients enrolled in present study; percentages included in the table refer to the total number of patients with at least one comorbidity.

Comorbidity	*n* (%)
Chronic gastritis	7 (18.4)
Hypertension	4 (10.5)
Bronchial asthma	4 (10.5)
Autoimmune thyroiditis	3 (7.9)
Diverticulosis	3 (7.9)
Steatohepatitis	2 (5.3)
Atopic eczema	2 (5.3)
Allergic rhinitis	2 (5.3)
Favism	2 (5.3)
Healthy carrier of thalassemia	2 (5.3)
Coeliac disease	2 (5.3)
Osteoporosis	2 (5.3)
Adenomyosis	2 (5.3)
Hypercholesterolaemia	1 (2.6)
Lymphangioma	1 (2.6)
Pulmonary emphysema	1 (2.6)
Von Willebrand disease type 1	1 (2.6)
Hepatic angioma	1 (2.6)
Vitiligo	1 (2.6)
Primary biliary cholangitis	1 (2.6)
Caroli disease	1 (2.6)
Papillary thyroid carcinoma	1 (2.6)
Basal-cell carcinoma of nose	1 (2.6)
Childhood rheumatic disease	1 (2.6)
Endometriosis	1 (2.6)
Arnold chiari malformation	1 (2.6)
Sensorineural hearing loss	1 (2.6)
Autoimmune pancreatitis	1 (2.6)
Leukocytoclastic vasculitis	1 (2.6)
Disorder of adrenal gland	1 (2.6)
Meniere's disease	1 (2.6)
Lichen sclerosus et atrophicus	1 (2.6)
Thrombophlebitis	1 (2.6)
Erythema nodosum	1 (2.6)
Ocular hypertension	1 (2.6)
Chronic renal failure	1 (2.6)
Epilepsy	1 (2.6)
Recurrent perimyocarditis	1 (2.6)
IgA Nephropathy	1 (2.6)
Urticarial rash	1 (2.6)
Angioedema	1 (2.6)
Cerebrovascular disease	1 (2.6)
Gout	1 (2.6)

onset of 10.6 ± 4.6 years (median: 12 years; mode: 12 years; range: 0.8–15 years).

SpA was diagnosed after the start of fever episodes in all cases; the mean age at the diagnosis of axial SpA (median: 42 years; mode: 42 50 50.5 55.6 years; range: 13.8–68.4 years) with a diagnostic delay of 9.3 years from the start of articular symptoms and a disease duration of 9.7 ± 10.7 years. Five (9.3%) patients carried HLA-B27. Thirty-eight (70.4%) patients had at least one comorbidity, as described in Table 1.

A genetic assessment was performed to rule out any variant affecting genes responsible for known monogenic autoinflammatory diseases. No pathogenic or likely pathogenic mutation was identified.

3.2. Features of fever attacks and triggers

The highest body temperature reached during flares was 42°C, with a mean temperature of 38.8 ± 1.1°C in the whole cohort. The median frequency of fever episodes at the time of the enrolment was 6 episodes per year. Figure 1A illustrates the distribution of patients according to the highest temperature reached during flares and the duration of fever episodes in days. Figure 1B provides information about the duration of fever episodes.

The clinical manifestations accompanying fever are described in Table 2. Peripheral arthritis was observed in 22 patients in the form of monoarthritis ($n = 3$), oligoarthritis ($n = 7$), and polyarthritis ($n = 12$). Intraocular inflammation was reported in 7 (13%) patients; 5 (9.3%) patients presented psoriasis and none of the other patients referred a positive family history for psoriasis; 3 (5.5%) patients suffered from intestinal inflammation. In detail, 2 patients were affected by undifferentiated intestinal inflammation and the last one suffered from Crohn's disease.

Triggers inducing relapses were reported in 17 (31.5%) patients at the time of the diagnosis: psychological stress in 11 patients, physical activity in 8 subjects, generalised cold exposure in 7 patients, menstrual phase in 7 females, and generalised exposure to warm temperatures in 4 patients. One patient relapsed after SARS-CoV-2 vaccination.

Laboratory investigations recorded during an intercritic period before starting any specific treatment with conventional and or biotechnological disease modifying anti-rheumatic drugs (cDMARDs and/or bDMARDs) showed increased inflammatory markers (CRP and/or ESR) in 30 (55.5%) patients and leucocytosis in 9 (16.6%) subjects.

3.3. Therapeutic approaches

Regarding treatment, 24 (44.4%) patients have taken daily or on-demand non-steroidal anti-inflammatory drugs (NSAIDs) and 31 (57.4%) patients have been treated with daily or on demand oral glucocorticoids. Therapy with colchicine up to 1 mg/day was attempted in 28 (51.8%) patients. Colchicine was discontinued in 17 (60.7%) patients due to: adverse events ($n = 5$, 29.4%), especially diarrhoea ($n = 4$), abdominal and/or pelvic pain ($n = 3$), nausea ($n = 2$) and exacerbation of hemorrhoids inflammation ($n = 1$); lack of efficacy

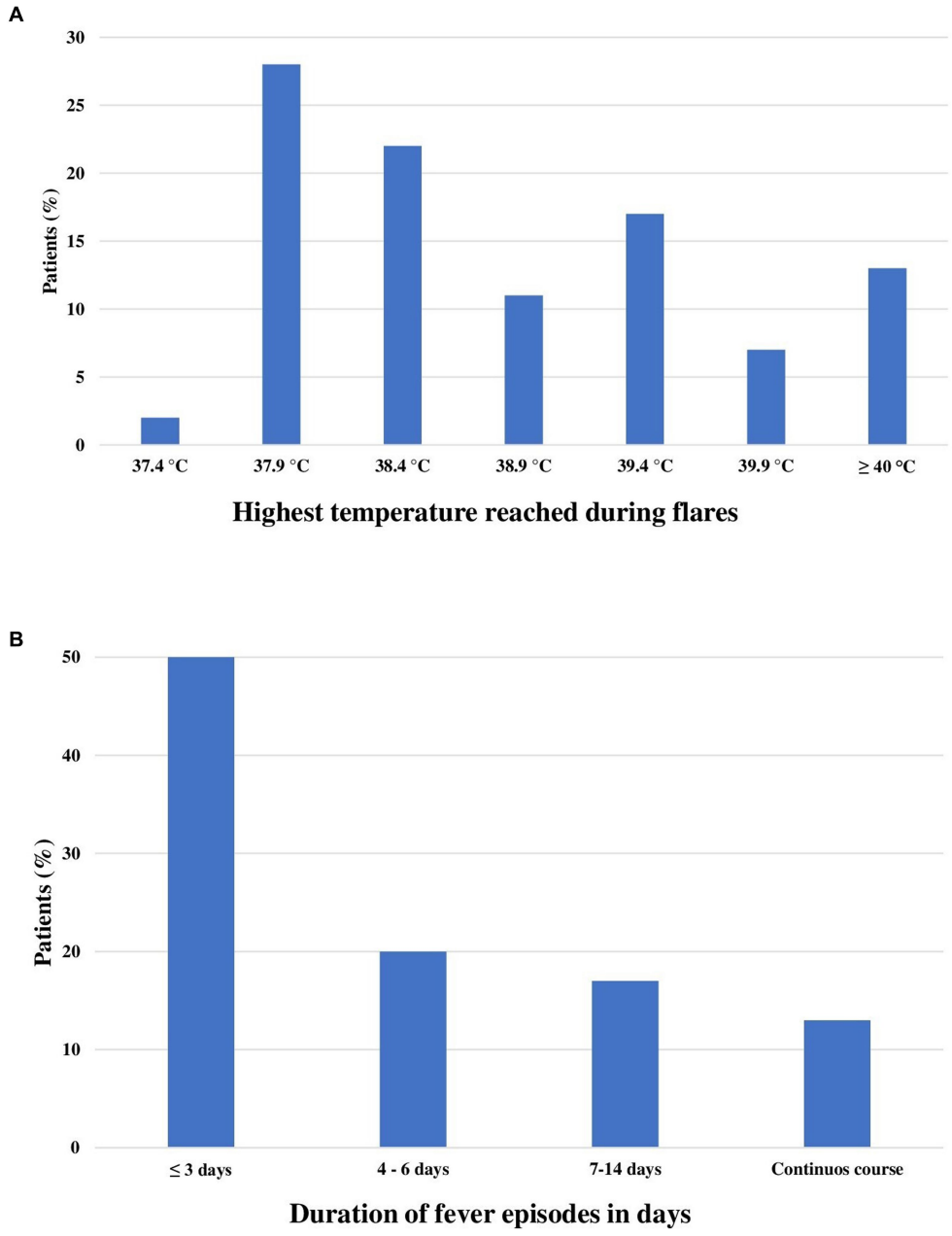

FIGURE 1
Bar charts describe the highest temperature observed during flares **(A)** and the mean duration of fever episodes **(B)** among the 54 patients enrolled.

