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Biologic drugs in immune-mediated inflammatory diseases: validation, drug-utilization, effectiveness, regulation, costs, and safety in the real world

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Biologic drugs in immune-mediated inflammatory diseases: validation, drug-utilization, effectiveness, regulation, costs, and safety in the real world

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Editorial: Biologic drugs in immune-mediated inflammatory diseases, validation, drug-utilization, effectiveness, regulation, costs, and safety in the real-world

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Editorial on the Research Topic
Biologic drugs in immune-mediated inflammatory diseases, validation, drug-utilization, effectiveness, regulation, costs, and safety in the real-world

Biologic drugs have significantly improved the therapeutic landscape for immune-mediated inflammatory diseases (IMIDs), including rheumatoid arthritis (RA), psoriasis, inflammatory bowel disease (IBD), and systemic lupus erythematosus (SLE) (El-Gabalawy et al., 2010). These targeted therapies, such as monoclonal antibodies and recombinant proteins, have shown remarkable efficacy in clinical trials (Blandizzi et al., 2017), offering hope to patients with chronic inflammatory conditions. However, translating the controlled success of biologics into real-world practice poses challenges (Ferraro et al., 2023), including heterogeneity in patient populations, adherence issues, switching and multiple switches, healthcare resource utilization, and cost concerns (Van Den Bemt et al., 2012; Trifirò et al., 2019; Spini et al., 2024; Convertino et al., 2021; Convertino et al., 2023), highlighted by the increasing prevalence of biological drug users affected by IMIDs over the years (Trifirò et al., 2021). For instance, Ingrasciotta et al. (2024) in the study comparing the characteristics of users of biologics in IMIDs between randomized clinical trials and the real-world setting highlighted that variables such as older age, previous cancer diagnoses and the occurrence of concomitant IMIDs led to the main differences in observations between these two types of investigations (Ingrasciotta et al., 2024).

This Research Topic focused on these challenges by including nine studies that offer valuable insights into the use of biologics in the real-world (Zhang et al.) The studies described below provide a comprehensive overview of drug utilization patterns, treatment outcomes, safety profiles, and economic implications in different healthcare systems across Countries.

Pera et al. conducted a disproportionality analysis using the FDA's Adverse Event Reporting System (FAERS) to assess the risk of parasitic infections associated with monoclonal antibodies targeting type 2 immune responses (such as biologic drugs used in asthma and eosinophilic disorders). The study revealed significant safety concerns by demonstrating a statistically significant association between certain biologics and the occurrence of parasitic infections, particularly in immunocompromised patients, emphasizing the need for rigorous post-marketing surveillance, especially in vulnerable populations.

Li R. et al. presented a case study of a patient with refractory intestinal Behçet's disease who was successfully treated with Vedolizumab. This report highlighted the potential of biologics for complex, off-label applications in patients with comorbidities.

Convertino et al. examined disease activity and drug utilization patterns of biologic disease-modifying antirheumatic drugs (bDMARDs) in a cohort of RA patients in the Tuscany region of Italy. This population-based study, which analyzed data from medical records for disease activity information, and a healthcare administrative database, for drug-utilization assessment, showed variability in bDMARD discontinuations driven by patient disease activity and influenced by the clinical guidelines and patient baseline characteristics. The study highlighted the importance of tailored treatment approaches in response to the disease activity.

Zeng et al. reviewed the evolution of anti-TNFα therapies in IBD, from the first-generation originator drugs to the newer biosimilars. Their findings underscored the potential of biosimilars to improve access to treatment while maintaining safety and efficacy, particularly in the management of chronic diseases like IBD. The authors recommended continuous monitoring of biosimilars in real-world practice to confirm their long-term safety and effectiveness.

Li Y. et al. investigated the impact of DMARDs and non-steroidal anti-inflammatory drugs (NSAIDs) on the clinical course of mild-to-moderate COVID-19 in patients with ankylosing spondylitis (AS). Their findings highlighted the need for personalized treatment strategies arising from the pandemic that balance the benefits of controlling AS symptoms with the potential risks of immunosuppressive therapies in the context of viral infections.

Fu et al. examined hepatitis-related adverse events in patients treated with immune checkpoint inhibitors, using data from the FAERS and they identified a significant, albeit relatively rare, risk of hepatitis in these users. The study showed the importance of monitoring liver function for the early detection of adverse events and the effective management of hepatotoxicity.

Vesikansa et al. analyzed healthcare resource utilization in psoriasis patients who received biologic therapies versus those treated with conventional drugs in Finland. The study showed that although biologics are more expensive than conventional treatments, they resulted in lower overall healthcare costs by reducing hospitalizations, emergency visits, and the need for frequent medical consultations. This study provided valuable insights into the economic burden of psoriasis treatment and the potential cost-effectiveness of biologic therapies in real-world practice.

Long et al. performed a systematic review and meta-analysis to evaluate the efficacy and safety of iguratimod, a novel DMARD, in the treatment of inflammation and joint degeneration in RA. The findings highlighted its efficacy and safety in treating both pathologic aspects of RA but highlighted the need for post-marketing monitoring and pharmacoepidemiologic studies to confirm its long-term safety and effectiveness.

Shehab et al. provided real-world data on the effectiveness of biologic therapies in achieving treatment targets in patients with IBD in the Middle East. The study assessed the clinical outcomes of patients treated with anti-TNFα therapies and integrin inhibitors, showing that biologics are effective in controlling disease activity and improving the quality of life for many patients. However, the authors also emphasized the challenges in drug access and adherence to biologics and advocated for improved healthcare infrastructure in their Region.

The studies collected in this Research Topic collectively highlight the importance of real-world data in complementing clinical trial findings, by providing critical insights into the long-term safety, effectiveness, and economic impact of biologics, and by addressing gaps in research. These suggest that future research should prioritize improving pharmacovigilance, increasing accessibility, and integrating personalized medicine. Notably, comprehensive post-marketing surveillance is essential to ensure patient safety, especially in large-scale populations. Biosimilars hold promise for reducing treatment costs, but equitable access to biologics remains a challenge globally and tailoring treatment strategies to individual patient characteristics and disease response can improve outcomes and reduce healthcare burdens.

In conclusion, biologic drugs have undeniably advanced the management of IMIDs, but their utilization in real-world practice requires addressing challenges related to safety, cost-effectiveness, and healthcare accessibility. The findings presented in this Research Topic provide a roadmap for optimizing biologic therapy in several clinical settings. By leveraging real-world evidence, clinicians, researchers, and policymakers can bridge the gap between clinical trials and everyday practice, ensuring better outcomes for patients worldwide.

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Successful treatment of a refractory intestinal Behcet's disease with an oncology history by Vedolizumab: a case report and literature review

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Objective: Behçet's Disease (BD) is an intractable systemic vasculitis. When accompanied by intestinal symptoms, the prognosis is usually poor. 5-Aminosalicylic acid (5-ASA), corticosteroids, immunosuppressive drugs, and anti-tumor necrosis factor-α (anti-TNF-α) biologics are standard therapies to induce or maintain remission for intestinal BD. However, they might not be effective in refractory cases. Safety should also be considered when patients have an oncology history. Regarding the pathogenesis of intestinal BD and the specific targeting effect of vedolizumab (VDZ) on the inflammation of the ileum tract, previous case reports suggested that VDZ might be a potential treatment for refractory intestinal BD.

Methods: We report a 50-year-old woman patient with intestinal BD who had oral and genital ulcers, joint pain, and intestinal involvement for about 20 years. The patient responds well to anti-TNF-α biologics but not to conventional drugs. However, biologics treatment was discontinued due to the occurrence of colon cancer.

Results: VDZ was intravenously administered at a dose of 300 mg at 0, 2, and 6 weeks and then every eight weeks. At the 6-month follow-up, the patient reported significant improvement in abdominal pain and arthralgia. We observed complete healing of intestinal mucosal ulcers under endoscopy. However, her oral and vulvar ulcers remained unresolved, which disappeared after adding thalidomide.

Conclusion: VDZ may be a safe and effective option for refractory intestinal BD patients who do not respond well to conventional treatments, especially those with an oncology history.

KEYWORDS

Behcet's disease, intestinal disease, vedolizumab, tumor, case report

1 Introduction

Behçet's Disease (BD) is systemic vasculitis that is usually refractory, mainly characterized by ulcers (oral and genital) and lesions (ocular and skin), which may be accompanied by joint, intestinal, neurological, and vascular involvement (1). The intestinal BD morbidity rate ranges from 5% to 20% globally, and it is more common in the Mediterranean region and East Asian countries, especially in South Korea, Japan, and China (2). When patients with BD present with abdominal pain, diarrhea, bloody stools, and abdominal masses, an endoscopy should be performed as soon as possible to confirm the diagnosis. It is also essential to distinguish it from inflammatory bowel disease (IBD), intestinal tuberculosis, or infectious enteritis, which may also present with the above non-specific intestinal symptoms (3). In the recent guidelines (1), anti-TNF-α biologics are recommended for refractory cases that do not respond to conventional drugs, including 5-ASA, corticosteroids, and immunosuppressive drugs. However, some patients continue to respond poorly due to limitations such as primary or secondary loss of response, intolerance, or contraindications (4). TNF-α also plays a vital role in apoptosis and tumor suppression, and interference with relative pathways may increase the risk of malignancy (5). Therefore, it is necessary to consider other alternative treatments for refractory intestinal BD patients with an oncology history.

Although the pathogenesis is unknown, many factors are thought to contribute to BD, including genetics, environment, infection, microbiota, and immune status (6–9). Imbalance in the numbers of T cells (especially Th1, Th2, and Th17), natural killer cells, and inflammatory cytokines play an essential role (10, 11). The elevated levels of IL-1β, IL-6 and TNF-α in the gastrointestinal mucosa of patients with intestinal BD play a pathogenic role in the increasing inflammatory responses (12). VDZ can specifically target α4β7 integrins expressed on the surface of intestinal lymphocytes, preventing the recruitment of pro-inflammatory cells to the intestine from reducing inflammation (13–15).

As far as we know, only one report of VDZ being used in patients with intestinal BD (16). Six months after the infusion of VDZ, the patient achieved clinical remission. Here we continue to report a case of an intestinal BD patient with an insufficient response to conventional therapy who achieved a better outcome after conversion to VDZ. We also discuss the safety of VDZ in patients with a combined oncologic history.

2 Case report

We here describe a 50-year-old female patient with intestinal BD. The clinical characteristics and treatment measures of the patient are shown in Table 1. The patient has had recurrent oral and vulvar ulcers since 2003. In March 2004, she developed nocturnal hyperthermia and dark red bloody stools. Colonoscopy showed terminal ileum ulcers and proliferative lesions. Pathological biopsies reported acute and chronic inflammation of the superficial mucosa. Antinuclear antibody (ANA) and pathergy test results were positive, and the pure protein derivative (PPD) test was negative. Indexes such as infection, tumor, and autoantibody series were normal. According to the diagnostic criteria of the International Study Group for Behçet's Disease (17), and combined with clinical symptoms, laboratory tests, colonoscopy, and pathological findings, the patient was diagnosed with BD. Prednisone (40mg PO daily), cyclophosphamide (50mg PO daily), and mesalazine (4g PO daily) were administered to control symptoms. Prednisone and cyclophosphamide decreased gradually. In December 2005, cyclophosphamide was stopped, and 5mg of prednisone was taken orally daily to maintain symptoms. In August 2007, she developed multiple joint pains. There were no abnormalities in Anti-Streptolysin "O" (ASO), rheumatoid factor (RF), human leukocyte antigen (HLA-B27), and anti-neutrophil cytoplasmic antibody (ANCA). The treatment regimens were adjusted repeatedly according to the patient's clinical symptoms, including prednisone (40mg PO daily), sulfasalazine (3.0mg PO daily), methotrexate (12.5mg PO weekly), thalidomide (100mg PO daily), cyclophosphamide (50mg PO daily) and colchicine (1mg PO daily), etc. In January 2019, the patient's condition worsened with persistent right lower abdominal pain, bloody stools, frequent episodes of oral ulcers, and arthralgia. Colonoscopy showed multiple ulcers in the distal ileum and large protuberant lesions in the cecum and ascending colon (Figures 1A, B). The biopsies revealed chronic inflammatory activity of the mucosa with ulcer formation, and no evidence of neoplasia was seen. Considering the patient's recurrent illness, no significant improvement in intestinal mucosal status, and the failure of previous medications, we decided to switch to treatment with anti-TNF-α biologics —– infliximab (IFX). We truthfully stated the benefits and risks of using biologics and obtained the informed consent of the patient. IFX was administered with a dose of 300 mg at 0, 2, 6 weeks, and then every eight weeks. The patient reported a significant reduction in oral and vulvar ulcers, abdominal pain, and arthralgia immediately after the first infusion. On August 9, 2019, a colonoscopy showed that the terminal ileal ulcer was better than

TABLE 1 Clinical characteristics and therapeutic interventions of the patient.

Items	
Sex	F
Age(yrs)	50
Intestinal BD course(yrs)	19
Clinical features	Oral ulcers, genital ulcers, Joint pain, intestinal symptoms and ulcers (terminal ileum)
Previous treatment	CS, CTX, IFX, MTX, SASP, THD, Colchicine, Mesalazine
VDZ combined therapies	THD
Present therapies	VDZ 300 mg every 8 weeks
Follow-up(mths)	16
Clinical response	success

BD, Behcet's Disease; CS, corticosteroids; CTX, cyclophosphamide; IFX, infliximab; MTX, methotrexate; SASP, salazosulfapyridine; THD, thalidomide; VDZ, vedolizumab.

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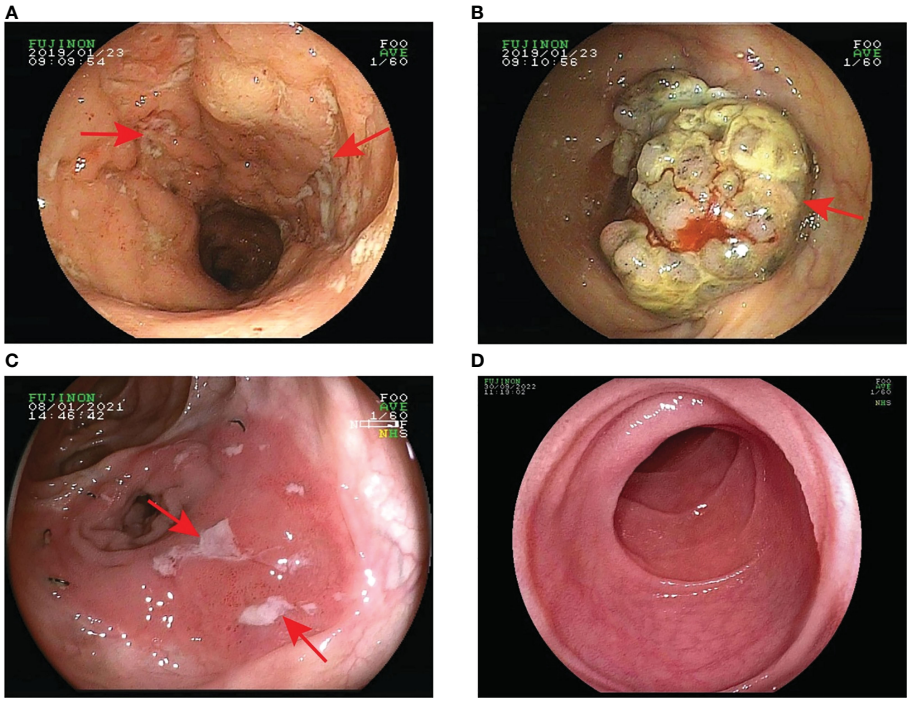

FIGURE 1
Changes in the patient's intestinal mucosa. **(A)** In January 2019, prior to the application of infliximab, colonoscopy showed multiple ulcers at the end of the ileum; **(B)** In August 2019, colonoscopy revealed a large bulging lesion in the cecum and ascending colon; **(C)** In January 2021, colonoscopy again showed multiple large ulcers in the ileum and anastomosis; **(D)** In September 2022, one year after vedolizumab treatment colonoscopy showed complete healing of the ileal ulcers.

before. However, there were no significant changes in ileocecal and ascending colon masses. Biopsies revealed acute mucous inflammation, small vessel dilatation and congestion, epithelial hyperplasia on the recessed surface with erosion and inflammatory exudation, and significant glandular hyperplasia and mucus secretion. There was no evidence of granuloma or neoplasia. Intestinal dual-source CT showed obvious thickening at the lower end of ascending colon, soft tissue shadow protruding into the lumen, and abundant blood supply. Endoscopists considered performing endoscopic submucosal dissection (ESD) to be risky. The gastrointestinal surgeon reported that the possibility of colon cancer could not be excluded from the ascending colonic mass and recommended surgical excision to determine its nature. Therefore, after multidisciplinary discussions, the patient underwent a right radical hemicolectomy on September 6, 2019. Post-operative pathology confirmed the mucinous tumor (Figure 2). IFX was suspended. The mFOLFOX6 chemotherapy regimen was administered for four cycles before being discontinued due to the global outbreak of the novel coronavirus. Long-term oral thalidomide (50mg PO daily) to control the disease. In January 2021, the patient's right lower abdominal pain worsened again. Colonoscopy showed multiple large ulcers in the ileum and anastomotic orifice (Figure 1C). Enhanced CT of the abdomen showed thickening of the anastomotic wall and the proximal ileal wall of the anastomosis with significant enhancement.

The intestinal BD recurred. The immunosuppressive effect of anti-TNF-α biologics may be risky for patients with an oncology history. Therefore, combined with the pathogenesis of intestinal BD and previous case reports, we decided to try VDZ for some clinical benefits. On October 9, 2021, the patient received an infusion of 300 mg VDZ (initially at 0, 2, and 6 weeks, then every eight weeks). After a short follow-up of 6 months, the patient reported that her lower abdominal pain and arthralgia were improved. No obvious adverse reactions occurred. The DAIBD score decreased from 85 to 0, and the WBC, ESR, and CRP levels were normal. On September 30, 2022, a colonoscopy showed a completely healed ileal ulcer with a smooth mucosal surface and well-dilated intestine (Figure 1D). However, at the 15th monthly follow-up, her oral and vulvar ulcers recurred, and the CRP concentration increased. Therefore, thalidomide was administered to alleviate systemic inflammation. As shown in Figures 3A–C, although all systemic inflammatory indices showed repeat increases, such as WBC, CRP, and ESR, these might be caused by the presence of inflammation outside of the gastrointestinal (GI) tract. As only focused on the GI tract (Figure 3D), the DAIBD showed the significant efficacy of VDZ on intestinal BD.

3 Discussion and literature review

We report here a case of a refractory intestinal BD patient. She had recurrent oral and genital ulcers, joint pain, and intestinal involvement for nearly 20 years. Anti-TNF-α biologics relieved symptoms when initially applied. However, the patient developed

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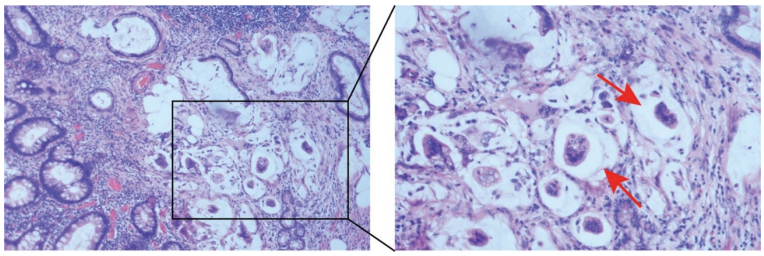

FIGURE 2
Pathology images from the right radical hemicolectomy. H&E staining revealed an irregular glandular arrangement of the mucosal epithelium with a large amount of mucus visible in the background and infiltrative growth.

colon cancer during BD. We performed surgical excision and chemotherapy intervention. During follow-up, her intestinal BD recurred. Considering the aggravation of the intestinal condition and the combined tumor history, we decided to try VDZ. At the 6-month follow-up, she achieved clinical remission, all laboratory test results were in normal ranges, and mucosal healing was observed under endoscopy. Several studies have demonstrated that VDZ are effective on extraintestinal manifestations of IBD (18, 19). However, oral and vulvar ulcers still occurred sporadically in the patient we report here, and the symptoms disappeared with the combination of thalidomide.

Unlike other gastrointestinal inflammatory diseases, which are primarily chronic and persistent, BD is a recurrent acute systemic vasculitis (20). Different clinical manifestations can occur individually or coexist in the same patient (21). Typical geographic distribution, infection, immunization, and environmental factors may contribute to the development of BD (10). Vascular damage, neutrophil hyperfunction, and autoimmune reactions are the key characteristics of BD. Analysis of HLA phenotype and serum IgD levels may help to make a diagnosis (20).

Intestinal involvement in BD is usually associated with poor prognosis and a risk of severe organ damage or even death. The

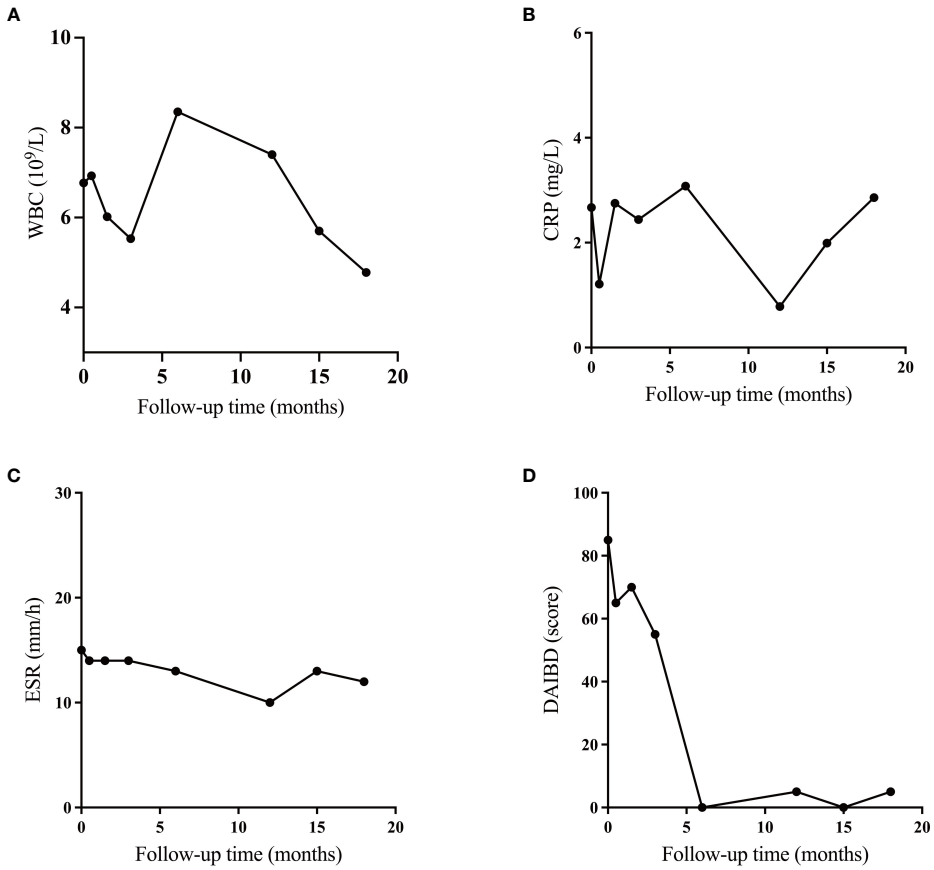

FIGURE 3
Efficacy of vedolizumab in the treatment of intestinal Behcet's Disease. **(A)** Changes of white blood cell (WBC); **(B)** Changes of C-reactive protein (CRP); **(B)** Changes in erythrocyte sedimentation rate (ESR); **(C)** Changes in indices of disease activity in intestinal Behcet's Disease (DAIBD).

spectrum can involve any digestive organ from the oral cavity to the anus, especially the ileocecal region, transverse colon, and ascending colon (22). In Asian countries, ileocecal involvement appears to be more common (23), and volcano type ulcers are typical endoscopic manifestations (1). Endoscopy, computed tomography, and magnetic resonance enterography are used to assess intestinal involvement and disease activity in BD (24).

The ultimate treatment goals for patients with intestinal BD are the disappearance of clinical symptoms, normalization of inflammatory indices, and intestinal mucosal healing (1). The acute phase is usually treated with corticosteroids combined with 5-ASA or azathioprine (AZA) (3). Alternative treatment options include salazosulfapyridine (SASP), mycophenolate mofetil (MMF), and methotrexate (MTX) (25). Patients with severe or refractory intestinal symptoms should be treated with anti-TNF-α biologics alone or in combination with thalidomide (THD) (1). Anti-TNF-α biologics have demonstrated promising results in inducing and maintaining remission of intestinal BD (26, 27). However, due to the role of TNF-α in NK cell- and CD8+ T cell-mediated clearance of tumor cells (28), it can trigger apoptosis through an exogenous pathway by activating caspases 8 and 10. It may also activate signaling through the NF-κB pathway, which indicates anti-TNF-α biologics may promote tumor recurrence, growth, and/or metastasis (5, 29, 30).

The patient we report here had multiple colonic mucosal biopsies, all of which indicated inflammatory lesions. In 2019, we again performed large biopsies of the ileal and ascending colon masses prior to the use of IFX. Neoplastic lesions were still excluded, suggesting chronic mucosal inflammatory activity. We obtained the patient's informed consent for the use of IFX and the symptoms remitted. However, colonoscopy showed no significant changes in the masses. After multidisciplinary discussion, we decided to surgically resect the hyperplastic lesions, and postoperative pathology revealed local tumor. It cannot be absolutely excluding that the appearance of cancerous lesions is due to the use of IFX. However, prior to the use of IFX, we have repeatedly performed pathological biopsies of the masses to exclude malignant lesions. The current reports on anti-TNF-α biologics and tumors are mainly on skin cancers, including melanoma (31–34). ECCO guidelines recommend that infliximab is best avoided in patients with a history of malignancy (35). Therefore, it is necessary to consider other alternative therapies for patients with refractory intestinal BD with an oncology history.

Our literature review found a case report of VDZ successfully treating refractory BD (16). The patient had erythema nodosum, oro-genital ulcers, and biopsy-proven intestinal BD, which was not successfully treated with conventional immunosuppressants and several biologics agents, including anti-TNF-α biologics. Based on previous reports of the efficacy of VDZ in IBD, the authors decided to administer VDZ to treat severe intestinal involvement. The results led to a satisfactory gastrointestinal response and the concomitant disappearance of ulcerations, arthralgia, and a reversion of the skin lesions. VDZ, an intestine-selective humanized monoclonal IgG1 antibody, has been approved for treating IBD (36, 37). VDZ blocks the recruitment of pro-inflammatory cells and dendritic cells to the inflamed gut by specifically targeting α4β7 integrins expressed on the surface of intestinal lymphocytes and monocytes and inhibiting their binding to cell adhesion molecules (CAMs) (15, 38, 39), leading to alterations in the innate and acquired immune cell program to suppress inflammation without interfering with transit to other organs (40). Compared to anti-TNF-α biologics or other immunosuppressive agents, integrin receptor antagonists reduce the side effects associated with systemic immunosuppression. Moreover, studies reported no increase in malignancy and mortality among VDZ-exposed patients (41).

Growing evidence shows that IBD and BD may be closely related and are part of a typical disease spectrum (42). They have similarities in plausible pathophysiological features. We should note that VDZ had a good response in the ileum portion and not in the whole tract of intestine. That in IBD there is a heterogeneous distribution of immune cells in the enteric tract, with the presence of CD4+ memory (mem), lymphocytes, B and dendritic cells in the ileum (43). The most α4β7 positive cells are CD4+mem, CD8+mem and B cells, which can explain not only as to why VDZ works better on lesions in some parts of the intestine (as ileum) and less so in others (44), but also as too why VDZ did not work on ulcer in the other mucous as oral and vulval ones. This is probably due to the heterogeneous distribution of the α4β7 positive cells in these mucous.

The relationship between IBD and colorectal cancer has been demonstrated (45). Although BD is clinically similar to IBD. Only a tiny series of tumor-related cases had been reported, of which colon cancer is less common (46–48). There is no clear evidence that BD causes epithelial cancer or sarcoma. The patient we reported was diagnosed with colonic mucinous carcinoma 16 years after the first presentation of BD symptoms. The severity and duration of inflammation may be risk factors for cancer (45, 49). As increasing numbers of potent drugs are used to treat BD, patients may live longer than before and therefore be more likely to develop the malignant disease. In addition, extensive vasculitis and abnormal immune regulation in BD are thought to be mechanisms of increased risk of malignancy (50). Further detailed pathological studies, cytogenetic analysis, and long-term sizeable prospective cohort studies are needed to clarify the relationship between BD and tumors.

4 Conclusion

VDZ specifically blocks T-cell chemotaxis to the ileum during inflammation and inhibits inflammatory factor signaling. It is suggested that it may serve as a potential treatment drug for intestinal BD, especially involving the ileum tract. The patients with intestinal BD we reported here had poor efficacy to conventional drugs. Anti-TNF-α biologics had shown better therapeutic effects. However, due to the occurrence of a colon tumor, we attempted to switch to VDZ. The intestinal symptoms and joint pain were reduced, and intestinal mucosa ulcers healed completely. No recurrence or other side effects occurred. Thus, our example provided possible evidence for the efficacy and safety of VDZ in patients with refractory intestinal BD who have an

oncology history. As an intestinal-specific antibody, VDZ has shown an inhibitory effect on ileal inflammation but is less effective in treating systemic vasculitis. During the follow-ups, the manifestations like oral and vulvar ulcers and increased CRP were further resolved by thalidomide.

Short follow-up time and only one case reported are our major limitations. Large and long-term clinical trials are needed to verify the efficacy and safety of VDZ in treating intestinal BD. In addition, in the intestinal BD the effect and mechanism of VDZ on the other tracts of intestine and on other mucous membranes need to be further explored.

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 authors.

Ethics statement

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

TW and JL contributed to conception and design of the study. RL organized the database. XL performed the statistical analysis. RL, XL and HZ wrote the main content of the manuscript. YS and FW provided tables and pictures. 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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Assessing disease activity of rheumatoid arthritis patients and drug-utilization patterns of biologic disease-modifying antirheumatic drugs in the Tuscany region, Italy

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Introduction: The disease activity associated with the drug-utilization patterns of biologic Disease Modifying Anti-Rheumatic Drugs (DMARDs) is poorly investigated in real-world studies on rheumatoid arthritis (RA) patients. To investigate the relationship between biologic DMARD initiation/discontinuations in RA patients identified in the healthcare administrative databases of Tuscany and the Disease Activity Score 28 (DAS28) reported in the medical charts.

Methods: This retrospective population-based study included RA's first-ever biologic DMARD users of the Pisa University Hospital from 2014 to 2016. Patients were followed up until 31 December 2019. We evaluated the DAS28 recorded before (T0) and after (T1) the biologic DMARD initiation and before (TD0) and after (TD1) discontinuations. Patients were classified as "off-target" (DAS28 > 3.2) or "in-target" (DAS28 ≤ 3.2). We described the disease activity trends at initiation and discontinuation.

Results: Ninety-five users were included (73 women, mean age 59.6). Among 70 patients (74%) with at least three DAS28 measures, 28 (40.0%) were off-target at T0 and 38 (54.3%) in-target at T1. Thirty-three (47%) patients had at least one discontinuation, among those with at least three DAS28 assessments. In the disease activity trend, disease stability or improvement was observed in 28 out of 37 (75.7%) patients at initiation and in 24 out of 37 (64.9%) at discontinuation.

Discussion: Biologic DMARD discontinuations identified in the healthcare administrative databasese of Tuscany are frequently observed in situations of controlled RA disease. Further studies are warranted to confirm that these events

can be used in studies using healthcare administrative databases as proxies of treatment effectiveness.

KEYWORDS

DAS28, initiation, discontinuation, biologic, DMARD, real-world, drug-utilization

1 Introduction

Healthcare administrative databases (HADs) are demonstrated to be reliable data sources for drug utilization studies (Gini et al., 2014; Trifirò et al., 2021). However, investigating clinical outcomes associated with drug use in these databases is conditioned by the aims these data are collected for, particularly the management of healthcare costs. Therefore, proxies must often define clinical outcomes (Convertino et al., 2021a). For example, the treatment initiation identified in these databases can be interpreted as a clinical need (i.e., an uncontrolled disease) and a change in therapy (switching) or interruption (discontinuation) as efficacy loss or as a consequence of tolerability problems.

The Pathfinder project (EUPAS29263) (Convertino et al., 2021d) was developed to describe the use of biological drugs in rheumatoid arthritis (RA) patients and the related clinical outcomes by combining data from the HAD of the Tuscan region with the information contained in the individual medical charts. The extraction algorithm of subjects with RA demonstrated high values of sensitivity (0.93; 95% confidence interval, CI, 0.86–0.97), specificity (0.84; 95% CI 0.78–0.90), and positive predictive value (0.78; 95% CI 0.70–0.85) (Convertino et al., 2021b). The project characterized the use of biological drugs in these patients, classifying them based on adherence trajectories. This evaluation observed that about 88% of the subjects fall into the adherence category of continuous users characterized by alternation of phases of treatment coverage with phases not covered by treatment (Convertino et al., 2021c). In accordance with the guidelines that provide for the biologic prescription in subjects with uncontrolled disease, and the treatment tapering in subjects showing disease remission (Smolen et al., 2010; Smolen et al., 2014; Smolen et al., 2017), we hypothesized that the disease activity is high in correspondence with events of biologic initiation and improves or remains stable in subsequent assessments. Disease activity is also expected to be reduced before discontinuations and to remain almost stable thereafter.

To test these hypotheses, we described the disease activity reported in the medical charts of an RA population in correspondence with the events of initiation and discontinuations of biologic disease-modifying antirheumatic drugs (DMARDs), identified from the HAD of the Tuscany Region (Italy).

2 Materials and methods

2.1 Study design and data sources

This investigation is part of the Pathfinder (Convertino et al., 2021d), a retrospective population-based cohort study on RA first ever biologic DMARD users extracted from the HAD of Tuscany. The regional healthcare system, comprising the national, universal, single-payer, and public health system, provides healthcare assistance to over 3 million Tuscan residents. All data about services supplied have been recorded electronically in the HAD since 2004. Data are periodically analyzed by the Agenzia Regionale di Sanità Toscana (ARST), and these have been used to conduct pharmacoepidemiological studies (Gini et al., 2014; Trifirò et al., 2021). The study was conducted from 1 January 2004 to 31 December 2019. We extracted data on 29 April 2020 from the HAD. We also collected information from the corresponding medical charts of the Rheumatology Unit of Pisa University Hospital. We used the following repositories encompassed in the Tuscan HAD: drug supply to inpatient and outpatient databases (Anatomical Therapeutic Chemical, ATC, Classification codes), exemptions from the co-payment database (exemption from co-payment codes), hospital discharge records, Emergency Department (ED) admission records (International Classification of Diseases Ninth Revision, ICD-9, codes), and outpatient services for specialist visits. The pseudo-anonymized information of Tuscan RA first ever biologic DMARD users identified by a validated algorithm (Convertino et al., 2021b) from the HAD was linked to the corresponding medical chart data in the Rheumatology Ward of Pisa University Hospital. According to the ethical and data protection requirements, data were managed by the Hospital Healthcare Office and through a unique identification number (Supplementary Material S1, Supplementary Figure S1). The informed consent for participating in the study was obtained from patients during the scheduled visits or by phone. From the medical charts, the following information was collected retrospectively: RA diagnosis date, Disease Activity Score 28 (DAS28), adverse events, adverse event dates, and dates of the DAS28 assessments. Information extracted from the HAD involved the biologic DMARD supplies, RA visits, RA diagnosis, RA exemption from co-payment, the first biologic DMARD supply date, the index date (ID), and the dates of the subsequent biologic DMARD dispensations.

The Pathfinder study received consent from the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) (EUPAS29263) (Convertino et al., 2021d) and was approved by the Ethical Committee of Pisa University Hospital (Protocol number 18724). This article was written in accordance with the guidelines on conducting and reporting drug utilization studies (Vrijens et al., 2012; De Geest et al., 2018; Dima et al., 2021).

2.2 Study population

During the validation analysis (Convertino et al., 2021b), we identified RA first ever biologic DMARD (infliximab, adalimumab, certolizumab pegol, etanercept, golimumab, abatacept, tocilizumab, sarilumab, and rituximab) users in the period between 1 January 2014 and 31 December 2016 (inclusion period), accessing healthcare facilities at the Rheumatology Unit of Pisa University Hospital in the year preceding the ID. First ever users were defined by no biologic DMARD dispensation recorded in the period ranging from the first record available in the Tuscan HAD to the ID (look-back period).