($n = 5$, 29.4%); and loss of efficacy ($n = 5$, 29.4%). Two further patients (11.8%) stopped colchicine after the introduction of the biotechnological treatment. Twenty-eight (51.9%) patients were treated with cDMARDs as follow: 16 (29.6%) with methotrexate, 15 (27.8%) with sulfasalazine, 6 (11.1%) with hydroxychloroquine, 4 (7.4%) patients with leflunomide, 1 (1.8%) with mesalazine and 1 (1.8%) with azathioprine. Figures 2A,B provides details about the response to colchicine and to cDMARDs. Four patients discontinued cDMARDs due to adverse events as follow: localized skin reaction to methotrexate ($n = 1$); severe nausea after sulfasalazine introduction ($n = 1$); epigastric pain during sulfasalazine ($n = 1$); diarrhea during leflunomide treatment ($n = 1$).

Adalimumab was the most widely biotechnological agent employed ($n = 28$, 51.8%), followed by anakinra and canakinumab used in 9 (16.6%) and 8 (14.8%) patients respectively; intravenous infliximab was employed in 5 (9.2%) patients, etanercept in 4 (7.4%) patients, secukinumab in 3 (5.6%) cases, golimumab in 2 cases (3.7%), tocilizumab in 1 subject (1.8%), and certolizumab pegol in 1 subject (1.8%). The therapy with the Janus kinase (JAK) inhibitor Tofacitinib was used in 2 (3.7%) patients.

A total of 40 (74.1%) patients performed a treatment with anti-TNF agents; treatment duration was 7.0 ± 6.6 months (median value: 3 months). A minimum follow-up of three months was available in 32 patients. Twelve (30%) patients were treated with glucocorticoids at the dosage of 9.6 ± 6.1 mg/day (prednisone or equivalent) at the start of anti-TNF treatment; this dosage decreased to 6.25 ± 2.5 mg/day at the last assessment ($p = 0.01$). Figure 2C highlights the response to

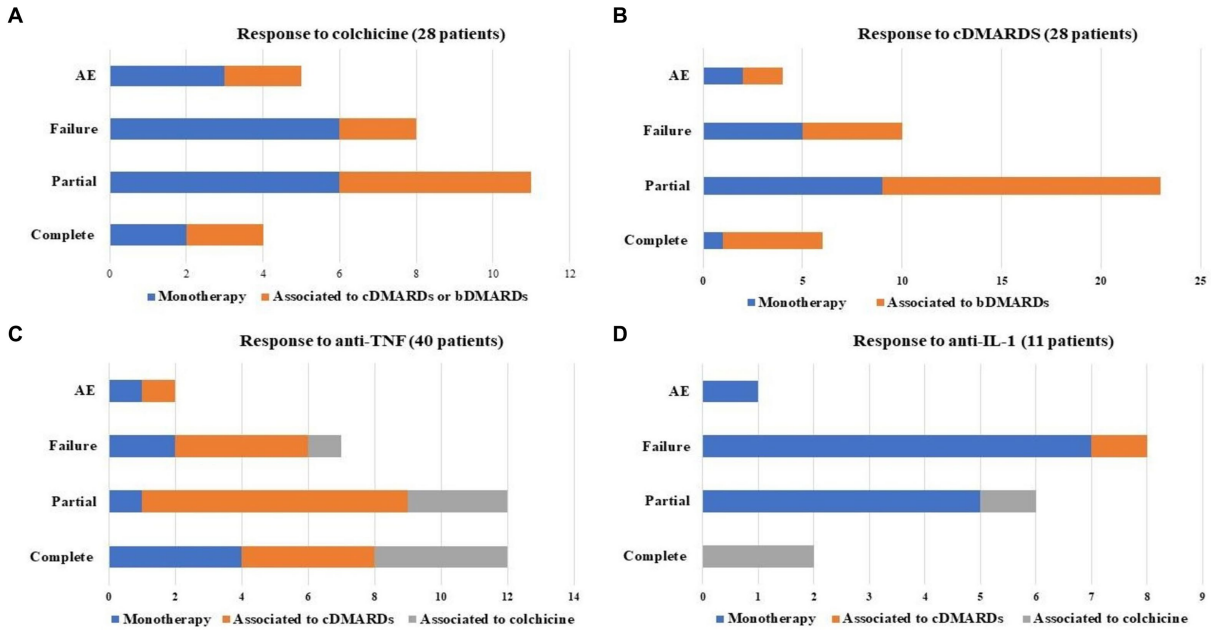

FIGURE 2
Response to different treatments performed by patients included in the study; monotherapy and combination treatment with conventional or biotechnological disease modifying anti-rheumatic drugs (cDMARDs and bDMARDs, respectively) or colchicine were pointed out. The figure specifically describes treatment with colchicine **(A)**, cDMARDs **(B)**, anti-tumor necrosis factor (TNF) **(C)**, and anti-interleukin (IL)-1 **(D)**.

TABLE 2 Frequency of most common clinical manifestations reported during fever episodes.

Clinical manifestations	Number of patients (%)
Arthralgia	33 (61.1)
Myalgia	24 (44.4)
Arthritis	22 (40.7)
Headache	15 (27.8)
Diarrhea	14 (25.9)
Abdominal pain	13 (24.1)
Skin rash	12 (22.2)
Oral aphthosis	10 (18.5)
Lymphoadenitis	10 (18.5)
Pharyngitis	9 (16.7)
Thoracic pain	7 (12.9)
Genital aphthosis	3 (5.5)
Splenomegaly	3 (5.5)
Vomiting	3 (5.5)

anti-TNF agents. Generalised skin reactions accounted for the adverse events leading to stop the anti-TNF treatment in two cases (treated with adalimumab and infliximab). Figure 3A provides the frequency of fever, arthritis, arthralgia, skin manifestations and abdominal pain at the start and at the last visit while on treatment with TNF inhibitors (last visit available in 32 patients). The BASDAI and BASFI at the beginning of anti-TNF therapy were 6.2 ± 2.4 and 4.3 ± 2.0, respectively; at the last assessment they were 4.2 ± 2.1 and 3.0 ± 2.5. The decrease of BASDAI ($p = 0.7$) and BASFI ($p = 0.24$) scores did not reach statistical significance.

Thirty out of 40 (75%) patients treated with anti-TNF agents showed increased ESR and/or CRP at the start of the treatment; the number of patients with increased inflammatory markers was 17 out of 32 (53.1%) patients at the last assessment ($p = 0.09$). The median CRP was 0.48 (IQR = 2.46) mg/dL at the beginning of anti-TNF therapy and 0.28 (IQR = 0.51) mg/dL at the last follow-up ($p = 0.06$); the median ESR was 20 (IQR = 26.75) mm/h at the start of treatment and 10 (IQR = 10.5) mm/h at last assessment ($p = 0.01$).

As a whole, 11 (20.4%) patients were treated with IL-1 antagonists, corresponding to 17 treatment courses. The median glucocorticoids dosage was 9.2 ± 5.9 mg/day (prednisone or equivalent) at the start of anti-IL-1 treatment and 9.2 ± 5.9 mg/day at the last assessment ($p = 1.000$). Figure 2D describes the response to IL-1 antagonists, while Figure 3B provides the frequency of fever, arthritis, arthralgia, skin manifestations and abdominal pain at the start of IL-1 antagonists and the last visit. One adverse event leading to anakinra discontinuation consisted of a generalised skin reaction.

Secukinumab was used as monotherapy in 3 cases, leading to complete response in 1 patient, failure in the second patient, discontinuation due to angioedema in the third patient. The patient treated with tocilizumab underwent complete response. The 2 patients treated with tofacitinib showed complete response in one case and partial response in the second case.

4. Discussion

Fever is one of the most common signs that physicians meet in clinical practice. It is generally associated to a widespread spectrum of

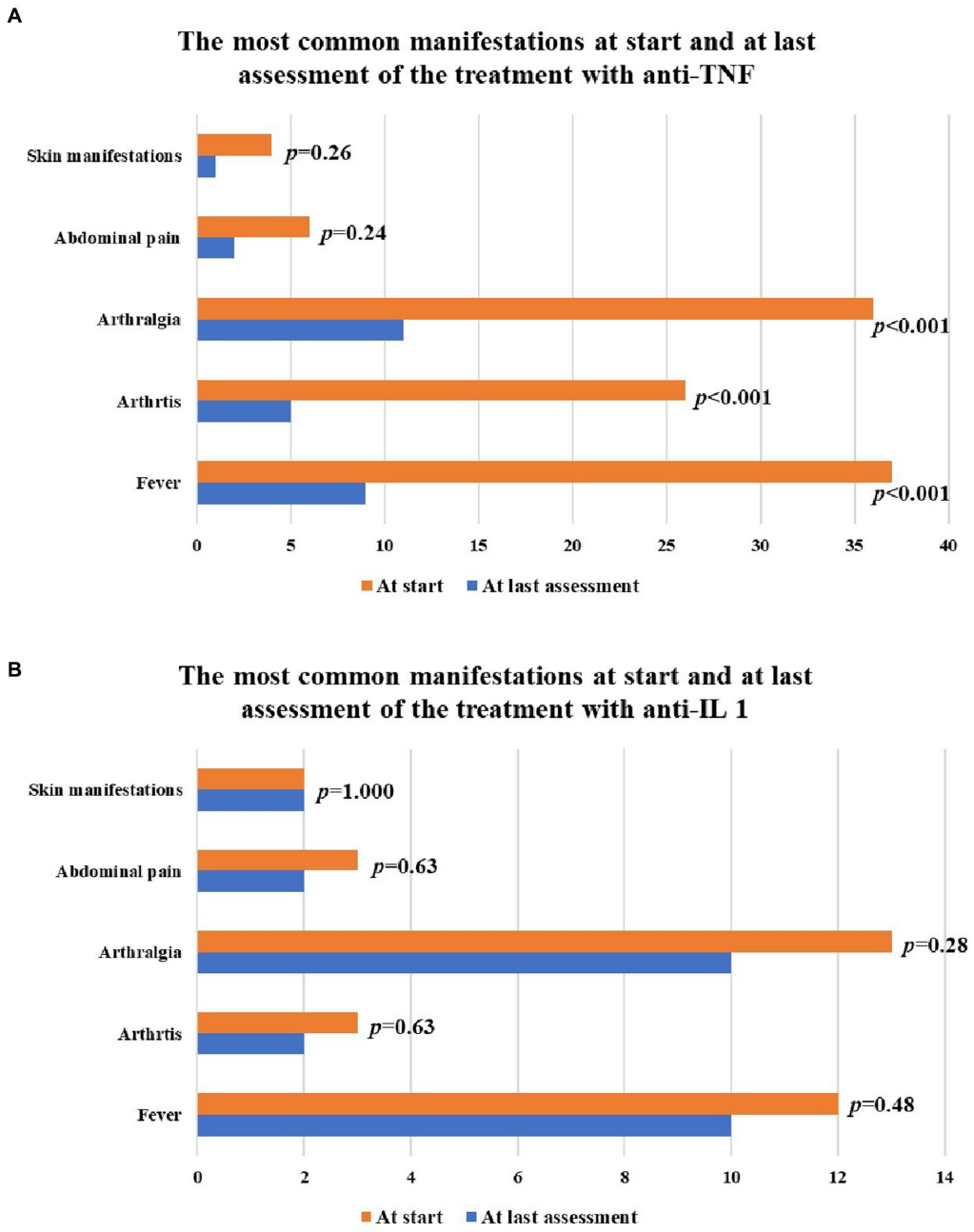

FIGURE 3
Bar charts describe the frequency of the main clinical manifestations observed during inflammatory attacks at the start and at the last assessment while on treatment with anti-tumor necrosis factor (TNF) agents **(A)** and interleukin (IL)-1 inhibitors **(B)**. Skin manifestations observed among patients treated with TNF inhibitors consisted of urticarial skin rash in 2 patients, pustular rash in one patient, erythematous skin rash in one patient; the latter one persisted at the last assessment. Skin manifestations observed among patients treated with IL-1 inhibitors consisted of erythematous skin rash in one patient and maculo-papular skin rash in a second patient. None of them resolved during IL-1 inhibition.

diseases, including infections, neoplastic pathologies, autoimmune diseases, and autoinflammatory disorders. Nevertheless, some patients do not have any defined diagnosis despite the full laboratory and radiological assessments, turning these clinical cases into a diagnostic and therapeutic conundrum. The recent advances in the field of autoinflammatory diseases have increasingly opened the door to the diagnosis in a greater number of patients, but at least 40% of cases with an autoinflammatory picture do not fall into any of the currently known diseases (30). This makes further efforts necessary to better understand the nature and the correct treatment of unexplained periodic fever episodes. In this context, the AutoInflammatory Disease Alliance (AIDA) project has recently supported the development of an international registry dedicated to undifferentiated autoinflammatory conditions, paving the way to suitable clinical research possibly leading to the identification of new clinical entities, among all patients with unexplained recurrent fever episodes (16).

The medical approach in the daily clinical practice is aimed at evaluating all elements capable of explaining a systemic inflammatory

condition in patients with not-otherwise explained recurrent fever episodes. In consideration of this, we have identified 54 patients with axial SpA during the past two years. None of them suffered from other known causes of fever at the time of the first assessment, while history recording, and physical examination corroborated the suspicion of SpA. A subsequent magnetic resonance of the sacroiliac joints highlighted the presence of radiologic signs consistent with an inflammatory skeletal involvement, with patients fulfilling the ASAS criteria for axial SpA (15).

Traditionally, axial SpA may be associated to extra-articular inflammatory manifestations, especially uveitis, inflammatory bowel diseases, and psoriasis (8). Conversely, despite episodes of recurrent fever have already been described in patients affected with SpA, fever does not figure among the common extra-articular SpA manifestations (6, 7, 31–33). Interestingly, Byun et al. have described 26 adult patients with SpA also suffering from recurrent fever episodes (7). Similarly, when comparing Behçet's disease patients with SpA patients to investigate the presence of fever as a clinical feature of these conditions, Seyahi et al. observed a history of recurrent fever episodes in 8 out of 100 SpA patients (6). Despite these preliminary clues, it is not clear whether recurrent fever episodes should be considered as an expression of extra-articular inflammatory involvement or whether the axial SpA could have been part of a larger pathological picture. Based on a relatively wide cohort of patients from the AIDA Network USAID registry, we have described the clinical, laboratory and therapeutic features of these patients (16).

Except for uveitis, the frequency of classical extra-articular manifestations was quite similar to what observed in the literature among SpA patients. In particular, in the present cohort psoriasis was encountered in 9.3% of cases and inflammatory bowel diseases in 5.5%; these percentages overlap with those reported in non-febrile axial SpA (4%–9% and 5.5%–13% of cases for psoriasis and inflammatory bowel diseases, respectively). On the contrary, inflammatory ocular diseases were observed in 13% of febrile patients, which is quite lower than generally observed in the literature (from 22 to 37% of cases) (34).

Arthralgia, myalgia and peripheral arthritis accounted for the most frequent clinical manifestations associated to fever, while headache, diarrhea, abdominal pain and skin rash also occurred with a considerable frequency, as reported in Tables 2, 3 provides absolute and percentage frequencies of clinical and laboratory items included in ASAS criteria. In detail, the skin lesions observed consisted of erythematous, maculo-papular, urticarial rash, and pustular lesions. Noteworthily, several triggers have been reported to induce disease flares in about one third of patients, especially after psychological stress, intense physical activity, menstrual period, generalised cold exposure, and exposure to warm temperatures; 1 patient relapsed after SARS-CoV-2 vaccination.

Whilst HLA-B27 is found in up to 90% of patients with SpA, the frequency of this haplotype was unusually low in our cohort (35). In addition, none of the patients enrolled in this study showed to suffer from radiographic ax-SpA. This evidence seems to suggest that patients with ax-SpA and fever episodes could differ from "classical" ax-SpA patients in the pathogenic aspects of musculoskeletal disease and in the extent of radiographic progression. This hypothesis is also strengthened by the low prevalence of HLA-B27 haplotype in our cases. These finding hints that other co-factors may play a major role in inducing this cluster of ax-SpA patients.