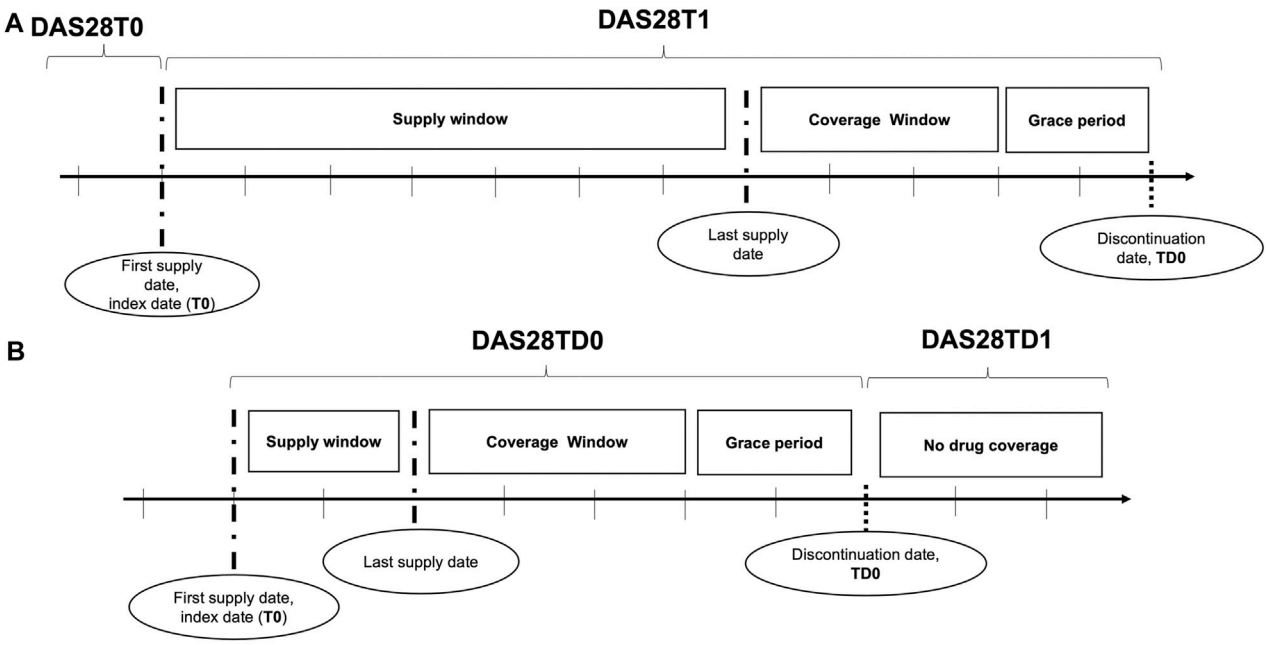

FIGURE 1
Disease activity assessments: **(A)** at the initiation of biologic DMARDs and **(B)** at the discontinuations. The disease activity was assessed through the DAS28 at initiation of biologic DMARDs **(A)** and at discontinuation **(B)**. Section A displayed how DAS28 was detected at initiation: the DAS28 recorded at the visit before (T0) the first biologic DMARD supply, corresponding to the index date, and that after the index date (T1) were used. Section B showed the DAS28 detection at discontinuations: the DAS28 reported in medical charts at the visit before (TD0) the discontinuation date, defined by the end of the drug coverage plus a grace period, and that after the discontinuation date (TD1) were adopted for the investigation.

We decided to exclude patients with rituximab as an index drug since the timing of administration is different from that of other biologic DMARDs, and this could have affected the frequency of DAS28 assessments. We followed up patients from the ID until the occurrence of the following events: disenrollment from the healthcare coverage plan, death, or end of the study period (31 December 2019), whichever came first.

2.3 Measurement

For each patient, we identified the ID and the date of each discontinuation event, defined as the first day not covered with biologic DMARDs. The coverage was calculated based on the defined daily dose (DDD) (WHO, 2021) and the number of doses supplied plus a grace period of 60 days not covered by treatment (i.e., without any other biologic DMARD supply). Disease activity was measured using the DAS28. The disease activity recorded during RA visits was classified according to EULAR guidelines into two clinical categories based on DAS28 values (Fransen and van Riel, 2005): i) in-target disease with DAS28 ≤ 3.2 and ii) off-target disease with DAS28 > 3.2.

We defined the DAS28T0 as the DAS28 value recorded in the closest date before the ID (T0) (including the ID), the DAS28T1 as the DAS28 recorded in the closest date after the ID (T1), the DAS28TD0 as the DAS28 recorded in the closest date before the date of any discontinuation event (TD0) (including the date of the discontinuation event), and the DAS28TD1 as the DAS28 recorded in the closest date after the date of any discontinuation event (TD1) (Figure 1). We measured improvements in DAS28 by classifying the changes according to the EULAR response criteria (Fransen and van Riel, 2005): i) good, when a change >1.2 of the DAS28 from DAS28T0 to DAS28T1 (or from DAS28TD0 to DAS28TD1) was recorded; ii) moderate, when a change > 0.6 of the DAS28 from DAS28T0 to DAS28T1 (or from DAS28TD0 to DAS28TD1) was registered; and iii) no improvement, when the change of DAS28 from T0 to T1 or from TD0 to TD1 ranged between −0.5 and 0.

We considered the following variables as baseline characteristics: time invariant (age at ID and gender), single event (index biologic DMARDs, conventional synthetic DMARDs, azathioprine, cyclophosphamide, ciclosporin, hydroxychloroquine sulfate, leflunomide, methotrexate, mycophenolate mofetil, and sulfasalazine supplied in 3 months prior to ID), and time variant (RA disease duration, as the time from the date of diagnosis in the medical chart to the ID recorded in the HAD, days).

2.4 Data analysis

We performed a step-by-step descriptive analysis by progressively classifying the population based on DAS28 measure availability and occurrence of discontinuation events (Figure 2). The results were reported as the numbers and percentages for categorical variables and as the mean and standard deviation (SD) or median and interquartile range [IQR] for continuous variables. In the first step, we described the baseline characteristics of all RA patients. In the second step, we classified patients based on the presence of at least three available DAS28 assessments, and we tested these two groups for differences at

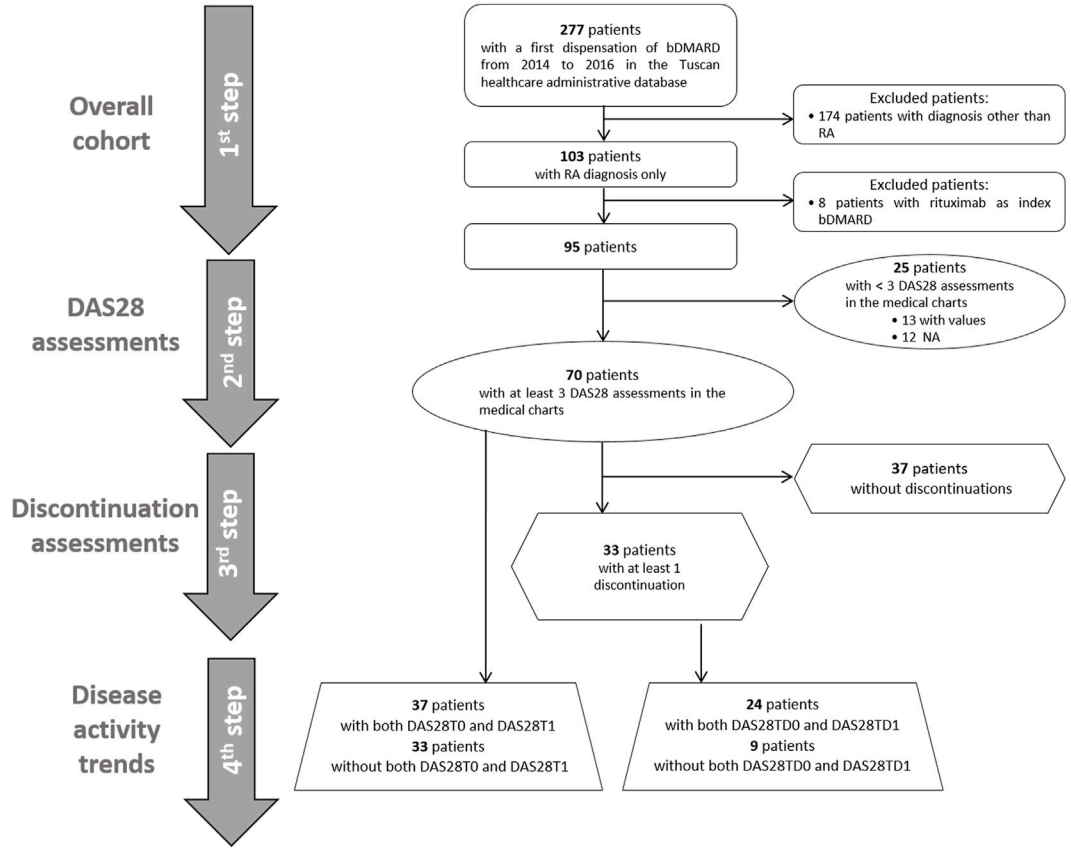

FIGURE 2
Flow chart of selection of the cohorts for the study analyses. First ever biologic DMARD users from 2014 to 2016 with rheumatoid arthritis were selected, and we included 95 patients in the first-step analysis. In the second step, patients were classified based on the presence of at least three DAS28 assessments reported in the medical charts or not. In the third step, patients were distinguished between those with at least one discontinuation and those without any discontinuation. In the fourth step, the disease activity trend was evaluated at initiation and at discontinuations in available patients with both DAS28T0 and DAS28T1 and DAS28TD0 and DAS28TD1, respectively.

the baseline by using the *t*-test and chi-square test, as appropriate. In the group with at least three DAS28 assessments, we described available DAS28T0 and DAS28T1. Discontinuation events were identified, and DAS28TD0 and DAS28TD1 were described. We computed discontinuations as dichotomous variables and categorical variables: no discontinuation, 1 discontinuation, 2–3 discontinuations, and ≥4 discontinuations. In the third step, among patients with at least three DAS28 available, we identified those with at least one discontinuation. We tested the baseline differences between continuers and discontinuers, and we described the related DAS28 observed at T0, T1, TD0, and TD1 and the corresponding time elapsed (days). In the fourth step, we separately analyzed the disease activity trends at the ID and at discontinuations. We restricted the evaluation to patients with records of both DAS28T0 and DAS28T1, and with records of both DAS28TD0 and DAS28TD1 within the group of patients with at least three DAS28 available. We used Sankey plots to illustrate the variation in disease activity with respect to the index date and discontinuation date, where the width of the flows represents the proportion of subjects. To check for discontinuations, possibly due to safety reasons, we retrieved adverse events recorded in patients from medical charts included in the analysis for disease activity trends, and we estimated the time between the date of the event and that of the discontinuation.

We performed a sensitivity analysis by varying the grace period for estimating discontinuations to 30 days. All these analyses were performed on anonymized data using R, version 3.6.3.

3 Results

Overall, 95 patients with RA first ever biologic DMARD use had the inclusion criteria (Figure 2). The majority of biologic DMARD first ever users were women (76.8%), and the mean age was 59.6 (SD 12.1). The index biologic DMARDs most frequently supplied were as follows: abatacept (33.7%), etanercept (29.5%), and adalimumab (15.8%). At baseline, 66 patients had at least one supply of csDMARDs, with hydroxychloroquine sulfate (33.7%) and methotrexate (30.5%) as the most frequently observed. The median time elapsed from the RA diagnosis date, and the first biologic DMARD supply was 2,633 [IQR = 966.5–5,518.5] days, i.e., 7.2 years, and most part of the biologic DMARD first ever users belonged to the categories exceeding the 5 years from RA diagnosis (Table 1 and Supplementary Figure S2).

TABLE 1 Baseline characteristics of the included RA first ever biologic DMARD users.

	RA first ever biologic DMARD users with DAS28 assessments			*p-value*
	Overall	With at least three DAS28 values	With <3 DAS28 values	
Patients, n (%)	95 (100)	70 (74)	25 (26)	—
Females, n (%)	73 (76.8)	55 (78.5)	18 (72)	0.461
Age, mean (SD)	59.6 (12.1)	59.3 (12.4)	60.4 (11.7)	0.708
Index biologic DMARDs				0.235
Adalimumab, n (%)	15 (15.8)	11 (15.7)	4 (16.0)	
Certolizumab pegol, n (%)	8 (8.4)	4 (5.7)	4 (16.0)	
Etanercept, n (%)	28 (29.5)	20 (28.6)	8 (32.0)	
Golimumab, n (%)	7 (7.4)	4 (5.7)	3 (12.0)	
Infliximab, n (%)	1 (1.1)	1 (1.4)	-	
Abatacept, n (%)	32 (33.7)	28 (40.0)	4 (16.0)	
Tocilizumab, n (%)	4 (4.2)	2 (2.9)	2 (8.0)	
csDMARDs				
At least one csDMARD, n (%)	66 (69.5)	48 (68.6)	18 (72.0)	0.947
Azathioprine, n (%)	-	-	-	-
Cyclophosphamide, n (%)	-	-	-	-
Cyclosporine, n (%)	2 (2.1)	2 (2.9)	-	-
Hydroxychloroquine sulfate, n (%)	32 (33.7)	25 (35.7)	7 (28.0)	0.650
Leflunomide, n (%)	19 (20.0)	16 (22.9)	3 (12.0)	0.382
Methotrexate, n (%)	29 (30.5)	20 (28.6)	9 (36.0)	0.660
Mycophenolate mofetil, n (%)	1 (1.1)	-	1 (4.0)	-
Sulfasalazine, n (%)	6 (6.3)	5 (7.1)	1 (4.0)	1.00
RA disease duration				
Mean days (SD)	3598.2 (3522.4)	3537.6 (3652.8)	3791.2 (3172.3)	0.804
Median days [IQR]	2633.0 [966.5–5518.5]	1533.0 [959.0–5612.0]	3230.0 [1008.3–5355.8]	0.477

DAS, disease activity score; DMARDs, disease-modifying antirheumatic drugs; csDMARDs: conventional synthetic DMARDs; IQR: interquartile range; n: number; RA: rheumatoid arthritis; and SD: standard deviation.

The median age observed at RA diagnosis was 54 [IQR = 41–60]. Overall, 91 discontinuations were identified (Supplementary Table S1), 67.0% had a DAS28TD0 and 59.3% DAS28TD1 (Supplementary Table S2). At TD0, 41.8% of discontinuations were associated with and in-target disease, while at TD1, the majority of discontinuations (40.7%) had no DAS28 recorded, and 35.2% reported an in-target RA (Supplementary Table S2).

Seventy patients (74.0%) had at least three DAS28 assessments recorded in the medical charts (Figure 2; Table 1). No statistical differences at the baseline were observed between these patients and those with less than three DAS28 values registered (Table 1). We identified 60 discontinuation events. Out of 70 patients with at least three DAS28 assessments available, 33 (47.1%) had at least one discontinuation; this distribution is similar to that observed in the general study population (47/95 patients, 49.5%) (Supplementary Table S1). Only six patients moved away from Tuscany, as reported in the medical charts, and no discontinuations of biologic treatment were detected before their moving. No significant differences were observed in the baseline characteristics between the population with at least one discontinuation and those without discontinuation (Supplementary Table S3). The DAS28T0 was available in 41 patients (58.6%) and the DAS28T1 in 66 (94.3%). At T0, 40% of patients were off-target and 41.4% had no DAS28 recorded, while at T1, 54.3% were in-target. At T1, patients with at least one discontinuation had a significant distribution of DAS28 associated with an off-target disease, while those continuing treatment displayed, most frequently, an in-target condition (Supplementary Table S4). Among the available 37 patients with both the DAS28T0 and DAS28T1 (Supplementary Table S5 and Table 2), 13 (35%) displayed a good improvement and six (16.2%) a moderate one (Table 2; Figure 3).

The median time elapsed between the DAS28T0 assessment and index date was 36 days (IQR 0–132), while the median time between DAS28T1 assessment and index date was 93 days (IQR 31–252). The

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TABLE 2 Assessment of DAS28 at T0 and T1 within patients with at least three available DAS28.

Patients with both DAS28T0* and DAS28T1°	
Overall, n	37
DAS28T0* off-target§, n (%)	27 (73.0)
DAS28T0 off-target AND DAS28T1 off-target, n (%)	14 (52.0)
Good improvement#, n (%)	3 (21.4)
Difference range	[−4.4; −1.5]
Moderate improvement+, n (%)	3 (21.4)
Difference range	[−1.1; −0.6]
No improvement^, n (%)	5 (35.7)
Difference range	[-0.4; 0.0]
Worsening£, n (%)	3 (21.4)
Difference range	[0.1–0.9]
DAS28T0 off-target AND DAS28T1 in-target, n (%)	13 (48.0)
Good improvement, n (%)	10 (77.0)
Difference range	[−5.3; −1.5]
Moderate improvement, n (%)	2 (15.0)
Difference range	[−1.0; −0.7]
No improvement, n (%)	1 (8.0)
Difference range	[−0.5]
Worsening£, n (%)	-
Difference range	-
DAS28T0* in-targetç, n (%)	10 (27.0)
DAS28T0 in-target AND DAS28T1 off-target, n (%)	3 (30.0)
Worsening, n (%)	3 (100.0)
Difference range	[1.0; 2.7]
DAS28T0 in-target AND DAS28T1 in-target, n (%)	7 (70.0)
Good improvement, n (%)	-
Difference range	-
Moderate improvement, n (%)	1 (14.3)
Difference range	[-0.9]
No improvement, n (%)	3 (42.9)
Difference range	[-0.1; 0.0]
Worsening, n (%)	3 (42.9)
Difference range	[0.1; 0.8]

DAS, disease activity score; DMARDs, disease-modifying antirheumatic drugs; n, number; RA, rheumatoid arthritis.
* DAS28T0: the closest DAS28 value recorded before the index date, including the index date.
° DAS28T1: the closest DAS28 value recorded after the index date.
§ off-target: DAS28 > 3.2.
Ç in-target: DAS28 ≤ 3.2.
#Good improvement: difference > −1.2; range [-∞; -1.2].
+Moderate improvement: difference > −0.6; range [-1.2; -0.6].
^No improvement: difference ≤ -0.6; range [-0.6; 0].
£Worsening: difference >0 range (0; +∞].