In over half of the cases, laboratory inflammatory markers showed to be increased before starting cDMARDs and/or bDMARDs. However, the concomitant use of corticosteroids in about 57% of patients could have reduced this frequency along with the baseline ESR and CRP values, which were substantially lower when compared to that reported by Byun et al. (7). Unfortunately, part of data collection was retrospective and did not allow an assessment of laboratory inflammatory markers during a fever attack in an adequate number of patients; consequently, this information was not statistically analysed.

Unlike findings reported by Byun et al. (7), a remarkable number of patients was treated with other than NSAIDs and glucocorticoids in this study. In particular, twenty-eight patients were treated with cDMARDs, while TNF antagonists represented the more frequently employed biotechnological treatment approach. Moreover, 11 patients have undergone anti-IL-1 treatment and 2 had been treated with the small molecule tofacitinib.

Anti-TNF agents appeared to play an important role in controlling febrile episodes and the other associated clinical inflammatory manifestations, allowing a significant glucocorticoid sparing effect. Most of the patients treated with TNF inhibitors benefited from at least a partial response, and more than one third of patients showed a complete response. A fair improvement was also observed in the clinimetry of the associated axial SpA. However, statistical significance was not reached, and this was probably due to the very short-term follow-up, corresponding to a median duration of 3 months. Along with clinical improvement, laboratory inflammatory markers showed a notable decrease. In particular, ESR decreased in a statistically significant manner, while the decrease of CRP bordered on statistical significance. The frequency of patients with increased inflammatory markers reduced without reaching statistical significance. This is probably due the relatively low values observed in the inflammatory markers at the start of treatment, as consequence of the concomitant glucocorticoids use.

TABLE 3 Frequency of the specific clinical and laboratory items included in the Assessment of SpondyloArthritis international Society (ASAS) criteria in the cohort of patients enrolled in the present study.

Clinical items of ASAS criteria	Number of patients (%)
Inflammatory back pain	54 (100)
Arthritis	22 (40.7)
Enthesitis (heel)	4 (7.4)
Uveitis	7 (13)
Dactylitis	4 (7.4)
Psoriasis	5 (9.3)
Chron's/colitis	3 (5.5)
Good response to NSAIDs	24 (44.4)[a]
Family history for SpA	8 (14.8)
Elevated C reactive protein	30 (55.6)[b]
HLA-B27 positivity	5 (9.3)

HLA, human leukocyte antigen; NSAIDs, non-steroidal anti-inflammatory drugs; SpA: spondyloarthritis.
[a]All the 24 patients treated with NSAIDs during their history experienced at least a partial improvement in the low back pain.
[b]C reactive protein assessed outside fever bouts.

Although recurrent fever episodes switch thought to autoinflammatory diseases, which are commonly treated with anti-IL-1 agents, the response to anakinra and canakinumab appeared less brilliant in the present cohort of patients. In particular, most of cases treated with IL-1 antagonists underwent a treatment failure and only a reduced number of patients benefited from a complete response. Noteworthily, when analysing the use of TNF inhibitors and IL-1 antagonists, a higher frequency of concomitant cDMARDs could be observed in patients treated with anti-TNF-agents. This could have favoured the therapeutic role of TNF inhibitors or have affected the response to anti-IL-1 agents. Regarding axial SpA activity during anti-IL-1 treatment, unfortunately BASFI and BASDAI were not collected during anakinra and canakinumab administration, as IL-1 antagonists are currently considered ineffective in axial SpA patients. It would have been interesting to look into this aspect, which should be the subject of further studies.

The use of colchicine and other cDMARDs as monotherapy led to a partial and complete response in a reduced number of patients. However, combination therapy of cDMARDs and bDMARDs showed a therapeutic role in increasing the frequency of complete and partial response, as observed in Figure 2.

Currently, we cannot provide a definitive conclusion about the pathogenetic nature of fever in these patients, but it may be assumed that fever represents an extra-articular, currently underestimated manifestation of SpA. Alternatively, we could address with a specific subgroup of axial SpA related to a primary involvement of innate immunity (11). Actually, whilst the reduced frequency of HLA-B27 allele positivity and the low frequency of uveitis seem to suggest this is a different clinical entity from the classical SpA, the pronounced response to anti-TNF therapy and the poor response to IL-1 inhibitors make this condition more similar to SpA than to a typical autoinflammatory conditions (36). The third hypothesis for which recurrent fever episodes can combine with axial SpA by a pure chance seems to be made unlikely by the relative high number of patients enrolled and by the good response obtained on both fever and musculoskeletal involvement with anti-TNF therapy. However, future research efforts with basic and clinical studies will have to clarify all these aspects.

Although the diagnostic delay of arthritic conditions is shrinking with the passing of decades and the increased awareness among physicians and patients, SpA is still widely under-recognized especially when extra-articular manifestations account for the presenting symptom (37–41). This seems especially true in axial SpA patients with fever, as previously observed by Byun et al., who reported a remarkable diagnostic delay and a lower chance to see a rheumatologist in early stage in such patients (7). In support of this, the diagnostic delay was about ten years in our cohort of patients, which is higher than generally observed in axial SpA (37, 39). Despite the wide diagnostic delay and the presence of generally negative prognostic factors toward radiographic progression, especially increased CRP, patients were diagnosed with non-radiographic axial SpA in all cases (42). This could be explained in different ways: we do not know the behavior of axial SpA associated with fever in the long-term. In addition, we do not know whether axial SpA and fever episodes started together or in different moments.

The major limitation of the present study is its pure clinical nature; it would be useful to investigate the issue of fever in axial SpA through laboratory studies. However, this work sheds new light on demographic, clinical and therapeutic features on the quite under-recognized subgroup of patients with recurrent fever episodes also suffering from axial SpA.

In conclusion, signs and symptoms referring to SpA should be inquired in patients with apparently unexplained recurrent fever episodes. The specific treatment for axial SpA may lead to a remarkable improvement in the frequency of fever episodes and in the control of concomitant inflammatory manifestations. Whether SpA is part of an already unrecognised systemic entity or fever is an underestimated extra-articular manifestation of SpA is subject of debate at current and requires further clinical and laboratory research.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Azienda Ospedaliero Universitaria senese. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

AV and VC wrote the first draft of the manuscript and conceived, and designed the study. BF, IS, DO, RF, PR, FC, JS, CG, HG, CF, and PF were included based on the number of patients recruited in the AIDA network registry for USAIDs by February1st, 2022. IV, AT, GL, IA, JH-R, EW-S, VS, GR, MS, and FI were included in the authorship as investigators from the top contributor centers for any of the other AIDA network registries. AB was the bioengineer involved in the technical management of the platform and registries. DR edited and supervised the manuscript. BF and LC took care of the final revision of the manuscript. LC accounted for AIDA registries coordinator. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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A patient-driven registry on Behçet's disease: the AIDA for patients pilot project

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Introduction: This paper describes the creation and preliminary results of a patient-driven registry for the collection of patient-reported outcomes (PROs) and patient-reported experiences (PREs) in Behçet's disease (BD).

Methods: The project was coordinated by the University of Siena and the Italian patient advocacy organization SIMBA (Associazione Italiana Sindrome e Malattia di Behçet), in the context of the AIDA (AutoInflammatory Diseases Alliance) Network

programme. Quality of life, fatigue, socioeconomic impact of the disease and therapeutic adherence were selected as core domains to include in the registry.

Results: Respondents were reached via SIMBA communication channels in 167 cases (83.5%) and the AIDA Network affiliated clinical centers in 33 cases (16.5%). The median value of the Behçet's Disease Quality of Life (BDQoL) score was 14 (IQR 11, range 0–30), indicating a medium quality of life, and the median Global Fatigue Index (GFI) was 38.7 (IQR 10.9, range 1–50), expressing a significant level of fatigue. The mean Beliefs about Medicines Questionnaire (BMQ) necessity-concern differential was 0.9±1.1 (range − 1.8–4), showing that the registry participants prioritized necessity belief over concerns to a limited extent. As for the socioeconomic impact of BD, in 104 out of 187 cases (55.6%), patients had to pay from their own pocket for medical exams required to reach the diagnosis. The low family socioeconomic status ($p<0.001$), the presence of any major organ involvement ($p<0.031$), the presence of gastro-intestinal ($p<0.001$), neurological ($p=0.012$) and musculoskeletal ($p=0.022$) symptoms, recurrent fever ($p=0.002$), and headache ($p<0.001$) were associated to a higher number of accesses to the healthcare system. Multiple linear regression showed that the BDQoL score could significantly predict the global socioeconomic impact of BD ($F=14.519$, OR 1.162 [CI 0.557–1.766], $p<0.001$).