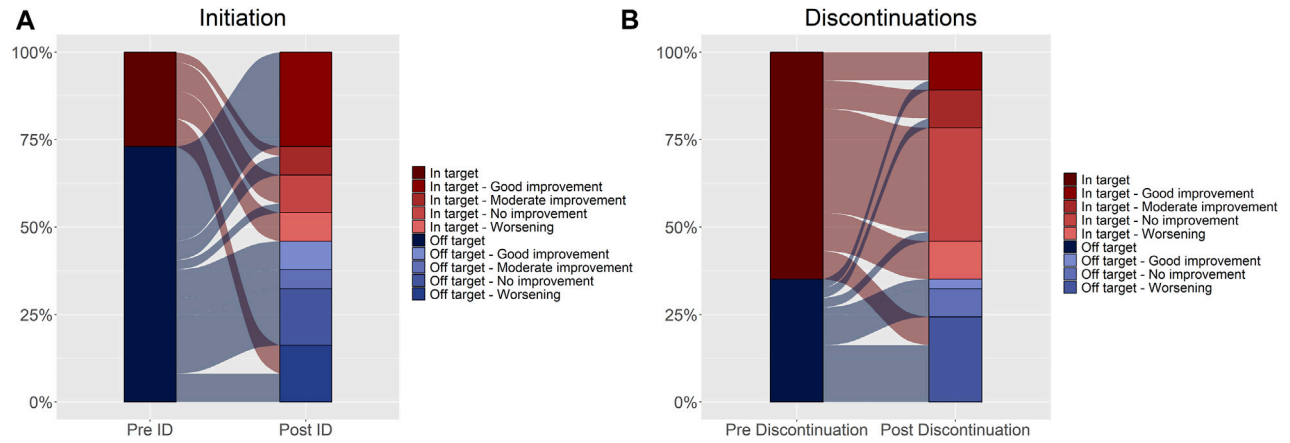

FIGURE 3
Disease activity trend assessed at initiation **(A)** and discontinuations **(B)**. Changes in DAS28 relative to the index date and discontinuations are shown in Figure 3 (Panel A, B, respectively). The reference unit is the subject in Panel A, and the discontinuation in Panel **(B)**. In the left column of both panels, disease activity expressed as DAS28 is reported and categorized as in-target (dark red) and off-target (dark blue) (pre-index date, Panel A and pre-discontinuation date, Panel **(B)**. In the right column, disease activity was further categorized based on the movement over time (post-index date, Panel A and post-discontinuation date, Panel **(B)** as good improvement, moderate improvement, no improvement, and worsening. Shades of red represent in-target conditions, and shades of blue represent off-target conditions. The flows connecting the different layers of the two bars represent the movement over time, relative to the index date (Panel A) and the discontinuation date (Panel B). The width of the flow reflects the proportion of subjects (Panel A) or discontinuations (Panel B).

subjects with both pre- and post-index DAS28 measurements within 180 days of it were 22 (59.5%), and 20/22 had off-target disease (91%), while 2/22 (9%) had an in-target RA. Of these, five (22.7%) experienced a deterioration, with one (20.0%) moving from in-target to off-target, three (60.0%) remaining off-target, and one (20.0%) remaining in-target.

Most of the patients showed disease stability or improvement after initiating biologic DMARDs (75.7%) (Table 2; Figure 3), as well as after the discontinuation events (64.9%) (Table 3; Figure 3).

Out of 33 patients with at least three DAS28 and a discontinuation, 24 had 37 events with both DAS28TD0 and DAS28TD1 (Supplementary Table S6). The reasons for discontinuations were deterioration of disease (13), adverse drug events (7), surgery/hospitalizations (5), pregnancy (4), and no information about were reported (8). Among these 37 discontinuation events (Supplementary Table S5 and Table 3), the disease activity showed a good or moderate improvement in 10 events (27.0%) (Table 3; Figure 3). The median time elapsed between the DAS28TD0 assessment and discontinuation date was 113 days (IQR 51–168), while the median time between the DAS28TD1 assessment and discontinuation date was 117 days (IQR 49–221). The subjects with both pre- and post-discontinuation DAS28 measurements within 180 days of it were 18 (48.6%), and 10/18 patients were in target and 8/10 off-target at TD0. Of these, nine (50.0%) experienced a deterioration, with one (11.1%) moving from in-target to off-target, six (66.7%) remaining off-target, and two (22.2%) remaining in-target.

Out of 24 patients with both DAS28TD0 and DAS28TD1, 11 had adverse events recorded. In particular, among the 37 discontinuations, we retrieved 15 adverse events, of which 9/15 occurred ±1 year at the discontinuation date and 3/9 showed off-target RA and disease worsening. These included neutropenia, bile acid increase, and pneumonia. Out of the six remaining adverse events reported within 1 year of the discontinuation, three (ovarian cancer, hypersensibility, and cough/sinusitis) occurred in a condition of the in-target disease and stability, one (intolerance) in an in-target and improvement disease, and one (hypersensibility) in an off-target and improvement condition. The drugs discontinued were etanercept, adalimumab, certolizumab, and abatacept. No further information was reported in the medical charts (Supplementary Table S7).

In sensitivity analysis, we almost confirmed the main analysis observations (Supplementary Table S8–S13).

4 Discussion

This study describing the relationship between drug utilization patterns assessed using HAD information and the disease activity reported in the medical charts of RA patients showed that over half of the discontinuation events had an in-target disease before and after the biologic interruption.

In line with the clinical recommendations (Smolen et al., 2014; Smolen et al., 2017) and literature evidence (Silvagni et al., 2018), in our study, etanercept and adalimumab were among the most frequently supplied index drugs. We found a high percentage of abatacept supplies in both the overall population and in the subgroup of patients with three available DAS28 assessments. A high number of DAS28 assessments could reflect closer monitoring of patients by rheumatologists, probably in relationship with the disease burden. At the time of observation, abatacept was recommended as a first-line biologic DMARD in subjects with co-morbidities (Smolen et al., 2010; Monti et al., 2017), and therefore its higher use in subjects with more assessments (i.e., those with more complicated disease) seems to be plausible. However, statistical significance was not confirmed; therefore, these results should be considered with caution.

When investigating the initiation of the first ever biologic drugs in subjects with available DAS28 measure before and after the ID, we

TABLE 3 Assessment of DAS28 in the discontinuation events, classified by chronological occurrence.

	Discontinuations available with both DAS28TD0* and DAS28TD1°			
	Overall	First event	Second event	Subsequent events
Patients, n	24	24	6	4
Events, n	37	24	6	7
DAS28 assessments				
DAS28TD0* off-target[$], n (%)	13 (35.1)	9 (37.5)	2 (33.3)	2 (33.3)
DAS28TD0 off-target AND DAS28TD1° off-target, n (%)	10 (76.9)	7 (77.8)	2 (100.0)	1 (50.0)
Good improvement[#], n (%)	1 (10.0)	1 (14.3)	-	-
Difference range	[−3.0]	[-3.0]		
Moderate improvement[+], n (%)	-	-	-	-
Difference range				
No improvement[‚], n (%)	3 (30.0)	2 (28.6)	1 (50.0)	
Difference range	[−0.5; 0.0]	[−0.5; 0.0]	[−0.1]	-[−0.1; 1.0]
Worsening[£], n (%)	6 (0.6)	4 (57.1)	1 (50.0)	1 (100.0)
Difference range	[0.1; 2.6]	[0.1; 2.6]	[0.8]	[0.6]
DAS28TD0 off-target AND DAS28TD1 in-target, n (%)	3 (23.1)	2 (22.2)	-	1 (50.0)
Good improvement, n (%)	1 (33.3)	1 (50.0)	-	-
Difference range	[−2.9]	[−2.9]		
Moderate improvement, n (%)	2 (66.7)	1 (50.0)	-	1 (100.0)
Difference range	[−1.0; -0.6]	[−1.0]		[−0.6]
No improvement[‚], n (%)	-	-	-	-
Difference range				
Worsening, n (%)	-			
Difference range	-			
DAS28TD0* in-target, n (%)	24 (64.9)	15 (62.5)	4 (66.7)	5 (71.4)
DAS28TD0 in-target AND DAS28TD1 off-target, n (%)	3 (13.0)	2 (13.3)	1 (25.0)	-
Worsening, n (%)	3 (100.0)	2 (100.0)	1 (100.0)	-
Difference range	[1.7; 2.0]	[1.7; 2.0]	[1.8]	
DAS28TD0 in-target and DAS28TD1 in-target, n (%)	21 (87.5)	13 (86.7)	3 (75.0)	5 (100.0)
Good improvement, n (%)	3 (15.0)	1 (7.7)	1 (33.3)	1 (20.0)
Difference range	[−1.4; −1.3]	[−1.4]	[−1.3]	[−1.3]
Moderate improvement, n (%)	3 (15.0)	2 (15.4)	-	1 (20.0)
Difference range	[−1.1;−0.7]	[−1.1;−0.7]		[−0.8]
No improvement, n (%)	11 (52.4)	9 (69.2)	1 (33.3)	1 (20.0)
Difference range	[−0.3; 0.0]	[−0.3; 0.0]	[0.0]	[−0.2]

(Continued on following page)

TABLE 3 (*Continued*) Assessment of DAS28 in the discontinuation events, classified by chronological occurrence.

	Discontinuations available with both DAS28TD0* and DAS28TD1°			
	Overall	First event	Second event	Subsequent events
Worsening, n (%)	4 (20.0)	1 (7.7)	1 (33.3)	2 (40.0)
Difference range	[0.2; 0.7]	[0.7]	[0.4]	[0.2]

DAS, disease activity score and n, number.
* DAS28TD0: the closest DAS28 value recorded before the discontinuation date, including the discontinuation date.
° DAS28TD1: the closest DAS28 value recorded after the discontinuation date.
§ off-target: DAS28 > 3.2.
Ç in-target: DAS28 ≤ 3.2.
#Good improvement: difference > −1.2; range [-∞; -1.2].
+Moderate improvement: difference > −0.6; range [-1.2; -0.6].
^No improvement: difference ≤ -0.6; range [-0.6; 0].
£Worsening: difference >0 range (0; +∞].

observed that 73% of patients (27/37) started with an off-target disease that provides the rationale for prescribing a biologic drug in accordance with the clinical guidelines. However, (10/37) 27% of patients started biologic treatment with an in-target disease. It is important to remark that the causal relationship between disease activity and the initiation of biologics is conditioned by the temporal distance between the available DAS28 assessments and the initiation event. It is unlikely that a DAS28 measure recorded several years before and after the ID can provide a reliable disease activity measure at the time of biologic DMARD initiation. In this regard, it is important to note that patients with DAS28 assessed within 6 months of the ID (i.e., those with the most reliable disease activity assessment) showed off-target disease in the majority of cases (20/22 patients, 91%). In 13/27 patients starting with an off-target disease (48%), the disease control was achieved at the subsequent assessment, while in six (22.2%) users, the improvements were without achieving the disease control. These results are in line with those of other real-world studies. For instance, a study using the Corrona registry data and evaluating biologic naïve patients with moderate and severe RA pointed out that among 817 patients with severe RA and 779 with moderate disease, 41.2% and 60.1% achieved a controlled disease after 1 year, respectively (Kavanaugh et al., 2017).

When disease activity was measured in relationship with discontinuations, 24 (64.9%) events with both DAS28TD0 and DAS28TD1 measures available presented an in-target disease before discontinuing the treatment and 17/24 (70.8%) displayed disease improvement or stability after the discontinuation. Adverse events recorded in the medical charts rarely occurred in plausible temporal relationships to suggest a causal role for discontinuation events. These results suggest that, according to our discontinuation definition, disease control could often drive the clinical decision of tapering biologic DMARDs in accordance with the clinical guidelines (Smolen et al., 2014; Smolen et al., 2017) and disease remains controlled after tapering. The robustness of these findings is confirmed by the sensitivity analysis, performed to evaluate whether the discontinuation definition could have affected our observations. Even in this case, the time distance between available DAS28 assessments and the date of the discontinuation event could affect the reliability of the results (18/24 patients, 75%, had DAS28 assessments within 6 months before and after the discontinuation date). Overall, 10/18 patients were in target and 8/18 were off-target. Nine discontinuation events showed a disease worsening, six starting from an off-target condition, and four from an in-target disease. Out of these, only one patient with an off-target disease switched to a JAK inhibitor. In these cases, the decision to discontinue the treatment should have been driven by reasons other than the achievement of disease control [i.e., patient deterioration due to co-morbidity-related events (Listing et al., 2015), lack of biologic DMARD response (Olsen et al., 2019), safety issues (Capogrosso Sansone et al., 2015; Codreanu and Damjanov, 2015; Antonazzo et al., 2022), or non-clinical events] that deserve further investigations.

Our results about the in-target disease observed before discontinuations and disease improvement or stability after the interruption are in line with those in the medical literature. A prospective observational study on 43 first ever biologic DMARD users interrupting treatment showed that 58.1% of patients maintained discontinuation along with the in-target condition for up to 1 year. In these patients, the disease activity recorded after the biologic DMARD initiation was significantly lower than in patients restarting biologic DMARD, who relapsed to off-target within 1 year (Ochiai et al., 2021). Another multicenter observational study performed in Japan using data from medical records of 102 RA infliximab users having DAS28 < 3.2 for at least 24 weeks displayed that 55% of patients maintained disease stability and 43% achieved RA remission after infliximab discontinuation (Tanaka et al., 2010). In the HOPEFUL-3 study, a follow-up to the HOPEFUL-1 and HOPEFUL-2 studies evaluating adalimumab users in Japanese patients with early RA, out of 74 patients discontinuing adalimumab for low disease activity, 59 (79.7%) retained the status of low RA activity for about 4 years (Tanaka et al., 2017). Schlager et al. (2020), in a recent systematic literature review and meta-analysis of clinical trials and observational studies, highlighted that the low disease activity at the time of discontinuation should be explored as a predictor of interruption. However, this study displayed that among patients discontinuing biologic DMARDs owing to the low disease activity, the probability for RA relapsing was high at 13 months of observation (overall Odds Ratio, OR 3.87; 95% CI 2.31–6.49).

Our study has some elements of strength. First, we used ecological data from Tuscan HAD that have been consolidated from previous population-based studies (Gini et al., 2014; Convertino et al., 2021a; Convertino et al., 2021b; Convertino et al., 2021c; Trifirò et al., 2021; Convertino et al., 2023). Second, while disease activity is usually measured by proxies in HAD studies, in our investigation, instead, we used the medical charts that represent a more reliable source of this information. Third, since therapeutic indications of drugs are not

recorded in the HAD in Italy, by linking information from medical charts, we could have the certainty that all biologic users included in our study had RA.

Some limitations have to be considered. First, the small number of patients included in the study could limit the extension of the results to the general population of RA patients. However, the majority of studies investigating similar topics in the literature are not more than ours (Tanaka et al., 2010; Tanaka et al., 2017; Schlager et al., 2020; Ochiai et al., 2021). Second, we have a limited number of disease activity assessments recorded in the medical charts, and this could affect our findings. Nevertheless, a UK study (Choy et al., 2012) showed that the baseline recording of DAS28 is available in about 45% starting a biologic DMARD therapy, which is lower than the frequency observed in our study (59%). The authors of this study hypothesized that disease activity is likely measured at any visit but recorded in medical charts more probably when a relevant improvement or worsening occurs. Therefore, the probability of not recording important disease activity modification in two consecutive measures, even distant in time, is unlikely. Third, the assessment of two consecutive DAS28 without time restriction could have influenced our results. However, the disease activity monitoring should be scheduled at least every 180 days (Smolen et al., 2010; Smolen et al., 2014; Smolen et al., 2017), which is not far from the 113 and 117 days in median observed before and after the discontinuation events in our study. Fourth, the quality of available data could have affected the results. However, we have carefully measured the characteristics of patients, and discontinuation events progressively dropped out from the analysis due to the lack of records of disease activities, and by comparing these with those remaining in the cohort, we controlled for the possible selection bias. Fifth, we cannot exclude that information bias (Grimes and Schulz, 2002) could have occurred. Sixth, the discontinuation measurement was based on drug coverage estimated through the DDD and not by the prescribed daily dose (PDD). Since the use of DDD could overestimate the persistence of patients and inversely underestimate the discontinuation assessment, we cannot exclude that a definition based on the actually prescribed dose could have changed by increasing the number and the timing of discontinuation events. However, we performed the sensitivity analysis by varying the discontinuation definition, which confirmed the robustness of the main analysis results.

5 Conclusion

In conclusion, half of the RA patients achieve an in-target disease after starting biologic DMARDs, and the disease activity trend mainly reveals RA stability or improvement. As far as discontinuations are concerned, the majority of discontinuation events reported an in-target condition before the interruption date, and disease control is also confirmed after the discontinuation. Future studies on a larger RA population are needed to confirm our findings and support the use of this discontinuation definition in Tuscan HAD as effectiveness proxy.

Data availability statement

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

Ethics statement

The studies involving humans were approved by this retrospective chart review study involving human participants which was in accordance with the ENCePP Code of Conduct, the ethical standards of the Institutional and National Research Committee, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Ethical Committee of the Pisa University Hospital approved this study (Protocol number 18724). Informed consent was obtained from all individual participants included in the study. All patients were required to give their consent to the publication of study results. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

IC, MaC, SG, RG, ST, VL, LT, GT, CoB, MM, EL, and MT: drafting the article, analysis, and interpretation of data. IC, MC, SG, RG, GV, EC, SF, ST, MB, CB, OP, VL, LT, MF, GT, MC, CoB, MM, EL, and MT: conception and design of the study, acquisition of data, analysis, and interpretation of data. IC, MaC, SG, RG, ST, VL, LT, GT, CoB, MM, EL, and MT: revising the manuscript critically for important intellectual content. 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

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1244486/full#supplementary-material

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Do disease-modifying antirheumatic drugs and non-steroidal anti-inflammatory drugs increase the burden on ankylosing spondylitis patients with mild-moderate COVID-19? evidence from a retrospective cohort study

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Objectives: The impact of non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and tumor necrosis factor inhibitors (TNFi) on the outcomes of mild-moderate COVID-19 in patients with ankylosing spondylitis (AS) remains unclear. This study aimed to evaluate the effects of NSAIDs, csDMARDs, and TNFi on AS patients with mild-moderate COVID-19.

Methods: This cohort study utilized patient-reported PCR/antigen tests to determine the occurrence of COVID-19 and assessed clinical manifestations to determine its severity. The study focused on two primary outcomes: an increased number of COVID-19 symptoms and a prolonged disease course (longer than 10 or 28 days). Modified Poisson regression was performed to analyze the association between exposures and outcomes.

Results: A total of 521 patients were included in the analysis. The median age was 34.8 (inter-quartile range: 27.2–46.7), with 420 (80.6%) being men. Among the patients, 52 (10.0%) had comorbidities and 443 (85%) had been vaccinated. After adjusting for confounding factors, there was no significant association between csDMARDs or TNFi and the presence of more than 5 symptoms in mild-moderate COVID-19 (adjusted relative risk (RRa) 1.08, 95% CI: 0.84–1.40 or 1.09, 0.92–1.29 for csDMARDs or TNFi, respectively), whereas the prevalence of experiencing more than 5 symptoms increased in patients with NSAID monotherapy (RRa 1.22, 95% CI: 1.01–1.46). Similarly, there was no significant association with having more than 10 symptoms (RRa 0.65, 95% CI: 0.26–1.64; 0.95, 0.36–2.54; and 1.01, 0.53–1.91 for NSAIDs, csDMARDs, and TNFi, respectively). Patients who had pre-existing use of NSAIDs, csDMARDs and TNFi had similar odds of experiencing a disease course longer than 10 days (RRa 1.17, 95% CI: 0.82–1.66; 1.18, 0.78–1.77; and 1.22, 0.92–1.63 for NSAIDs,

csDMARDs, and TNFi, respectively) and longer than 28 days (RRa 0.94, 95% CI: 0.31–2.81; 0.97, 0.25–3.74 and 1.05, 0.44–2.49, respectively) compared to those not using medication.

Conclusion: AS patients treated with csDMARDs or TNFi did not show inferior outcomes in terms of symptom burden or recovery compared to those not using medication in mild-moderate COVID-19. The observed inverse association between pre-existing NSAIDs use and COVID-19 symptom burden in AS deserves further investigation.

KEYWORDS

coronavirus disease 2019 (COVID-19), ankylosing spondylitis, TNF-inhibitor, DMARDs (synthetic), cohort study, NSAID (non-steroidal anti-inflammatory drug)

1 Introduction

Despite the World Health Organization (WHO) declaring an end to the COVID-19 pandemic as a public health emergency (Graham, 2023), it had a significant impact on individuals with chronic inflammatory diseases such as ankylosing spondylitis (AS). This is particularly true for those taking immunomodulatory or immune-suppressive medications known as conventional synthetic or biological disease-modifying antirheumatic drugs (cs/bDMARDs), in addition to the compromised immune system associated with AS itself (Deodhar et al., 2022). Over the past 4 years, new variants of the virus have emerged, which exhibit increased transmissibility but fortunately, have been found to be less virulent than the original virus (Nyberg et al., 2022). For the majority of patients, COVID-19 presents as a mild or moderate disease, with 70%–80% of those infected experiencing mild flu-like symptoms and not requiring hospitalization, even during the early stages of the pandemic (Kun et al., 2023). Previous research has predominantly focused on severe outcomes of COVID-19 in patients with AS, such as hospitalization, admission to intensive care units, mechanical ventilation, and death. Therefore, the outcomes and predictive factors of severe COVID-19 in AS patients have been well-documented (Gianfrancesco et al., 2020; Strangfeld et al., 2021). However, there is a lack of reporting on the outcomes of mild-moderate COVID-19 in AS patients, even though these cases make up the majority of patients during the pandemic. Additionally, it remains unknown whether AS patients are at a heightened risk of experiencing increased symptoms or prolonged recovery periods with mild-moderate COVID-19.

Tumor necrosis factor inhibitor (TNFi) is a widely used bDMARD in the treatment of AS and is known for its immunosuppressive properties. Traditionally, TNFi has been associated with an increased risk of infection (Wroński and Fiedor, 2019). However, during the pandemic, TNFi has been suggested as a treatment option for individuals with severe COVID-19 due to its anti-inflammatory characteristics (Guo et al., 2022). Recent studies have reported that TNFi is associated with reduced odds of severe COVID-19 in people with axial spondyloarthritis, but its impact on individuals with AS and mild-moderate COVID-19 has not been extensively studied (Gianfrancesco et al., 2020; Machado et al., 2023). The objective of this study is to evaluate the effects of csDMARDs and TNFi on the outcomes of individuals with mild-moderate COVID-19. Improving our understanding of these effects will help fill gaps in knowledge regarding the outcomes of AS patients with COVID-19 andmore importantly, provide evidence for modifying the treatment strategy for AS.

2 Materials and methods

2.1 Study design and patients

This retrospective cohort study was conducted at the outpatient rheumatology clinics of the First Medical Center of the Chinese People's Liberation Army (PLA) General Hospital, a tertiary referral center in Beijing, China. Patients attending the clinics were invited to participate in the study and complete questionnaires that included demographic data, AS disease characteristics, and COVID-19 infection details. Besides, evaluation of AS disease activity (Bath Ankylosing Spondylitis Disease Activity Index, BASDAI) (Garrett et al., 1994), function level (Bath Ankylosing Spondylitis Functional Index, BASFI) (Calin, et al., 1994) and physical mobility (Bath Ankylosing Spondylitis Metrology Index, BASMI) (Jenkinson et al., 1994) were conducted by a fellowship-trained physician.

COVID-19 infection details included the results of SARS-CoV-2 PCR or antigen tests, vaccination status, COVID-19 symptoms, and the time taken for patients to recover. Patients aged 18 years or older were enrolled in the study from 20 December, 2022, to 31 March, 2023, if they met the 1984 modified New York criteria for AS (van der Linden et al., 1984) and had mild-moderate COVID-19. Patients were identified as having COVID-19 if they had a positive SARS-CoV-2 PCR or antigen test, and the day of the positive test was considered as the index day. The severity of COVID-19 was determined based on the Chinese Diagnosis and Treatment Protocol for COVID-19 (Trial Version ten) (General Office of the National Health Commission, 2023). Mild COVID-19 was defined as patients having upper respiratory infection symptoms as their predominant manifestation, such as fever, cough, or sore throat. Moderate COVID-19 was defined as patients having persistent fever, cough, or dyspnea, but without any of the following signs: respiratory rate ≥30 times per minute, oxygen saturation ≤93% when breathing ambient air, PaO2/FiO2 ≤ 300 mmHg, or lung infiltrates >50% area on images. Patients who denied having COVID-19 or whose AS medications were something other than non-steroidal anti-inflammatory drugs (NSAIDs), TNFi, and csDMARDs were excluded from the study. We retrospectively reviewed exposure variables before the index day and prospectively explored their influences on outcomes.

This study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and complied with the Declaration of Helsinki.

2.2 Exposure variables

NSAIDs, TNFi, and csDMARDs exposure was defined as patients being prescribed NSAIDs, TNFi, and csDMARDs within 12 months before the index date, respectively. TNFi included etanercept and its biosimilars, adalimumab, and infliximab. The range of csDMARDs in this study included sulfasalazine, methotrexate, leflunomide, thalidomide, and iguratimod. Given the clinical practice and the real-world background of the study, patients taking AS medications were grouped as NSAIDs monotherapy, NSAIDs + csDMARDs, csDMARDs monotherapy, and TNFi (with or without NSAIDs/csDMARDs).

Covariates such as age, sex, comorbidity, body mass index (BMI), smoking, alcohol consumption, and vaccination status might be associated with different outcomes in COVID-19. Therefore, they were considered confounding factors and adjusted for in further multivariable analysis. Comorbidities included diabetes, cardiovascular disease (CVD, including hypertension), and chronic obstructive lung disease (COPD). Vaccination status was classified as unvaccinated, partially vaccinated (one dose of inactive vaccine), fully vaccinated (two doses of inactive vaccine or one dose of adenovirus vaccine), and booster vaccinated (three doses of inactive vaccine or two doses of adenovirus vaccine).

2.3 Outcomes

The two key outcomes in this study were symptom burden and disease course. Fifteen symptoms related to COVID-19 were collected, including fever (peak temperature >37.3°C), chill, sore throat, hoarse voice, cough, nasal congestion, runny nose, headache, dizziness, dyspnea, myalgia, otologic symptoms, palpitation, abdominal pain, and diarrhea. Following a previous study (Hopkinson et al., 2021), we considered the number of self-reported COVID-19 symptoms as a proxy for disease burden and did not attempt to weigh different symptoms. In this study, the presence of more than 5 symptoms or 10 symptoms was arbitrarily categorized as increased symptom burden at two levels.

Defining long COVID in AS is challenging due to the lack of a globally accepted definition and the overlap of symptoms between long COVID and AS, such as fatigue and arthralgia (Baimukhamedov, 2023). In this study, we calculated the period between the index day and the day when patients reported returning to their "usual health." Patients with a period longer than 10 days (LC10) or 28 days (LC28) were defined as having long COVID, to different extents.

2.4 Statistical analysis

In the descriptive analysis, we assessed the differences in proportions and medians of variables between the exposure group and the unexposed group using chi-squared tests for categorical variables and *t*-tests or Mann-Whitney *U* tests for continuous variables. Missing data were addressed using multiple imputations with five iterations, assuming that the data were missing at random.

The main analysis compared baseline medication exposure *versus* no medication use on COVID-19 symptom burden and disease course. First, to evaluate the association between COVID-19 symptom burden and baseline medication exposure, we used modified Poisson regression with a robust (sandwich) estimation of variance (which allows for binary variables) (Zou, 2004) to calculate the relative risk (RR) and 95% confidence interval (CI). We performed multivariable analysis to adjust for confounding factors, including age, gender, comorbidity, overweight (BMI >25) (Carnethon et al., 2012), smoking, alcohol consumption, and vaccination status. Similar analyses were conducted for the outcome of long COVID. Subsequently, we subgrouped patients treated with TNFi into TNFi monotherapy or combination with NSAIDs or csDMARDs to further explore the influence of TNFi on COVID-19 outcomes using the same approach. Forest plots were used to visualize the results using the R statistical program (Ver 4.0.3) with the forest plot package. Other statistical analyses were performed using SPSS Statistics (version 22; IBM Corp.). A p-value <0.05 was considered statistically significant for all analyses.

3 Results

3.1 General information

Questionnaires were collected from 658 AS patients, out of which 112 patients reported negative results for COVID-19 infection. Additionally, 25 patients were taking other AS medications, including 11 patients using Secukinumab, 6 patients using Tofacitinib, and 8 patients using traditional Chinese medicines. These patients were excluded from the analysis, leaving a total of 521 patients (Figure 1). Among these patients, the median age was 34.8 (interquartile range, IQR: 27.2–46.7). Of the 521 patients, 420 (80.6%) were male, 52 (10.0%) had at least one comorbidity, 442 (84.8%) had HLA-B27 positivity, and 443 (85%) had been vaccinated (Table 1).

Regarding AS treatments, 71 patients (13.6%) underwent NSAIDs monotherapy, 95 (18.2%) received NSAIDs in combination with csDMARDs, 38 (7.3%) had csDMARDs monotherapy, 232 (44.5%) were treated with TNFi, and 85 (16.3%) did not receive any of the mentioned medications. Compared to patients who reported no AS medication usage, patients who received TNFi were more likely to be men (196 [84.5%] vs 66 [77.6%]) and less likely to be older than 55 years (6 [2.6%] vs 5 [5.9%]). Patients with NSAIDs monotherapy were more likely to be overweight (38 [53.5%] vs 31 [36.5%]) and have COPD (4 [5.6%] vs 1 [1.2%]), but less likely to be older than 55 years (1 [1.4%] vs 5 [5.9%]). On the other hand, patients with csDMARDs monotherapy were more likely to be older than 55 years (5 [13.2%] vs 5 [5.9%]), but less likely to be male (26 [68.4%] vs 66 [77.6%]). Besides, patients treated with csDMARDs monotherapy, NSAIDs & csDMARDs or TNFi had

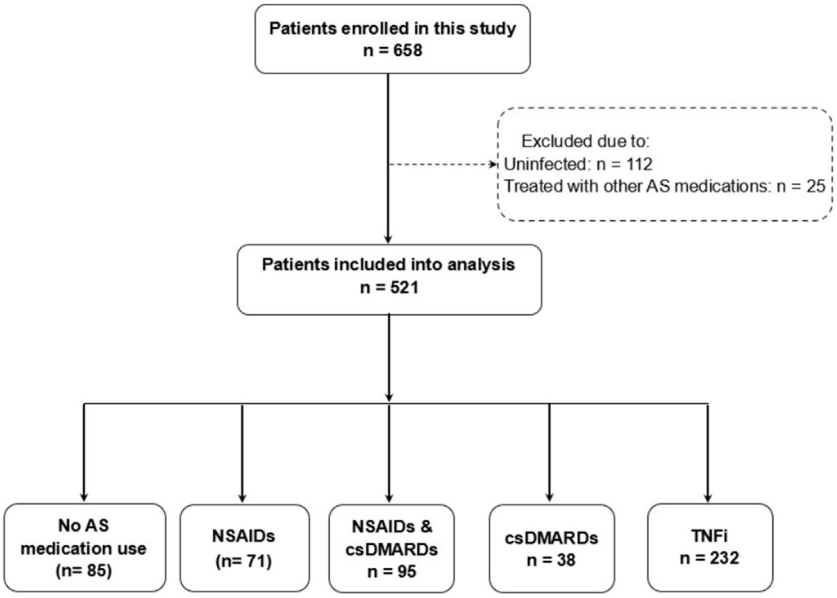

FIGURE 1
Flow-chart of analytical approach. Abbreviation: NSAIDs, non-steroidal anti-inflammatory drugs. csDMARDs, conventional systhetic disease-modifying antirheumatic drugs. TNFi, Tumor necrosis factor inhibitors.

lower BASDAI (median and IQR was 2.2, (1.2, 3.8), 2.1 (1.0, 3.5) and 2.2 (1.2, 4.0), respectively) and BASMI (3.0 (0, 6.3), 1.0 (0, 5.0) and 3.0 (0, 5.0), respectively) than patients without previous medication use (3.0 (1.6, 4.4) for BASDAI and 4.0 (0, 5.0) for BASMI), whereas patients with NSAIDs monotherapy had worse BASFI (1.8 (0.2, 4.8)) and comparable BASDAI (3.0 (1.4, 4.2)), BASMI (4.0 (0, 5.0)) than patients without previous medication use ((3.0 (1.6, 4.4) for BASDAI, 4.0 (0, 5.0) for BASMI and 1.2 (0.1, 4.4) for BASFI) (Table 1).

3.2 Association of AS medications with COVID-19 disease burden

The median (IQR) number of symptoms reported by patients with no medication usage, NSAIDs monotherapy, csDMARDs monotherapy, and TNFi were 6.0 (5.0, 8.0), 8.0 (6.0, 9.0), 7.5 (5.0, 9.0), and 7.0 (5.0, 9.0), respectively (Table 2). Detailed COVID-19 symptoms are presented in Supplementary Table S1. The univariate analysis revealed that patients treated with AS medications had similar odds of experiencing more than 5 symptoms compared to those without medication use, except for patients with NSAIDs monotherapy (RR 1.26, 95% CI: 1.05–1.51). After adjusting for age, gender, obesity, smoking, alcohol drinking, coexisting comorbidities, and vaccination status, the association of csDMARDs or TNFi with the risk of experiencing more than five symptoms remained insignificant (adjusted RR (RRa) 1.07, 95% CI: 0.83–1.39 or 1.10, 0.93–1.30, respectively). However, patients with NSAIDs monotherapy still had increased odds of experiencing more than 5 symptoms (RRa 1.22, 95% CI: 1.01–1.46). Additionally, patients with COPD had a significantly increased risk of experiencing more than 5 symptoms compared to those without baseline coexisting diseases (RRa 1.34, 95% CI: 1.16–1.56) (Figure 2).

A similar analysis was conducted to evaluate the risk of experiencing more than 10 symptoms in AS patients. Patients treated with NSAIDs, csDMARDs and TNFi had similar odds of experiencing more than 10 symptoms compared to those without medication use in both univariable analysis and after adjusting for confounding factors (RRa 0.65, 95% CI: 0.26–1.64; 0.95, 0.36–2.54; and 1.01, 0.53–1.91 for NSAIDs, csDMARDs and TNFi, respectively). Likewise, COPD was associated with greater odds of experiencing more than 10 symptoms (RRa 5.94, 95% CI: 2.54–13.90) (Figure 2).

3.3 Association of AS medications with long COVID

The median (IQR) duration of COVID-19 symptoms in patients with no medication use, NSAIDs monotherapy, csDMARDs monotherapy, and TNFi were 8.0 (5.5, 13.5), 9.0 (6.0, 13.0), 9.5 (6.8, 14.5), and 9.0 (6.0, 16.0) days, respectively (Table 2). The univariate analysis revealed that patients with different AS medications had similar odds of long COVID (LC10) compared to those without medication use. Importantly, these associations were reproduced after adjusting for confounding factors (RRa 1.17, 95% CI: 0.82–1.66; 1.18, 0.78–1.77; and 1.22, 0.92–1.63 for NSAIDs, csDMARDs and TNFi, respectively) (Figure 3).

Similarly, when LC28 was considered as an increased disease course in COVID-19, patients with NSAIDs, csDMARDs, and TNFi had similar odds of LC28 compared to those without medication usage, both in univariate analysis and after adjustment (RRa 0.94, 95% CI: 0.31–2.81; 0.97, 0.25–3.74; and 1.05, 0.44–2.49 for NSAIDs csDMARDs and TNFi, respectively). Additionally, having cardiovascular disease (CVD) was found to be associated with greater odds of LC10 (RRa 1.52, 95% CI: 1.12–2.06), but not LC28 (RRa 1.53, 95% CI: 0.59–3.92) in the population (Figure 3).

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TABLE 1 Baseline characteristics of the participants.