Discussion: Preliminary results from the AIDA for Patients BD registry were consistent with data available in the literature, confirming that PROs and PREs could be easily provided by the patient remotely to integrate physician-driven registries with complementary and reliable information.

KEYWORDS

Behçet's disease, patient-driven registries, rare diseases, autoinflammatory diseases, patient involvement, patient-reported outcomes

1. Introduction

Patient-driven or patient self-reported registries are organized systems collecting uniform data directly from patients to evaluate specified outcomes in a defined population (1). They integrate the classical physician-driven data collection with patient-reported outcomes (PROs) and patient-reported experiences (PREs), adding invaluable contents to research studies. They are also expected to improve the doctor-patient relationship, building trust and mutual connection through the patient's transition from passive to active participant in all the steps of clinical research. When based on user-friendly electronical records accessible online via remote devices, they allow the widest participation even among people with disabilities or living far from the research center, ensuring that geographical and social inequalities are overcome.

The AIDA Network has been established in 2020 as a collaborative framework for international research on autoinflammatory diseases and ocular immune-mediated diseases, with more than 170 clinical sites worldwide.[1] As one of its main efforts, the AIDA Network Registries action led to the development of nine clinical registries, all of them being physician-driven (ClinicalTrials.gov Identifier: NCT05200715). In this context, since the beginning of the project, international experts from the AIDA Network made strategic collaborations with national patient advocacy organizations (PAOs) sharing the programme goals and vision. Among these, there is the development of a patient-driven registry named "AIDA for Patients" covering the whole spectrum of diseases under surveillance and declined in all the national languages spoken in the Network, to complement data collection with PROs and PREs directly entered by patients.

This paper is aimed at describing methods and preliminary results of the AIDA for Patients pilot project, a patient-driven registry for Italian persons affected by Behçet's disease (BD) and their caregivers, which has been developed in collaboration with the Italian PAO SIMBA (Associazione Italiana Sindrome e Malattia di Behçet, https://www.behcet.it/). The registry data were preliminarily analyzed to evaluate the quality of life, fatigue level and therapeutic adherence of people affected by BD, and the socioeconomic impact of the disease in Italy.

2. Methods

2.1. Registry development

The AIDA for Patients registry is hosted by the REDCap platform (Research Electronic Data Capture, https://projectredcap.org), a secure web application designed to support data capture for research studies. Data were entered into electronic forms directly by the participants, recruited through SIMBA communication channels (mailing list and social media) and the AIDA Network affiliated clinical centers in Italy. Participants were able to access the registry

1 https://aidanetwork.org/en/

through their mobile devices or computers via a QR code or a web link to the REDCap homepage of the project. They were initially screened for inclusion through a short survey addressing the respondents to 7 different profiles: (1) adult patient >17 year-old, (2) pediatric patient 13- to 17 year-old, (3) pediatric patient 8- to 12 year-old, (4) 13- to 17 year-old patient's parent, (5) 8- to 12 year-old patient's parent, (6) 5- to 7 year-old patient's parent, and (7) 2- to 4 year-old patient's parent. Respondents were automatically excluded by the system if the diagnosis of BD was only suspected or under evaluation, and in case of parents of <2 year-old patients. Each profile comprised 3 to 5 data collection instruments appropriate to the age and role of the participant, which overall required about 10 min for completion.

The core domains addressed by the registry were identified through a literature analysis, including also the Omeract Core Set of Domains for Outcome Measures in Behçet's Syndrome (2), and discussed among a panel of BD experts and patients' representatives from SIMBA. They included quality of life, fatigue, socioeconomic impact of the disease and therapeutic adherence. Three domains were investigated through validated questionnaires in the Italian language: Behçet's Disease Quality of Life (BDQoL) (3), Beliefs about Medicines Questionnaire (BMQ) (4), PedsQLcore (5), PedsQLfatigue (5), and Multidimensional Assessment of Fatigue (MAF) (6). The BDQoL score has a 0–30 validity range, where higher scores indicate lower quality of life in adults. The PedsQLcore score has a 0–100 validity range, with higher scores meaning better quality of life in children aged 2–18 years. The BMQ questionnaire is made up of two sections: the BMQ concern (BMQc), which investigates the strength of concerns about the safety of specific medications taken by the subject for BD, and the BMQ necessity (BMQn), which measures how much the subject feels important to take the specific medications prescribed for BD. Both sections have a 1–5 validity range, with higher scores indicating stronger beliefs; the BMQ necessity-concern differential has a – 4–+4 validity range, indicating that necessity exceeds concern if the differential is >0, or concern exceeds necessity if <0. The global fatigue index (GFI) resulting from the MAF questionnaire ranges 0–50, where a higher index indicates more severe fatigue in adults. The PedQLfatigue score has a 0–100 validity range, with a higher score meaning less severe fatigue in children aged 2–18 years. On the other hand, a new questionnaire (including 10 to 20 items according to the age and role of the respondent) was specifically developed by the authors and approved by SIMBA representatives to investigate the patient's diagnostic journey and socioeconomic impact of the disease. The family socioeconomic status was defined "average" when the subject stated "I earn enough money to meet the needs of my family," "poorer than average" if the answer was "my financial situation is troublesome" and "healthier than average" in case of the answer "I lead a very comfortable life." The total number of accesses to medical services resulted from the sum of the number of accesses to the general practitioner, the emergency department and the specialistic services in the last 3 months. The social burden index (SBI) resulted from the sum of the days lost at work/school by the subject and by his/her relatives due to BD and the number of days of hospitalization in the previous 3 months. The total socioeconomic impact for each subject was calculated as the sum of the total number of accesses to medical services and the SBI.

The study protocol conformed to the tenets of the Declaration of Helsinki and was approved by the local Ethics Committee of the University of Siena (Reference No. 14951). Informed consent for using clinical data for research purposes was obtained electronically at the start of the pre-screening survey via the following statement in the Italian language "By clicking this button, you are expressing your willing to participate in this survey study and voluntarily give your consent." Patients were informed by the physician or through the accompanying message of invitation that their personal information would be separated from their clinical data by using a pseudonym. The researcher who handled clinical data and performed statistical analysis had no access to the mailing list of the subjects invited by SIMBA nor to any personal information potentially capable to identify the subjects. On the other hand, the representatives from SIMBA and the treating physicians who invited the possible candidates had no access to the clinical data entered by the participants.

2.2. Statistical analysis

Statistical analysis was performed by using JASP open-source statistics package version 0.16.3. Descriptive statistics included sample sizes, mean and standard deviation or median and interquartile range (IQR), as appropriate. Shapiro–Wilk test was used to assess normality distribution of data. Differences in continuous data between independent groups were compared by Mann–Whitney U test or Kruskal–Wallis H test with Dunn's post-hoc test. Relationships between continuous variables failing to meet parametric assumptions were tested through Spearman's rho (ρ). Multiple regression analysis was used to predict outcomes of multiple continuous variables (95% CI). The threshold for statistical significance was set to $p < 0.05$ and all p-values were two-sided.

3. Results

During the period from March to October 2022, 200 participants (M:F = 1:2.5) entered the registry. Respondents were reached via SIMBA communication channels in 167 cases (83.5%) and the AIDA Network affiliated clinical centers in 33 cases (16.5%). Out of 200 respondents, 187 fulfilled inclusion criteria and were able to enter data into the registry as patients ($n = 180$) or patients' parents ($n = 7$); the remaining 13 respondents were excluded by the system because the diagnosis of BD in the participant ($n = 4$) or in the participant's child ($n = 3$) was not confirmed by a physician, or for other reasons ($n = 6$). The median age of affected subjects was 43 years (IQR 17, range 18–69) for adults and 15 years (IQR 3.5, range 9–16) for children. The median disease duration was 13 years (IQR 15, range 1–54), the median diagnostic delay was 4 years (IQR 7.8, range 0–48). There was a negative correlation with large effect size between the diagnostic delay and the year of disease onset ($\rho = -0.72$, $p < 0.001$).

Descriptive clinical and socioeconomic information of the participants is provided in Table 1.