	Total (n = 521)	AS treatment				
		None (n = 85)	NSAIDs (n = 71)	NSAIDs & csDMARDs (n = 95)	csDMARDs (n = 38)	TNFi (n = 232)
Male sex	420 (80.6%)	66 (77.6%)	55 (77.5%)	77 (81.1%)	26 (68.4%)	196 (84.5%)
Age, years						
18–35	290 (55.7%)	48 (56.5%)	39 (54.9%)	55 (57.9%)	19 (50.0%)	129 (55.6%)
36–45	165 (31.7%)	28 (32.9%)	24 (33.8%)	29 (30.5%)	13 (34.2%)	71 (30.6%)
46–55	47 (9.0%)	4 (4.7%)	7 (9.9%)	9 (9.5%)	1 (2.6%)	26 (11.2%)
≥55	19 (3.7%)	5 (5.9%)	1 (1.4%)	2 (2.1%)	5 (13.2%)	6 (2.6%)
BMI	24.5 (22.1, 27.1)	23.9 (21.3, 25.9)	25.3 (22.3, 27.3)	24.6 (22.0, 27.0)	23.8 (21.9, 25.9)	24.6 (22.6, 27.1)
Overweight	233 (44.7%)	31 (36.5%)	38 (53.5%)	42 (44.2%)	14 (36.8%)	108 (46.6%)
Comorbidities						
None	469 (90.0%)	77 (90.6%)	63 (88.7%)	83 (87.4%)	32 (84.2%)	214 (92.2%)
Diabetes	8 (1.5%)	2 (2.4%)	1 (1.4%)	2 (2.1%)	1 (2.6%)	2 (0.9%)
CVD	41 (7.9%)	8 (9.4%)	4 (5.6%)	11 (11.6%)	4 (10.5%)	14 (6.0%)
COPD	10 (1.9%)	1 (1.2%)	4 (5.6%)	1 (1.1%)	1 (2.6%)	3 (1.3%)
Smoking status						
None	328 (63.0%)	51 (60.0%)	46 (64.8%)	69 (72.6%)	24 (63.2%)	138 (59.5%)
Ever smokers	193 (37.0%)	34 (40.0%)	25 (34.2%)	26 (27.4%)	14 (36.8%)	94 (40.5%)
Alcohol consumption						
None	221 (42.4%)	38 (44.7%)	33 (46.5%)	48 (50.5%)	19 (50.0%)	83 (35.8%)
With drinking habit	300 (57.6%)	47 (55.3%)	38 (53.5%)	47 (49.5%)	19 (50.0%)	149 (64.2%)
HLA-B27 (+)	442 (84.8%)	74 (87.1%)	59 (83.1%)	81 (85.3%)	30 (78.9%)	198 (85.3%)
Vaccination status						
Unvaccinated	78 (15.0%)	13 (15.3%)	9 (12.7%)	13 (12.7%)	7 (18.4%)	36 (15.5%)
Partially	19 (3.6%)	0	2 (2.8%)	3 (3.2%)	0	14 (6.0%)
Fully	131 (25.1%)	20 (23.5%)	15 (21.1%)	22 (23.2%)	12 (31.6%)	62 (26.7%)
Booster	293 (56.2%)	52 (61.2%)	45 (63.4%)	57 (60.0%)	19 (50.0%)	120 (51.7%)
BASDAI	2.5 (1.2, 4.0)	3.0 (1.6, 4.4)	3.0 (1.4, 4.2)	2.1 (1.0, 3.5)	2.2 (1.2, 3.8)	2.2 (1.2, 4.0)
BASFI	1.1 (0, 3.2)	1.2 (0.1, 4.4)	1.8 (0.2, 4.8)	0.6 (0, 2.7)	1.4 (0, 2.2)	1.1 (0, 2.9)
BASMI	3.0 (0, 5.0)	4.0 (0, 5.0)	4.0 (0, 5.0)	1.0 (0, 5.0)	3.0 (0, 6.3)	3.0 (0, 5.0)

Data are n (%) for categorical variables and median (IQR) for continuous variables, respectively. Percentages might not sum to 100% due to rounding. Abbreviation: NSAID, non-steroidal anti-inflammatory drugs; csDMARD, conventional synthetic DMARD; TNFi, tumor necrosis factor inhibitor; BMI, body mass index; COPD, chronic obstructive pulmonary disease; cardiovascular disease (CVD, including hypertension).

3.4 Subgroup analyses by TNFi monotherapy or combination therapy

Among the 232 patients treated with TNFi, 104 patients received TNFi monotherapy (Group 1), while 128 patients were prescribed NSAIDs or csDMARDs concomitantly (Group 2). The median (IQR) number of symptoms reported by patients in Groups 1 and 2 were 7.0 (5.0, 9.0) and 8.0 (6.0, 10.0), respectively (Table 2). After adjustment for potential confounding factors, patients with TNFi monotherapy or combination therapy had similar odds of experiencing more than five symptoms compared to those without medication use (RRa 1.02, 95% CI: 0.84–1.24 and 1.18, 0.99–1.40 for Group 1 and 2, respectively). It was also revealed that combining NSAIDs or csDMARDs did not affect the odds of experiencing more than 10 symptoms in TNFi treatment (RRa 0.65, 95% CI: 0.29–1.45 and 1.32, 0.68–2.56 for Group 1 and 2, respectively) (Figure 2).

The median (IQR) duration of COVID-19 symptoms in Groups 1 and 2 were 9.0 (6.0, 14.0) and 10.0 (6.0, 18.0) days, respectively (Table 2). In multivariable analysis, patients with TNFi monotherapy or combination therapy had similar odds of long COVID (LC10) compared to those without medication use (RRa 1.10, 95% CI: 0.79–1.54 and 1.32, 0.97–1.78 for Group 1 and 2, respectively). Similar results were obtained when LC28 was used as the outcome variable (RRa 1.33, 95% CI: 0.54–3.28 and 0.82, 0.30–2.23 for Groups 1 and 2, respectively) (Figure 3).

TABLE 2 Symptom burden and disease course of mild-moderate COVID-19 in AS with no medications, NSAIDs, csDMARDs, and TNFi.

	None (n = 85)	NSAIDs (n = 71)	csDMARDs (n = 38)	TNFi (n = 232)	TNFi subgroups	
					Group1 (n = 104)	Group2 (n = 128)
Number of symptoms	6.0 (5.0, 8.0)	8.0 (6.0, 9.0)	7.5 (5.0, 9.0)	7.0 (5.0, 9.0)	7.0 (5.0, 9.0)	8.0 (6.0, 10.0)
>5 symptoms	57 (67.1%)	60 (84.5%)	27 (71.1%)	171 (73.7%)	71 (68.3%)	100 (78.1%)
>10 symptoms	11 (12.9%)	8 (11.3%)	5 (13.2%)	31 (13.4%)	9 (8.7%)	22 (17.2%)
COVID course, days	8.0 (5.5, 13.5)	9.0 (6.0, 13.0)	9.5 (6.8, 14.5)	9.0 (6.0, 16.0)	9.0 (6.0, 14.0)	10.0 (6.0, 18.0)
LC10	35 (41.2%)	35 (49.3%)	19 (50.0%)	114 (49.1%)	45 (43.3%)	69 (53.9%)
LC28	7 (8.2%)	5 (7.0%)	3 (7.9%)	20 (8.6%)	11 (10.6%)	9 (7.0%)

Data are n (%) for categorical variables and median (IQR) for continuous variables, respectively. Abbreviation: NSAID, non-steroidal anti-inflammatory drugs; csDMARD, conventional synthetic DMARD; TNFi, tumor necrosis factor inhibitor. Group1 and 2 indicate patients with TNFi, monotherapy or combination therapy.

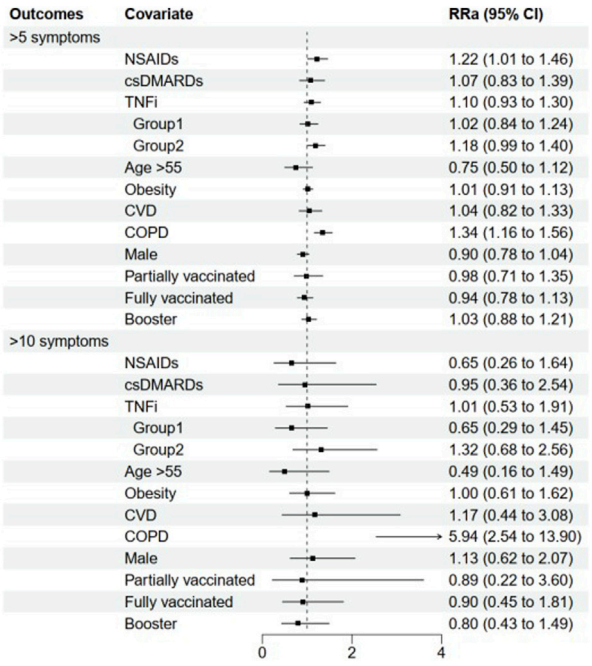

FIGURE 2
The influence of AS medications and baseline characteristics on symptom burden in mild-moderate COVID-19. Abbreviation: NSAIDs. non-steroidal anti-inflammatory drugs: csDMARDs. conventional synthetic disease-modifying antirheumatic drugs: TNFi, Tumor necrosis factor inhibitors: COPD. chronic obstructive pulmonary disease. Horizontal lines indicate the ranges of the 95% CIs and the vertical dash lines indicate the relative risk of 1. Some variables had oversized ranges of 95% CI and they were shown to be lines with arrow.

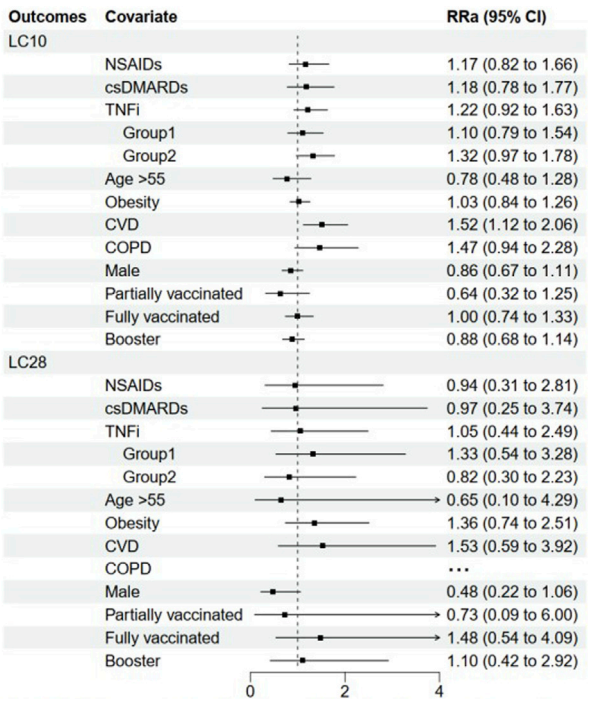

FIGURE 3
The influence of AS medications and baseline characteristics on disease course in mild-moderate COVID-19. Abbreviation: NSAIDs, non-steroidal anti-inflammatory drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; TNFi, Tumor necrosis factor inhibitors; COPD, chronic obstructive pulmonary disease. Ellipsis (. . .) means that the model does not converge due to limited outcomes. Horizontal lines indicate the ranges of the 95% Cis and the vertical dash lines indicate the relative risk of 1. Some variables had oversized ranges 95% CI and they were shown to be lines with arrow.

4 Discussion

In this study, we examined a cohort of patients with AS and mild-moderate COVID-19. We found no association between previous use of csDMARDs or TNFi and worse COVID-19 outcomes. To our knowledge, this is the first study to investigate the impacts of csDMARDs and TNFi on AS patients with mild-moderate COVID-19. Our findings are significant as they alleviate concerns about the potential increased disease burden of COVID-19 in AS populations using csDMARDs or TNFi. These findings can potentially guide future treatment decisions.

Despite the emergence of studies reporting the characteristics, outcomes and associated factors for COVID-19 in individuals with systemic autoimmune diseases (Gianfrancesco et al., 2020; Strangfeld et al., 2021), there are limited predictive factors and

prognosis analyses available specifically for AS. AS is an auto-inflammatory disease with distinct pathogenesis and treatments compared to classic autoimmune diseases. Furthermore, previous studies have focused more on severe cases of COVID-19, neglecting to fully investigate mild-moderate cases in individuals with AS, despite the fact that these cases comprised the majority of the population during the pandemic.

To assess the disease burden of mild-moderate COVID-19, we measured the number of self-reported symptoms and the duration of recovery in patients. Obviously, higher number of symptoms and longer recovery time indicate a greater burden of illness. After accounting for potential confounding factors, patients treated with csDMARDs or TNFi had similar odds of experiencing more than five symptoms compared to those not taking AS medications. The exception was patients on NSAIDs monotherapy, which presented a subtly worsening effect on symptom burden with borderline significance (RRa 1.22, 95% CI: 1.01–1.46). However, when we evaluated the outcome of having more than 10 symptoms, no significant association with COVID-19 symptoms burden was detected for all medications, both in univariable and multivariable analyses. Initially, there were concerns about the use of NSAIDs in the early stages of the pandemic due to their theoretical potential to worsen COVID-19 outcomes (Day, 2020). However, these concerns have been largely alleviated by numerous studies (Abu Esba et al., 2021; Drake et al., 2021), though the association between pre-existing NSAIDs use and COVID-19 outcomes in AS was still not fully investigated. In our study, patients on NSAIDs monotherapy had a higher percentage of COPD than patients without medication use (5.6% vs 1.2%). COPD was a known independent risk factor for severe COVID-19 (Strangfeld et al., 2021). This may affecte the association between COVID-19 symptoms and NSAIDs. Although the confounding effect of COPD was adjusted in multivariable analysis, the limited COPD cases (only 10 cases total) rendered the evaluation of its confounding effect difficult. AS disease activity may also play a role in the outcome of COVID, as patients with NSAIDs monotherapy had higher BASDAI than patients with other medications. In consideration of the possibility of confounding bias and the borderline significant effect of NSAIDs, the interpretation of this finding should be cautious and it needs re-examination in further research.

Persistent COVID-19 symptoms, also known as "long COVID," are widespread among individuals with COVID-19 (Hopkinson et al., 2021; Davis et al., 2023). It is evident that long COVID can also occur after a mild-moderate infection, placing a greater burden on affected populations, decreasing their quality of life, and instilling fear (Davis et al., 2023). However, there is limited research on long COVID in individuals with AS, and no universally accepted definitions of long COVID in AS have been reported. In our study, the median duration of COVID-19 symptoms in the overall population was 9.0 days. Therefore, we classified patient-reported symptoms persisting for more than 10 days (LC10) as long COVID, in line with a previous study (Sudre et al., 2021). Additionally, an illness duration surpassing 28 days (LC28) was considered as another definition of long COVID. We found that the risk of LC10 was comparable for individuals using NSAIDs, csDMARDs and TNFi, compared to those not using AS medications, both in univariate analysis and after adjusting for confounding factors. Similarly, there was no significant increase in the risk of LC28 among individuals using NSAIDs, csDMARDs, and TNFi, compared to those not using AS medications. Traditionally, csDMARDs and TNFi have been associated with an increased risk of infection, although TNFi has been shown to have lower odds for severe COVID-19 outcomes (Kridin et al., 2021; Machado et al., 2023) and csDMARDs have not been found to increase the severity of COVID-19 infection in previous studies (Gianfrancesco et al., 2020; Machado et al., 2023). In line with these findings, our study demonstrates that csDMARDs and TNFi do not elevate the risk of increased symptom burden or prolonged recovery in individuals with mild-moderate COVID-19. This information may aid in the development and updating of AS management strategies during the COVID-19 pandemic.

Our study has several limitations that should be acknowledged. Firstly, there existed sampling bias due to various factors, including a single geographical area, high COVID-19 vaccination coverage (85%), a relatively young population, and limited comorbidities, which generally resulted in better COVID-19 outcomes. Secondly, in this study, patients were classified as having mild-moderate COVID-19 retrospectively. However, it should be noted that patients presenting with mild-moderate symptoms initially can progress to severe outcomes, especially among older individuals, men, and those with comorbid conditions such as cardiometabolic and pulmonary conditions (Conway et al., 2022; Kroon et al., 2022). Previous studies have examined the outcomes and characteristics of individuals with AS and severe COVID-19 (Gianfrancesco et al., 2020; Strangfeld et al., 2021; Machado et al., 2023), while these were not evaluated in our study. Therefore, caution should be exercised when interpreting our results as applicable to the entire AS population with mild-moderate COVID-19, although our sample did represent the majority. Thirdly, our study relied on self-reported laboratory results and symptoms rather than medical records to determine the occurrence and severity of COVID-19. While previous studies have reported agreement between self-reported symptoms and SARS-CoV-2 test results (Hopkinson et al., 2021), it is important to acknowledge the presence of recall bias, given the retrospective nature of this study. Moreover, we identified COVID-19 as patients with positive SARS-CoV-2 PCR or antigen test. Antigen-detecting test of SARS-CoV-2 may be less reliable than the SARS-CoV-2 PCR test, while they were both used as diagnostic methods in previous COVID-19 studies. Lastly, during the study period, the Omicron variant was the dominant SARS-CoV-2 variant in China (Sun et al., 2023). The persistence of our findings across emerging variants of SARS-CoV-2 remains unknown. However, it is worth noting that there is a general tendency for SARS-CoV-2 variants to become less virulent but more transmissible.

In conclusion, our findings suggest that the use of csDMARDs or TNFi does not result in an increased symptom burden or longer recovery time in individuals with AS following a mild-moderate COVID-19 infection. This information should be taken into account when making treatment decisions between patients and physicians.

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 authors.

Ethics statement

The studies involving humans were approved by the Ethical Committee of the Chinese PLA General Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because of the retrospective nature of this study.

Author contributions

YL: Conceptualization, Investigation, Writing–original draft. ZH: Investigation, Methodology, Writing–original draft. YG: Data curation, Methodology, Writing–review and editing. ZZ: Investigation, Validation, Writing–review and editing. KL: Supervision, Validation, Writing–review and editing. XW: Methodology, Supervision, Writing–review and editing. JieZ: Data curation, Methodology, Writing–review and editing. DL: Formal Analysis, Supervision, Writing–review and editing. JiaZ: Resources, Supervision, Validation, Writing–review and editing. XH: Methodology, Writing–review and editing. JianZ: Conceptualization, Investigation, Project administration, Supervision, Validation, Writing–review and editing. FH: Conceptualization, Project administration, Supervision, Validation, Writing–review and editing.

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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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2023.1266915/full#supplementary-material

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Parasitic infections related to anti-type 2 immunity monoclonal antibodies: a disproportionality analysis in the food and drug administration's adverse event reporting system (FAERS)

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Introduction: Monoclonal antibodies (mAbs) targeting immunoglobulin E (IgE) [omalizumab], type 2 (T2) cytokine interleukin (IL) 5 [mepolizumab, reslizumab], IL-4 Receptor (R) α [dupilumab], and IL-5R [benralizumab]), improve quality of life in patients with T2-driven inflammatory diseases. However, there is a concern for an increased risk of helminth infections. The aim was to explore safety signals of parasitic infections for omalizumab, mepolizumab, reslizumab, dupilumab, and benralizumab.

Methods: Spontaneous reports were used from the Food and Drug Administration's Adverse Event Reporting System (FAERS) database from 2004 to 2021. Parasitic infections were defined as any type of parasitic infection term obtained from the Standardised Medical Dictionary for Regulatory Activities® (MedDRA®). Safety signal strength was assessed by the Reporting Odds Ratio (ROR).

Results: 15,502,908 reports were eligible for analysis. Amongst 175,888 reports for omalizumab, mepolizumab, reslizumab, dupilumab, and benralizumab, there were 79 reports on parasitic infections. Median age was 55 years (interquartile range 24–63 years) and 59.5% were female. Indications were known in 26 (32.9%) reports; 14 (53.8%) biologicals were reportedly prescribed for asthma, 8 (30.7%) for various types of dermatitis, and 2 (7.6%) for urticaria. A safety signal was observed

Abbreviations: ADR, Adverse drug reaction; AE, Adverse event; AEOLUS, Adverse Event Open Learning through Universal Standardization; ATC, Anatomical Therapeutic Chemical classification; CI, Confidence interval; CRSwNP, Chronic rhinosinusitis with nasal polyps; DEC, Drug-event count; EMA, European Medicines Agency; FDA, Food and Drug Administration; FAERS, FDA Adverse Event Reporting System; HLGT, High Level Group Term; HLT, High Level Term; IgE, Immunoglobulin E; IL, Interleukin; mAb, Monoclonal Antibody; MedDRA®, Medical Dictionary for Regulatory Activities®; NEC, Not elsewhere classified; OR, Odds Ratio; PT, Preferred Term; R, Receptor; RCT, Randomized clinical trials; ROR, Reporting Odds Ratio; SDR, Signal of disproportionate reporting; T2, Type 2.

for each biological, except for reslizumab (due to lack of power), with the strongest signal attributed to benralizumab (ROR = 15.7, 95% Confidence Interval: 8.4–29.3).

Conclusion: Parasitic infections were disproportionately reported for mAbs targeting IgE, T2 cytokines, or T2 cytokine receptors. While the number of adverse event reports on parasitic infections in the database was relatively low, resulting safety signals were disproportionate and warrant further investigation.

KEYWORDS

biologicals, monoclonal antibodies, disproportionality analysis, parasitic infections, spontaneous reporting, FAERS, pharmacovigilance, helminth infections

Introduction

The discovery of human immunoglobulin E (IgE) in 1968 (Bennich et al., 1968) and an increased understanding of type 2 (T2) inflammatory pathways since the 1990s contributed to the development of today's monoclonal antibodies (mAbs) targeted at T2 inflammation driven diseases (Fahy, 2015). Within asthma there is an endotype that is broadly characterized by T2 inflammation, namely, T2 asthma (Kuruvilla et al., 2019). T2 asthma demands a different treatment strategy than non-T2 asthma. Besides T2 asthma, also chronic urticaria, chronic rhinosinusitis with nasal polyps (CRSwNP), and atopic dermatitis are characterized by T2 inflammation (Garcovich et al., 2021; Matucci et al., 2021). While increased blood eosinophils are a biomarker for T2 asthma, a differential diagnosis is extensive and includes CRSwNP, vasculitis, and parasitic disease (Piggott et al., 2022). These eosinophils contribute to innate immune responses against helminths (i.e., multicellular parasitic worms) through phagocytosis, release of cytotoxic proteins and formation of extracellular traps (Klion, et al., 2020).

The availability of biologicals has aided patients with severe asthma in reducing exacerbations and oral corticosteroid use, while improving lung function and quality of life, especially in patients with T2 asthma (McGregor et al., 2019). The IgE-binding mAb omalizumab was approved in 2002 for the treatment of moderate-to-severe allergic asthma among adults and adolescents by the Therapeutic Goods Administration in Australia (BioDrugs, 2002). After that, more mAbs targeting T2 asthma were approved, namely, mepolizumab, reslizumab, benralizumab, and dupilumab (Papi et al., 2020). Dupilumab was primarily registered for the treatment of moderate-to-severe atopic dermatitis in 2017 (Shirley, 2017), for the treatment of asthma in 2018, and for the treatment of CRSwNP in 2019 (Boyle et al., 2020). Omalizumab was additionally registered for the treatment of chronic urticaria in 2014 (Kaplan et al., 2017). Clinical trials have shown that these biologicals contribute to disease control of T2 inflammatory diseases, especially in patients with T2 asthma (Agache et al., 2021; Matucci et al., 2021). While the effectiveness of these biologicals in real life has been demonstrated, further evaluation of the long-term safety of biologicals is needed as safety profiling studies are limited (Brusselle and Koppelman, 2022). In the clinical trials safety profiles were similar for patients in the intervention group and placebo group, with a low number of serious adverse events (AEs) (Ortega et al., 2014; Bleecker et al., 2016; Castro et al., 2018). More recently post-marketing studies confirm the low incidence of serious AEs in patients receiving anti-T2 biologicals, while identifying previously unknown risks (Sousa et al., 2020; Bettuzzi et al., 2022; Galletti et al., 2023). Anaphylaxis signals have been described for omalizumab, benralizumab, reslizumab, and mepolizumab (Li et al., 2021). Dupilmab has been linked with eye disorders, especially in patients with atopic dermatitis (Park et al., 2021).

In recent years, concerns were expressed for a hypothesized increased risk of parasitic infections among patients using biologicals affecting the T2 immune response (Tan et al., 2019). Such biologicals are dupilumab, omalizumab, mepolizumab, benralizumab, and reslizumab. Omalizumab binds to free IgE, inhibiting further binding of IgE to high-affinity IgE receptors on mast cells and basophils (Brusselle and Koppelman, 2022), while IgE is considered an important part of the multi-component T2 immune response towards parasitic infections (Cooper et al., 2008; Fitzsimmons et al., 2014). Dupilumab binds to interleukin (IL-) 4 receptor α, which inhibits IL-4 and IL-13 signaling (Brusselle and Koppelman, 2022), while both cytokines contribute to the elimination of parasites through increased mucus production and eosinophilic mucosal inflammation in the gut (Klion and Nutman, 2004; Braddock et al., 2018). Benralizumab binds to IL-5Rα, resulting into depletion of eosinophils in the blood and mucosal tissues via antibody-dependent cell-mediated cytotoxicity (Brusselle and Koppelman, 2022), and might thus interfere with the eosinophil-mediated killing and expulsion of gastro-intestinal helminths (Klion and Nutman, 2004). Reslizumab and mepolizumab bind to circulating interleukin IL-5 (Brusselle and Koppelman, 2022), likewise an important cytokine contributing to eosinophilic differentiation and activation (Klion and Nutman, 2004; Maizels and Adam, 2004).

In current clinical studies and routine practice, reporting of parasitic infections is based on spontaneous reporting, rather than systematic anamnestic or biochemical screening. Especially in endemic regions, routine screening for parasitic infections may be useful. So far, no studies were performed on the Food and Drug Administration's (FDA) Adverse Event Reporting System (FAERS) investigating the risk of parasitic infections among patients using biologicals affecting the T2 immune response. Therefore, the objective of this study was to determine if parasitic infections are disproportionately reported for biologicals affecting the T2 immune response.

Methodology

Data source

For this study, we used publicly available quarterly data files from FAERS covering the period 2004–2021 (Food and Drug

Administration, 2021; FAIRsharing Team, 2022). FAERS data represents data from spontaneous reports on (product quality complaints resulting in) AEs and medication errors in relation to medication (excluding vaccines) and medical devices (Questions and Answers on FDA's Adverse Event Reporting System (FAERS), 2019). The FDA receives reports from healthcare professionals, consumers, manufacturers, and lawyers. The FDA's MedWatch Online Voluntary Reporting Form is freely available to the worldwide public and facilitates sending in a report (MedWatch Online Voluntary Reporting Form, 2019). Preferred Terms (PTs) from the Medical Dictionary for Regulatory Activities® (MedDRA®) are used as a standardized coding practice for the reported events in a received report.

Data processing

Data processing of the quarterly files was performed by the Adverse Event Open Learning through Universal Standardization (AEOLUS) system (Parry, 2021a). AEOLUS performs standardization of the FAERS data, case deduplication, and disproportionality analyses as described in further detail by Banda et al. (2016). The algorithm removes any duplicate cases based on exact matches on the combined demographic fields, list of drugs and list of outcomes (FAERS reactions). Additionally, the FDA and manufacturers provide a list of suggested cases to be deleted within each batch of quarterly datafiles since the first quartile of 2019 for various purposes, including combining cases. The original AEOLUS scripts were adapted for downloading and processing data up to the final quarter of 2021. Mapping of drug names to the Anatomical Therapeutic Chemical (ATC) coding system was performed by the locally developed AIOLI system (Parry, 2021b). Only drugs mapped to an ATC code and marked as primary suspect within a FAERS report were included in the analysis. All age units in the data were converted to years. The age variable was marked as invalid in case of a negative value, no indicated age unit, or missing age.

Case definition and selection process

All the selected FAERS reports from the FAERS database as described previously were processed. The reported AE of interest was a parasitic infection, which was defined as any PT falling under the MedDRA® High Level Group Term (HLGT) "Helminthic Disorders" or a PT related to parasitic infections noted under High Level Term (HLT) "Infections—Not elsewhere classified (NEC)" according to MedDRA® version 24.1. All these PTs are listed in Supplementary Table S1. Descriptive statistics and disproportionality results were presented for reports stating a parasitic infection and one of the following mAbs marked as the primary drug suspect: dupilumab (ATC: D11AH05), omalizumab (ATC: R03DX05), mepolizumab (ATC: R03DX09), benralizumab (ATC: R03DX10), and reslizumab (ATC: R03DX08).

Disproportionality analyses

Signals of disproportionate reporting (SDRs) were produced by AEOLUS and expressed as Reporting Odds Ratio's (RORs) with a 95% confidence interval (CI). The ROR and 95% CI were calculated according to Eqs 1, 2. Letters A, B, C, and D in Eqs 1, 2 represent drug-event combinations (DECs) as specified in Table 1.

$$ROR = \frac{A/C}{B/D} \tag{1}$$

$$95\%\ CI\ for\ ROR = e^{ln(ROR)\ \pm 1.96\sqrt{\frac{1}{A}+\frac{1}{B}+\frac{1}{C}+\frac{1}{D}}} \tag{2}$$

A SDR was considered disproportionate if the lower boundary of the 95% CI was greater than 1 and the drug-event count was at least 3, in accordance to guidelines from the European Medicines Agency (EMA) (European Medicines Agency, 2016). Three disproportionality analyses were performed as described in Table 1: i) using DECs over the entire FAERS database, ii) using DECs over the entire FAERS database excluding drugs under ATC group P [antiparasitic products, insecticides, and repellents] and iii) using DECs of only dupilumab, omalizumab, mepolizumab, benralizumab, and reslizumab. Descriptive statistics were performed on the reports relating to parasitic infections and users of the mAb therapies of interest.

Results

Primary analysis

The FAERS database contains 16,757,507 AE reports from 2004 to 2021. The data extraction process is displayed with a flowchart (Figure 1). A total of 15,502,908 (93%) reports were eligible for the primary disproportionality analysis based on the availability of an ATC code for the primary drug suspect. Among the 175,888 AE reports concerning anti-T2 immunity biologicals in FAERS, 97,196 (55%) were on dupilumab, followed by 55,774 (32%) for omalizumab, 16,435 (9%) for mepolizumab, 6,052 (3%) for benralizumab, and 431 (<1%) for reslizumab. For these biologicals, 79 reports on parasitic infections were found within FAERS, mentioning 81 PTs related to parasitic infections. The following report characteristics are displayed in Table 2. Reported median age within the 79 reports was 55 years with an interquartile range of 24–63 years. Most of the reports indicated sex [47 (59.5%) individuals were female]. The reports were mostly submitted by consumers, accounting for 44 (55.7%) reports, followed by 25 (32.9%) submitted by physicians. Most reports originated from the United States of America (USA), being 58 (73.4%). Indications were mentioned in 26 reports; 14 (53.8%) biologicals were reportedly prescribed for asthma, 5 (19.2%) for atopic dermatitis and 2 (7.7%) for dermatitis. The following indications were reported only once: "chronic spontaneous urticaria," "eosinophil count increased," "nasal polyps," "neurodermatitis," and "urticaria chronic." FAERS case numbers and data on case level for these reports can be found in Supplementary Table S2.

Health outcomes varied per mAb of interest (Figure 2). Omalizumab reports had proportionally the most reported health outcomes and the least missing outcomes. The most commonly reported outcome was "other serious (important medical event, unspecified)," accounting for 16 (61.5%) of the omalizumab reports. The highest proportion for no health outcome reported was for benralizumab, being 6 (66.7%) reports. Death has been reported in 1 (7.7%) report for mepolizumab and 1 (3.8%) in omalizumab. The "life-threatening" health outcome was reported

TABLE 1 Overview of report counts based on various drug-event combinations (DECs) expressed by the letters A, B, C, and D, including variations on counts C and D, represented by the dagger (†) and double dagger (‡), for the purpose of various disproportionality analyses as previously represented by Eqs 1, 2 in the manuscript. The found fixed A and B counts for every biologic of interest were used in every analyses, while the C and D counts were different per analysis.

	Parasitic infection	Other events	Target analysis
A biologic of interest	A	B	All analyses
All other drugs	C	D	Primary analysis
All other drugs, excluding ATC group P drugs	C †	D †	1st secondary analysis
All other biologics of interest	C ‡	D ‡	2nd secondary analysis

ATC, anatomical therapeutic chemical classification, group P, antiparasitic products, insecticides and repellents.

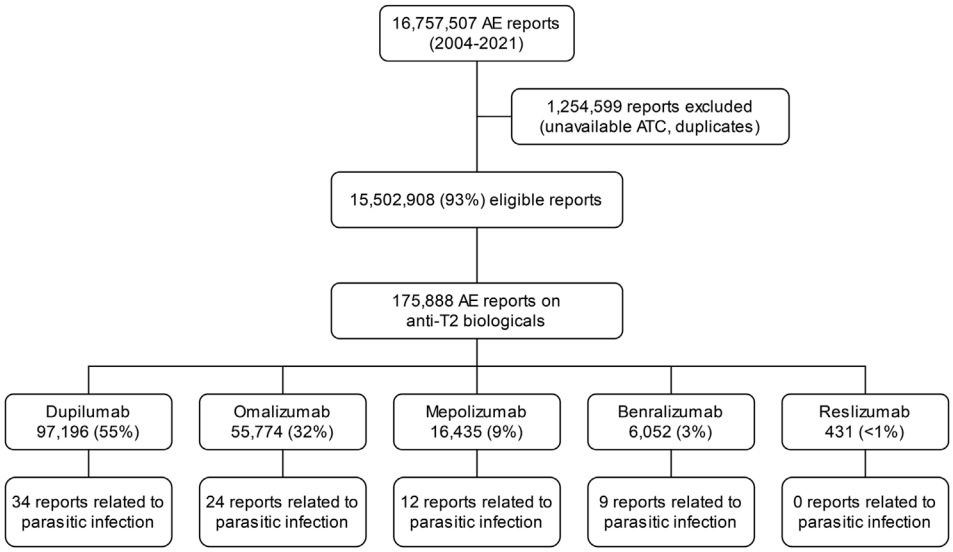

FIGURE 1
Overview of the data extraction process.

in 2 (7.7%) reports of omalizumab and 1 (2.6%) report of dupilumab. Available raw data on start date therapy, end date therapy, and time of event were provided in Supplementary Table S3.

Parasitic infections were found in 34 (43%) reports for dupilumab, followed by 24 (30.4%) reports for omalizumab, 9 (11.4%) for benralizumab, and 12 (15.2%) for mepolizumab. No parasitic infections were reported for reslizumab. The specific parasitic infections for each biological can be found in Supplementary Table S2. Benralizumab showed the strongest SDR for the primary analysis (Figure 3), with a ROR of 15.7 (95% CI: 8.4–29.3). The second strongest SDR was for mepolizumab, showing a ROR of 5.9 (95% CI: 3.4–10.4). The SDRs for omalizumab and dupilumab were similar, with RORs of 3.9 (95% CI: 2.6–5.8) and 4 (95% CI: 2.8–5.6), respectively. For reslizumab no ROR could be calculated in any analysis because there were no AE reports on parasitic infections for this biological.

Secondary sensitivity analyses

In the 1st secondary analysis [Figure 3, results marked by a dagger (†)], we excluded 30,748 AE reports concerning drugs under ATC level 5 group P [Antiparasitic products, insecticides and repellents], to minimize the risk of bias (e.g., due to "reverse causation"). In this secondary analysis, the SDRs for the biologicals of interest were similar to those in the primary analyses, however with a slight increase in ROR for all biologicals. In the 2nd secondary analysis, we tested the disproportionality on parasitic infections only within the group of selected biologicals (Figure 4). Parasitic infections were disproportionately reported for benralizumab compared to the other biologicals of interest. The ROR for benralizumab was 3.8 (95% CI: 2–7.4), while the RORs for dupilumab, omalizumab, and mepolizumab were not signifying disproportionality. Details of various DECs are illustrated in Supplementary Tables S4–S6 in the Online Repository.

Discussion

Even though a limited amount of AE case reports on parasitic infections were retrieved from the FAERS database, we demonstrated SDRs for parasitic infections associated with anti-IgE omalizumab and anti-T2 cytokine (receptor) antibodies

TABLE 2 Characteristics of reports related to the monoclonal antibodies of interest with a mention of parasitic infection.

Total reports of interest	79
Median Age, in years (IQR)	55 (24–63)
	Count (proportion)
Sex	
Female	47 (59.5%)
Male	18 (22.8%)
Unknown	14 (17.7%)
Reporter type	
Consumer	44 (55.7%)
Physician	26 (32.9%)
Pharmacist	1 (1.3%)
Other health-professional	5 (6.3%)
Unknown	3 (3.8%)
Reporter country	
United States	58 (73.4%)
15 other countries, each contributing <5%	21 (26.6%)
Indication	
Asthma	14 (17.7%)
Dermatitis atopic	5 (6.3%)
Dermatitis	2 (2.5%)
Chronic spontaneous urticaria	1 (1.3%)
Eosinophil count increased	1 (1.3%)
Nasal polyps	1 (1.3%)
Neurodermatitis	1 (1.3%)
Urticaria chronic	1 (1.3%)
Unknown	53 (67.1%)

IQR, interquartile range.

dupilumab, mepolizumab, and benralizumab. In addition, we discovered that within the group of these biologicals parasitic infections were disproportionately reported for benralizumab. Given the mechanism of action of benralizumab [binding to IL-5R on eosinophils and basophils, and consequently depleting eosinophils in the blood and mucosal tissues such as the gastro-intestinal tract through antibody-dependent, cell-mediated toxicity] (Brusselle and Koppelman, 2022), it could be reasoned why proportionally more AE reports on parasitic infections were found in FAERS for benralizumab compared to the other biologicals. These SDRs should be taken seriously since a major clinical impact has been reported in the case reports, including death, life-threatening situations, hospitalizations, and other serious (unspecified) medical events.