3.1. Quality of life

The median value of BDQoL at the time of the survey completion was 14 (IQR 11, range 0–30) and the mean score of PedQLCore was 61.5 ± 24.3 (range 40.3–85.8). The median value of BDQoL was higher in patients showing cutaneous ($p = 0.029$), gastro-intestinal ($p < 0.001$), neurological ($p = 0.002$), musculoskeletal ($p < 0.001$)

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TABLE 1 Descriptive clinical and socioeconomic information of the participants.

BD-related manifestations experienced by the participants anytime during the clinical history			
Oral ulcers	137 (73.3%)	Recurrent fever	73 (39.0%)
Articular manifestations	113 (60.4%)	Ocular involvement	60 (32.1%)
Headache	99 (52.9%)	Neurological manifestations	52 (27.8%)
Genital ulcers	93 (49.7%)	Vascular thrombosis	37 (19.8%)
Cutaneous manifestations	89 (47.6%)	Axial arthritis	35 (18.7%)
Gastro-intestinal manifestations	79 (42.2%)		
Major organ involvement (ocular, neurological excluding headache, gastro-intestinal, vascular)			
Yes 120 (64.2%)			
No 26 (13.9%)			
Missing 41 (21.9%)			
BMI classification		**Regular physical exercise**	
Normal weight	71 (37.9%)	Yes	29 (15.5%)
Overweight	39 (20.9%)	No	114 (60.9%)
Obese	21 (11.2%)	Missing	44 (23.5%)
Underweight	11 (5.9%)		
Missing	45 (24.1%)		
N. of years in school		**Socioeconomic status**	
0–8	10 (5.3%)	Healthier than average	10 (5.3%)
9–13	49 (26.2%)	Average	62 (33.2%)
14–18	54 (28.9%)	Poorer than average	44 (23.5%)
>18	30 (16.0%)	Missing	71 (38.0%)
Missing	44 (23.5%)		
Median N. of specialistic centers visited before the diagnosis			
3 (IQR 3, range 0–21)			
Necessity to pay for medical exams*		**Disease information at diagnosis**	
Yes	104 (55.6%)	By medical professionals	109 (58.3%)
No	37 (19.8%)	By patient associations	8 (4.3%)
Missing	45 (24.1%)	Autonomous	25 (13.4%)

BMI, body mass index; BD, Behçet's disease; IQR, interquartile range. *Medical consults, laboratory, and radiological exams, genetic tests or other procedures required during the diagnostic journey up to the diagnosis of Behçet's disease.

symptoms and headache ($p = 0.004$). The median value of BDQoL was higher in patients not practicing any sport (median 15, IQR 10 versus 10, IQR 9, $p = 0.008$) and positively correlated with the BMI value with small effect ($\rho = 0.28$, $p < 0.001$) as shown in Figure 1A. Subjects defining their socioeconomic status as poorer than average had higher values of BDQoL (median 18, IQR 10.8) compared to average (median 9.5, IQR 8.3, $p < 0.001$) and healthier than average (median 11, IQR 8.3, $p = 0.002$), as shown in Figure 1B. Also, a positive correlation was found between BDQoL value and the number of specialistic centers visited before the diagnosis ($\rho = 0.24$, $p = 0.005$), the number of accesses to medical services in the previous 3 months ($\rho = 0.58$, $p < 0.001$), the social burden index ($\rho = 0.40$, $p < 0.001$), the GFI ($\rho = 0.67$, $p < 0.001$) (Figure 1C), the BMQn score ($\rho = 0.19$, $p < 0.031$) and the BMQc score ($\rho = 0.38$, $p < 0.001$). Multiple linear regression using backward data entry showed that GFI (OR 0.43 [CI 0.17–0.68]), the number of accesses to medical services in the previous 3 months (OR 0.59 [CI 0.04–1.14]) and BMQn score (OR −3.01 [CI −6.36–0.33]) could significantly predict BDQoL ($F = 12.95$, $p < 0.001$).

3.2. Fatigue

The median GFI was 38.7 (IQR 10.9, range 1–50) and the mean PedQLFatigue total score was 63.9 ± 32.9 (range 31.9–100). The median value of GFI was higher in patients not practicing any sport (median 39, IQR 10.4 versus 36.5, IQR 11.8, $p = 0.022$) and in patients complaining of gastro-intestinal ($p < 0.001$), neurological ($p = 0.048$) and musculoskeletal ($p = 0.015$) symptoms, and headache ($p < 0.001$). Subjects estimating the socioeconomic status of their family as poorer than average had higher values of GFI (median 39.4, IQR 12.5) compared to average (median 37.1, IQR 10.9, $p = 0.009$) and healthier than average (median 35.9, IQR 29.6, $p = 0.028$). Also, participants who autonomously searched for information about their disease showed higher values of GFI than those

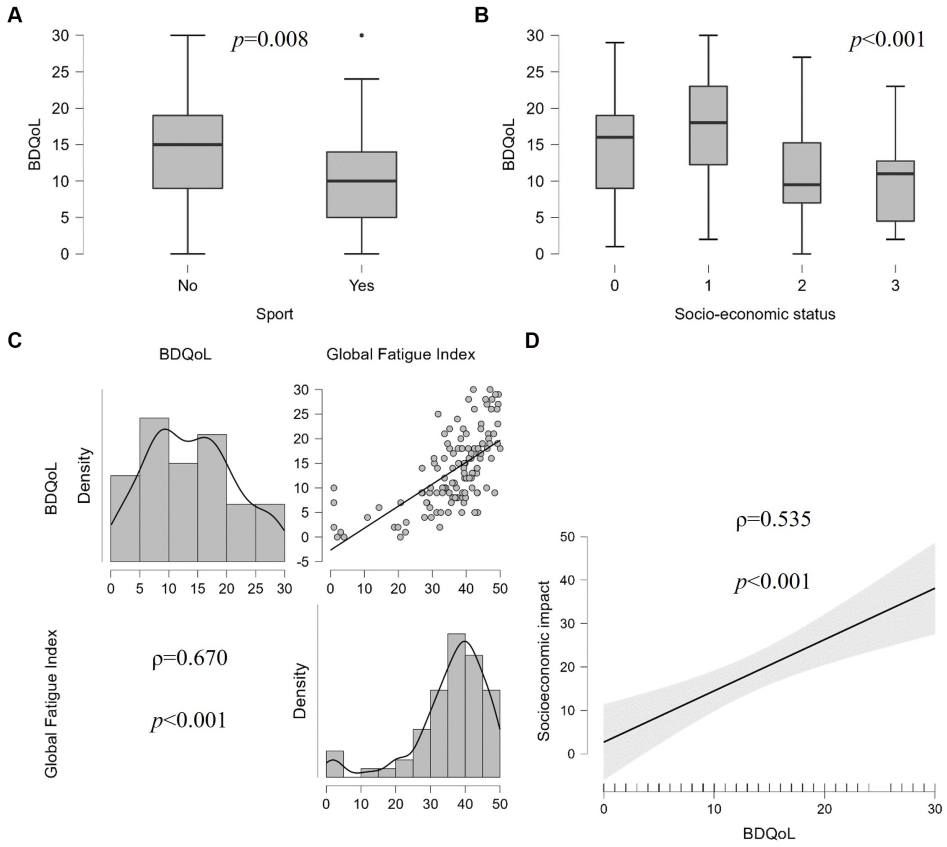

FIGURE 1
Correlation of the quality-of-life variation – measured by Behçet's Disease Quality of Life (BDQoL) questionnaire – and **(A)** sport habit, **(B)** socioeconomic status of the family [0=not disclosed; 1=poorer than average; 2=average; 3=healthier than average], **(C)** fatigue level measured by Multidimensional Assessment of Fatigue (MAF), and **(D)** global socioeconomic impact of the disease.

receiving information from medical professionals (43.2, IQR 9.9 versus 37.5, IQR 9.9, $p=0.009$). A positive correlation was also found between GFI value and the number of accesses to medical services in the previous 3 months ($\rho=0.43$, $p<0.001$), the SBI ($\rho=0.34$, $p<0.001$), the BMQn score ($\rho=0.24$, $p=0.008$), and the BMQc score ($\rho=0.29$, $p<0.001$).

3.3. Therapeutic adherence

The mean BMQn score was 4.1 ± 0.7 (range 1.4–5), the mean BMQc score 3.2 ± 0.8 (range 1–5) and the mean BMQ necessity-concern differential 0.9 ± 1.1 (range – 1.8–4). Subjects with major organ involvement had higher values of BMQn score than those with only minor BD manifestations (median 4.2, IQR 1 versus 3.8, IQR 0.6, $p=0.019$). Participants with more than 18 school years had higher values of BMQn score (median 4.6, IQR 1) than those with 14–18 school years (median 4, IQR 1, $p=0.003$) and 9–13 school years (median 4, IQR 0.8, $p=0.01$). Subjects with a socioeconomic status defined as poorer than average had higher BMQc score (median 3.4, IQR 1.2) compared to average (median 3, IQR 1, $p=0.003$) and healthier than average (median 2.7, IQR 0.5, $p=0.005$). In addition, a positive correlation was found between both the BMQn and BMQc score and the number of accesses to medical services in the previous 3 months ($\rho=0.24$, $p=0.006$ and $\rho=0.20$, $p=0.023$, respectively) and between the BMQn score and the SBI ($\rho=0.29$, $p=0.001$).

3.4. Socioeconomic impact of the disease

During the previous 3 months, the median number of accesses to medical services was 4.5 (IQR 6.0, range 0–35): median 2 (IQR 3) visits to the general practitioner (range 0–51), median 0 (IQR 0) visits to the emergency department (range 0–51), median 2 (IQR 3) specialistic visits (range 0–20). The median SBI was 4.0 (IQR 15, range 0–120): median 2 (IQR 10) days lost at work (range 0–90), median 0 (IQR 3) days lost at work by relatives (range 0–30), median 0 (IQR 0) days of hospital admission (range 0–40). Overall, subjects with major organ involvement had a higher number of medical services accesses (median 5, IQR 5.75) and a higher SBI (median 4, IQR 24.3) than those with only minor BD manifestations (median 3, IQR 4, $p=0.031$, and median 0, IQR 8, $p=0.012$, respectively) (Figure 2A). A higher number of accesses to medical services was reported by participants with gastro-intestinal ($p<0.001$), neurological ($p=0.012$), musculoskeletal ($p=0.022$) symptoms and those with recurrent fever ($p=0.002$), and headache ($p<0.001$), while subjects with gastro-intestinal symptoms ($p<0.001$), recurrent fever ($p=0.015$), and axial arthritis ($p<0.001$) had higher SBI than those without these manifestations. The global socioeconomic impact of different clinical manifestations of BD is displayed in Figures 2B–D. Also subjects defining their socioeconomic status as poorer than average accessed medical services more frequently (median 6.5, IQR 6.7) compared to average

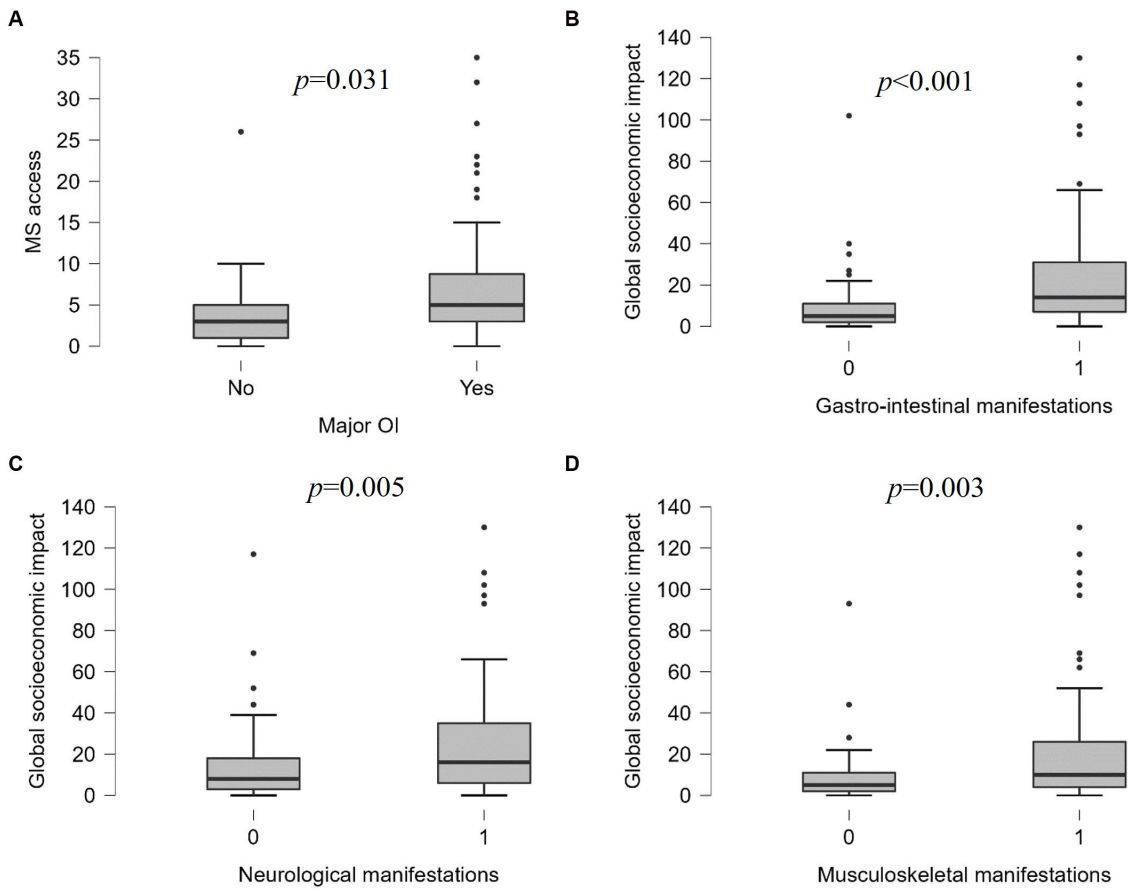

FIGURE 2
Socioeconomic impact of different clinical manifestations of Behçet's disease: **(A)** number of medical service (MS) accesses in the last 3 months in patients with or without major organ involvement (OI); global socioeconomic impact of the disease in patients with or without gastro-intestinal **(B)**, neurological **(C)**, and musculoskeletal **(D)** manifestations.

(median 3.5, IQR 4, $p < 0.001$) and healthier than average (median 4, IQR 3, $p = 0.006$). Multiple linear regression using backward data entry showed that the BDQoL score can significantly predict the global socioeconomic impact of BD ($F = 14.519$, OR 1.162 [CI 0.557–1.766], $p < 0.001$), as shown in Figure 1D.

4. Discussion

This paper describes the methodology and preliminary data of a patient-driven registry for Italian-speaking people affected by BD, which can be easily accessed online by patients of different age groups and their caregivers. Over a period of 8 months, the registry access link and QR code were emailed and posted on Facebook by SIMBA and advertised directly by physicians through an informative leaflet given to patients during routine follow-up visits. Preliminary statistics of the registry enrolment clearly show that the most promising channel is the non-medical one, with 83.5% of spontaneous enrolments via SIMBA channels versus 16.5% via medical professionals. This can be explained by the fact that direct email/Facebook access to the screening survey is more immediate than access through the QR code or link printed on the leaflet. In addition, the context of the hospital visit may not be ideal to capture the attention of the patient, who naturally focuses on information about his/her health condition, the examinations that are prescribed, and therapeutic changes. The physician may also find it challenging to recruit patients in the short timeframe of the follow-up visit. According to these insights, the AIDA for Patients recruitment strategy should be remodulated in the future, on one hand, by boosting the role of national PAOs and running a wider internet and social-media campaign, on the other, by generating automatic email invitations linked to the AIDA physician-driven registry records to match physician- and patient-reported data.

The age distribution of participants corresponded to the epidemiology of the disease, with a peak in the 4th and 5th decades of life and a very limited representation of children (7). Recruiting children was even more challenging because of a limited access to email and Facebook in the 8–17 age group [https://www.statista.com/statistics/376128/facebook-global-user-age-distribution/ accessed on 26/01/2023]. In addition, we observed an unbalanced gender distribution in this study, with an unexpected prevalence of the female sex (M/F ratio 0.4). Indeed, the M/F ratio in BD subjects varies from 0.8 to 2.4 in the largest cohorts from the literature, with a similar frequency among men and women in most part of the world or a slight preference for males (7–12). On the other hand, a recent epidemiology study on 1,323 patients from the US reported a 0.3 M/F

ratio (13). In this context, given the methodology of this study, we cannot exclude a bias caused by the multiple recruitment channels with a preference for the spontaneous enrolment versus the traditional hospital-based one. However, there is also a chance that our remote recruitment strategy may have allowed a wider inclusion of women in this research compared to the traditional hospital-based recruitment. Indeed, a gender gap in inclusion in clinical studies owing to cultural, biological and economic factors (including necessity to travel) has been widely demonstrated within various patient populations, including rare disease cohorts (14, 15).

The diagnostic delay was around 4 years, similar to what has been observed in historical cohorts of both adults and children with BD (16, 17); however, according to our results, the timeliness of the diagnosis improved over the last decades, reflecting the increasing awareness about BD and general improvement of rare diseases diagnostic paths. Nevertheless, we observed that most patients had to pay for clinical and instrumental exams from their own pocket to achieve the diagnosis of BD, even though the public Italian healthcare system fully covers medical expenses within the rare diseases diagnostic journey. This inconsistency sheds light on the existence of procedural pitfalls of the system, which should be discussed among all the stakeholders to improve the efficacy of existing procedures and introduce new operative measures where required. We also observed that major organ involvement, low socioeconomic status and impaired quality of life are the major determinants of the social burden of BD, in terms of number of accesses to the healthcare system, days of hospitalization and days lost at work by affected people. As for the specific disease manifestations, subjects with gastro-intestinal, neurological, and musculoskeletal manifestations were more likely to access medical services and lose days of work, but also recurrent fever and headache had a remarkable impact on productivity.

According to our data, people affected by BD have medium quality of life (median BDQoL 14, ranging from 0 to 30) and significant level of fatigue (median GFI 38.7, ranging from 1 to 50), in line with the results of a recent systematic review and meta-analysis by Masoumi et al. (18). Quite predictably, quality of life and fatigue were also associated reciprocally and with sport habits, BMI variability and therapy-related necessity/concern perception. A higher impact of physical activity on quality of life in BD has been reported also by Senusi et al. (19). On the other hand, Bodur et al. identified a correlation between disease activity and psychological well-being, measured as Life Satisfaction Index and Nottingham Health Profile, with specific regard to the presence of fatigue, joint involvement, gastro-intestinal involvement, headache and mucosal ulceration (20). Moreover, mucosal, neurological, musculoskeletal and ocular manifestations have been found capable to impact independently on specific SF-36 subscales in an Italian cohort (21). With this respect, the preliminary results of the AIDA for Patients registry confirmed that people complaining of BD-related articular, gastro-intestinal, cutaneous symptoms, headache and fatigue have lower quality of life. However, the measurement of disease activity cannot be separated from the medical examination, which makes necessary to align the patient-driven data collection with the physician-driven prospective records of the AIDA registry. Finally, we found among factors associated to a lower quality of life and fatigue complaint a poor socioeconomic status, a high frequency of medical services and a high work/school absenteeism rate.

Therapeutic adherence has not been studied thoroughly in BD. In an Egyptian cohort, they observed a moderate level of therapeutic adherence measured through the Compliance Questionnaire of Rheumatology (mean CQR score of 69.2 ± 11.79), without identifying statistically significant relationship with sociodemographic or clinical characteristics or the SF-36; on the contrary, they found that the necessity and concern BMQ scores were, respectively, positive and negative predictors of a higher CQR score (22). Our results add further knowledge to the complex evaluation of therapeutic compliance in BD. We calculated a BMQn-c differential of 0.9 ± 1.1 indicating that, when dealing with medications prescribed for BD, the registry participants prioritized necessity belief over concerns to a limited extent. This would conceivably result in a weaker therapeutic adherence, which is in line with further data on therapeutic adherence for patients with BD in the literature (23, 24). Respondents with a more severe disease course characterized by major organ involvement had higher necessity belief than those with minor disease manifestations. Also, more educated participants had higher sense of necessity of treatment, while lower-income people had higher concerns of possible harm from their therapies.

Aligned with the international research agenda on BD, the AIDA for Patients registry may be a key instrument to overcome several barriers identified in the path towards the application of a treat-to-target strategy in everyday clinical practice, including patients' perceptions about drugs efficacy and safety, socioeconomic aspects like access to healthcare facilities, lack of resources (time, personnel, and financial) required by treat-to-target strategy and adherence to medication (25). However, like all web-based patient-driven registries, the AIDA for patients registry has both advantages and limitations compared to the traditional data collection methodology. The main advantages are the high number of potential study respondents across geographical and cultural boundaries, access to hidden populations and sensitive/ difficult to discuss topics, speed of the participant recruitment and data collection phases, reduced costs, patients' full and active participation. On the other hand, concerns may arise about sampling issues such as the degree of fit between an online sample and the target population, the reliability of self-reported data, the possibility of multiple submissions and consequent duplication of records, the disparity of access to different web channels and ethical concern for intentional or unintentional misuse (26). These aspects should be considered when applying the results of patient-driven registry-based studies to the general population.

In the case of this study, participants were engaged with the mediation of physicians working in reference centers for BD and a patient advocacy group specifically devoted to BD via mailing list of the association subscribers and its Facebook page. The respondents were directed to a landing page with detailed information on the study aims and inclusion criteria and instructions about how to complete the surveys, in order to mitigate the aforementioned risks of bias. After accepting the study conditions, participants were addressed to a screening survey directly asking whether a definite diagnosis of BD was made by a physician, or the disease was under evaluation or merely suspected by the respondents themselves. Despite these mitigation strategies, we cannot ascertain that all the respondents enrolled via SIMBA communication channels have BD because participants data were fully anonymized. However, the results of the pilot study are consistent with the literature on BD, regardless of the different methodology used, which allowed a consistent sparing of resources in terms of time and dedicated medical personnel. The preliminary analysis of data entered by BD participants suggests that PROs and PREs may be easily provided by the patient remotely, integrating physician-driven registries with complementary and reliable information, which represents one of the major strengths of

the AIDA for patient action. In the future, the AIDA for patients instrument will be integrated in the AIDA Network Behçet's Syndrome Registry to complement it with PROs and PREs directly collected by patients, making them available for clinical research on a wide international cohort. At that stage, it will be also possible to reach the critical numbers allowing comparisons between different recruitment channels to assess in a more comprehensive way the reliability and consistency of data entered by patients themselves.

The AIDA for patients pilot project represents the starting point of a broader initiative that is expected to involve patients affected by autoinflammatory diseases and ocular immune-mediated diseases, their advocates, and caregivers in the next 5 years. Aimed at the development of four-handed registries for clinical research purpose, the project will facilitate interactions among all the figures involved in the co-production of health in all the Countries where AIDA Network partner centers operate. In the light of the AIDA for Patients pilot project experience, the alliance with patient advocates proves itself crucial for the prioritization of the registry domains, for the questionnaire approval, raising awareness, building trust, and getting people actively involved into research.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation. Requests to access these datasets should be directed to the corresponding author: LC, Research Center of Systemic Autoinflammatory Diseases and Behçet's Disease Clinics, Department of Medical Sciences, Surgery and Neurosciences, University of Siena, cantariniluca@hotmail.com.

Ethics statement

The protocol of this study involving human participants was reviewed and approved by the Ethics Committee of Azienda Ospedaliero Universitaria Senese (protocol number: 14951). Written informed consent to participate in this study was provided by the participants or their legal guardian/next of kin electronically at the start of the survey.

Author contributions

CG designed the study, performed statistical analysis with support from JS, and wrote the first draft of the manuscript. ABi was involved in the registry development as patient representative and enrolled participants via email and social media campaign. LC conceived and designed the study, revised the draft of the manuscript, and accounts for AIDA Registries Coordinator. ABa was involved as bioengineer in the technical development of the registry platform. DR revised the draft of the manuscript. CG, JS, StG, PR, RG, MP, FCr, SM, GEm, AP, AV, MT, VC, RN, VP, CF, and BF enrolled participants in the project during hospital visits. GL, AMai, MC, DR, MG, FL, SeG, PP, AMar, FCi, MM, EA, EBartoloni, AIa, OV, GS, SiG, AIn, EG, GC, PB, AO, ABr, FCa, PT, AMau, GT, AF, HG, GR, ST, JH-R, PS, KL, AK, GEs, FS, HD, AH-A, DO-B, IA, GH, ME, FÖ, EW-S, NA, AT, AS, ŞE, SO, and EBatu were included in the authorship as investigators from the top contributor centres of the AIDA Behçet's syndrome registry. The authorship was established based on the number of patients recruited in the AIDA registries up to Mar 9th, 2023. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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