For reslizumab no AE reports were found on parasitic infections within FAERS, which could be attributed to a general low reporting rate for this biological and most probably due to lack of power. Indeed, spontaneous reports for the other biologicals were roughly a 12–16-fold more often received by the FDA than for reslizumab. The lower reporting rate for reslizumab might be due to a low number of patients receiving the drug because reslizumab has to be administered intravenously in the hospital. In contrast, other biologicals can be self-administered subcutaneously (e.g., at home), making treatment with reslizumab less practical and potentially more costly within the healthcare system (Kavanagh et al., 2021). Excluding drugs from the ATC drug group P in the 1st secondary analysis showed a slight increase in disproportionality for all the biologicals of interest, indicating a confounding effect.

Notably, 50 out of 79 parasitic infections were unspecified, raising concerns on the validity of the submitted reports. The parasitic infections might have been reported by individuals, such as consumers or even healthcare workers, with no experience in the diagnosis of parasitic infections. On the other hand, sufficient information might have been provided by an experienced or treating healthcare professional to the reporter of the AE. The validity of the start date of treatment, end date of treatment, and event date (i.e., date of parasitic infection) should be carefully interpreted, as in most cases these data elements were not reported, and in some cases the parasitic infection was reported before the start date of the mAb treatment. The latter would be unlikely as only primary drug suspects for the reported events were selected for analysis. Recently, a correspondence article by Lifar et al. (2023) has been published describing a disproportionality analysis of parasitic infections among omalizumab, mepolizumab, benralizumab, and dupilumab within the VigiBase using a case/noncase design in which the control group was represented by the disease concept “asthma” in combination with at the time approved inhalation therapies. Lifar et al. (2023) showed that only benralizumab among the biologicals of interest was disproportionately reported for parasitic infections compared to the control group. In comparison, our study showed disproportionality for all biologicals of interest, except for reslizumab, while utilizing the entire FAERS database representing a broader range of patients and medication.

While theoretically it can be expected that patients using these biologicals would be at an increased risk for parasitic infections, literature is relatively scarce on the topic, and evidence on the increased risk is weak. A 2007 clinical trial performed in Brazil reported that 50% (34 of 68) of the omalizumab arm experienced at least 1 intestinal helminth infection, compared to 41% (28 of 69) of the placebo arm (Cruz et al., 2007). The odds ratio (OR) was 1.47 with a 95% CI of 0.74–2.95. The OR was 2.2 (95% CI: 0.94–5.15) after adjusting for study visit, baseline infection status, sex, and age. In a 2013 omalizumab study in Turkey with 19 participants having severe asthma, 1 case of giardiasis was reported (Yalcin et al., 2013). An observational Italian study between 2007 and 2016 in which 91 patients received omalizumab did not report any parasitic infections (Di Bona et al., 2017). A 2021 clinical trial showed that 7 out of 271 (2.6%) children with uncontrolled moderate-to-severe asthma in the dupilumab arm experienced a non-severe parasitic infection compared to 0 out of 134 subjects in the placebo arm (Bacharier

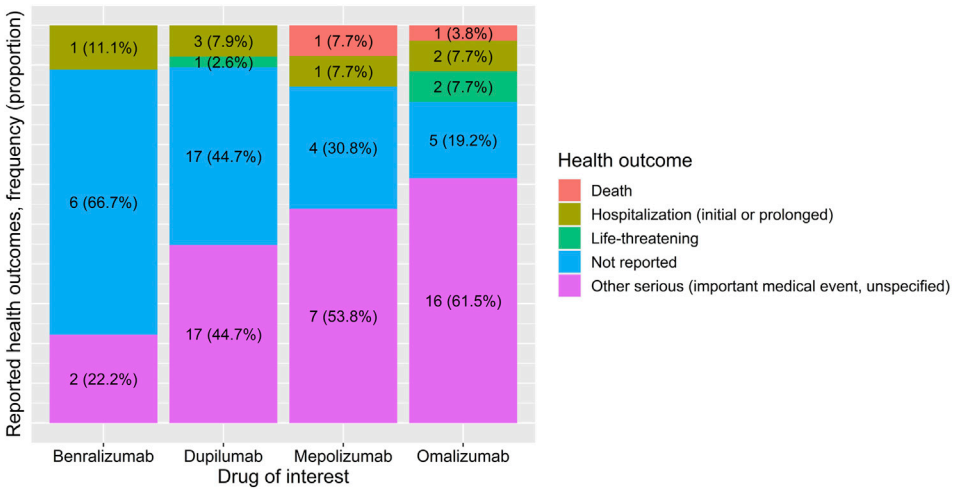

FIGURE 2
Reported health outcomes for benralizumab, dupilumab, mepolizumab, and omalizumab, expressed in absolute numbers and proportions per drug.

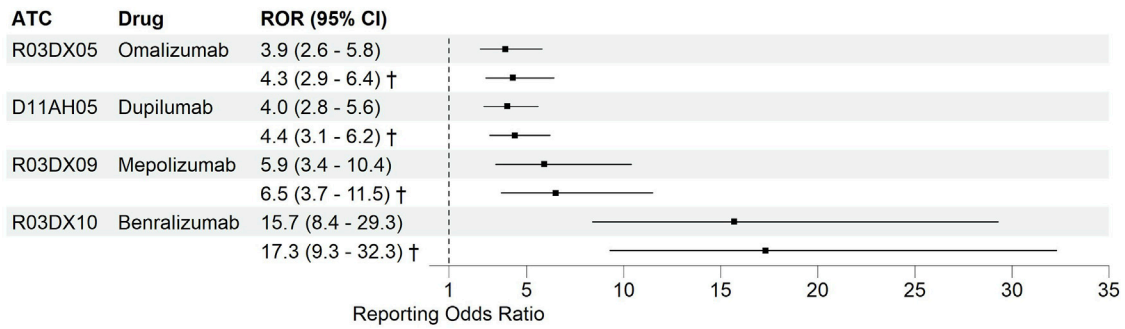

FIGURE 3
Signals of disproportionate reporting for biologics of interest compared to other drugs concerning parasitic infections. Results are shown of the primary analysis utilizing the entire database and of the 1st secondary analysis. No signal could be produced for reslizumab due to lack of power. † Results from the 1st secondary analysis utilizing the entire database, excluding drugs under Anatomical Therapeutic Chemical classification group Antiparasitic products, insecticides and repellents [see methods for detailed description]. ATC, Anatomical Therapeutical Chemical classification; CI, Confidence Interval; ROR, Reporting Odds Ratio.

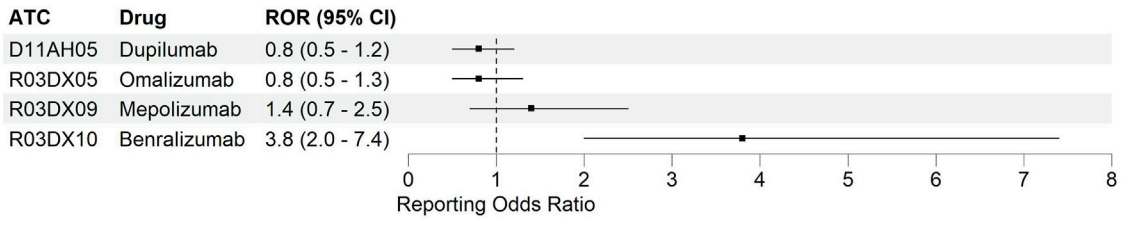

FIGURE 4
Signals of disproportionate reporting within the group of biologics of interest concerning parasitic infections. Results are shown of the 2nd secondary analysis utilizing reports only from dupilumab, omalizumab, mepolizumab, benralizumab, and reslizumab [see methods for detailed description]. No signal could be produced for reslizumab due to lack of power panel. ATC, Anatomical Therapeutical Chemical classification; CI, Confidence Interval; ROR, Reporting Odds Ratio.

et al., 2021). A 2019 pooled analysis on infections in 1841 atopic dermatitis patients using dupilumab showed that no parasitic infections were reported (Eichenfield et al., 2019). In a review from 2019 by Tan et al. (2019) no cases of parasitic infections were reported in clinical trials assessing dupilumab, benralizumab, reslizumab, and mepolizumab in patients with severe asthma. A more recent 2021 review by Dragonieri and Carpagnano highlighted additional studies for mepolizumab and reslizumab, however, did not find reported cases with parasitic infections (Dragonieri and Giovanna Elisiana, 2021). In all of the summary of product characteristics (SmPCs) of the studied biologicals, it is recognized that IgE and eosinophils are involved in the immunological response for parasitic infections, hence some caution should be considered when individuals at high risk of parasitic infection are treated with the discussed biologicals (European Medicines Agency, 2015; European Medicines Agency, 2020; European Medicines Agency, 2021; European Medicines Agency 2022b; European Medicines Agency 2022a).

Besides the well-known shortcomings of randomized clinical trials (RCTs) compared to observational studies (Hannan, 2008), RCTs involving the discussed biologicals often excluded patients with a (history of) parasitic infection or a recent (or planned) visit to a country with prevalent parasitic infections (Hodsman et al., 2013; Wenzel et al., 2013; Beck et al., 2014; Braddock et al., 2018; Eichenfield et al., 2019; Paller et al., 2022). A 2022 open-label extension study on the safety and efficacy of dupilumab also excluded individuals which were suspected or at high risk of parasitic infections (Wechsler et al., 2022). Therefore, more real world studies on this topic should be performed to gain deeper understanding on the effect of anti-T2 immunity biologicals on parasitic infections.

Limitations and strengths

While the FAERS database contains a rich dataset which is publicly available, it is subject to underreporting and selective reporting of cases (Alatawi and Hansen, 2017), potentially leading to biased results. Unmeasured and unknown confounders related to the population of the select mAb users and the population which contracted parasitic infections while being on any kind of drug therapy might have biased the results. To the best of our knowledge, there are no (strong) confounders theorized in literature which should be taken into account to produce less biased results. Potential confounding effect was addressed by excluding reports where the primary drug suspect was related to ATC group P. If the seriousness of a parasitic infection is low, then it might not be reported, as previous research among physicians showed that AEs are most probably reported in case of being a serious unknown AE of an established drug or new drug, or a serious known Adverse Drug Reaction (ADR) attributed to a new drug (Hasford et al., 2002). Even though most of the biologicals showed disproportionate reporting for parasitic infections, further root cause analysis is necessary to conclude if these biologicals were truly causative for the parasitic infections. Pharmacovigilance studies are based on spontaneous reports which allow for the calculation of RORs, however event rates cannot be calculated as these would require data on the total number of patients exposed to these biologicals. A major limitation of spontaneous reporting is indeed that causation does not have to be proven. Due to a relatively low reporting of reslizumab cases, a SDR could not be calculated. Besides underreporting, in-depth analysis of these data are hampered by missing data for the available reports, and the scarcity of demographic and clinical metadata for these cases. While dupilumab is on the market since 2002, the public FAERS database has only been made available since 2004, potentially missing more cases of parasitic infections on dupilumab. It should be noted that this is the first study, with a thoroughly described analysis and in-depth case details, performed with FAERS data on the disproportionate reporting of parasitic infections associated with biologicals targeting IgE, T2 cytokines or T2 cytokine receptors, opening up further discussions on the safety profile of these biologicals and motivating additional studies on the proposed association.

Conclusion

Parasitic infections were disproportionately reported for mAbs targeting IgE, T2 cytokines, or T2 cytokine receptors. While the number of AE reports on parasitic infections in the FAERS database was relatively low, the resulting safety signals were disproportionate and warrant further investigation.

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.

Author contributions

VP: Conceptualization, Formal Analysis, Visualization, Writing–original draft, Writing–review and editing. GB: Conceptualization, Writing–original draft, Writing–review and editing. SR: Writing–original draft, Writing–review and editing. JK: Software, Writing–review and editing. EV: Software, Writing–review and editing. RP: Software, Writing–review and editing. MdW: Software, Writing–review and editing. PR: Supervision, Writing–review and editing. KV: Conceptualization, Supervision, Writing–original draft, Writing–review and editing.

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Conflict of interest

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Healthcare resource utilization patterns in psoriasis patients using biologic and conventional treatments in Finland

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Introduction and aim: Psoriasis vulgaris is associated with a significant healthcare burden, which increases over time as the disease progresses. The aim of this retrospective, population-based registry study was to characterize healthcare resource utilization (HCRU) in patients with psoriasis using biologics and oral immunosuppressants (conventionals) in Finland.

Materials and methods: The study cohort included all patients with a diagnosis of psoriasis vulgaris in the secondary healthcare setting between 2012–2018, who initiated a biologic (n=1,297) or conventional (n=4,753) treatment between 2013–2017. Data on primary and secondary HCRU were collected from nationwide healthcare registries.

Results: The results indicated a remarkable decrease in contacts with a dermatologist after the treatment initiation among patients starting biologic (mean annual number of contacts 5.4 per person before and 2.3 after the initiation), but not conventional (3.3 and 3.2) treatment. For conventional starters there was a high level of contacts with a dermatologist surrounding times of treatment switching, which was not observed for biologic starters.

Conclusion: Overall, primary and other secondary care contacts did not decrease after the initiation or switch of treatment. The results highlight the importance of thorough consideration of the most optimal treatment alternatives, considering the overall disease burden to patients and healthcare systems.

KEYWORDS

biologic, biological treatment, healthcare resource utilization, oral immunosuppressants, Psoriasis vulgaris, real-world evidence

Introduction

Psoriasis is a chronic, immune-mediated, inflammatory skin disease, which generally affects people of working age (1). Psoriasis vulgaris (henceforth psoriasis) is the most common form of the disease, accounting for more than 80% of psoriasis cases (1). The disease is associated with an increased risk of developing comorbidities, such as psoriatic arthritis (PsA), metabolic syndrome, cardiovascular diseases, rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) (2, 3).

Several studies have demonstrated that psoriasis is associated with a significant healthcare burden, which increases over time as the disease progresses (4–6). Due to its chronicity and high prevalence (1–5% of the population in Europe), psoriasis is considered one of the costliest dermatological diseases (7–9). Patients with psoriasis use more healthcare resources not only in the specialty area of dermatology, but they also experience a higher healthcare resource utilization (HCRU) and economic burden of comorbidities compared to the general population with the same comorbidities (10).

The introduction of biologics targeting the immune-mediated pathways of psoriasis has provided a significant therapeutic advancement in the treatment of moderate to severe psoriasis. Biologics inhibiting the tumor necrosis factor–α (TNF–α), interleukin (IL) -12/23, IL-17 and IL-23, as well as a small molecule inhibitor of phosphodiesterase 4 (PDE4), provide an efficacious alternative to broadly-acting oral immunosuppressants (conventionals) that have been considered the primary systemic medications for decades (1, 11, 12). However, discontinuation and switching among biologics are common in real-world clinical practice (13, 14). In the studies based on the US and Japanese databases, switching has been shown to result in higher HCRU and direct costs than remaining on the same biologic (15, 16).

In Finland, the treatment of psoriasis follows the uniform practices determined by the Current Care Guidelines (17). Biologics can be used for patients with severe psoriasis who have not responded to first-line conventionals or phototherapy. However, the order in which individual biologics should be taken is not defined. During 2012–2018, approximately 29% of psoriasis patients identified in the Finnish secondary care register (representing patients with moderate to severe disease) used conventionals and 7% used biologics (18). However, real-world data on the overall HCRU patterns associated with different treatment options is lacking.

The aim of this retrospective, population-based registry study was to characterize HCRU patterns in patients with psoriasis using biologics and conventionals in Finland. The HCRU in different care categories (primary care, dermatology, and secondary care excluding dermatology) was assessed before and after the initiation and switch of the biologics/conventionals, and by subgroups of treatment non-switchers, switchers, and discontinuers.

Materials and methods

Study cohort, data collection, and subgroups

For this retrospective, register-based study, all adult patients (≥18 years of age) with a diagnosis of psoriasis (International Classification of Diseases, Tenth Revision [ICD-10], diagnosis code L40.0) in the Finnish Care Register for Health Care (CRHC, secondary public healthcare) between January 1, 2012, and December 31, 2018, were identified (Figure 1). Individual-level data on the use of public healthcare services and diagnoses were collected from the CRHC and the Register of Primary Health Care Visits, and medication data from the Register of Reimbursed Drugs, registers with national coverage, as described in detail in (18).

For the primary analyses, the total cohort was divided into two main study groups based on purchases of reimbursable drugs from community pharmacies. The main study groups included patients who initiated A) biologic, and B) conventional during the period from January 2013 to December 2017 and had no prior use of A) biologics, and B) conventionals during the observation period (January 2012 onward; ≥12 months clean period) (Figure 1; Supplementary Table S1, and Supplementary Methods). The subgroup analyses included biologic and conventional starters who had at least 2 years of follow-up (Figure 1; Supplementary Methods). Additionally, for the subgroup of biologic starters and for the subgroup of conventional starters, further sub-cohorts were identified based on discontinuation, persistence or switching of biologic/conventional therapy. Subgroups were defined as patients who, a) were on treatment for <12 months from the initiation (discontinuers), b) persisted on a single treatment for ≥12 months (non-switchers), and c) switched a biologic or conventional once during the 2-year period after the initiation of the first treatment (one-time switchers, total treatment duration ≥12 months), and d) switched a biologic or conventional more than once during the 2-year period after the initiation of the first treatment (multiple switchers, total treatment duration ≥12 months). The subgroup follow-up started one year before and ended two years after the initiation of the first biologic/conventional (Figure 1).

Outcome measures

The two outcome measures of the study were 1) the mean annual number of healthcare contacts (including all contact types, e.g. visits and phone calls) per person before and after the initiation/switch of the treatment in biologic and conventional starters, and 2) the mean and cumulative number of healthcare contacts per person one year before to two years after the initiation of the first treatment in the subgroups of biologic and conventional starters. The healthcare contacts were reported as number of days the patient had any contact with a healthcare provider, divided in the following categories: primary care, dermatology specialty in secondary care,

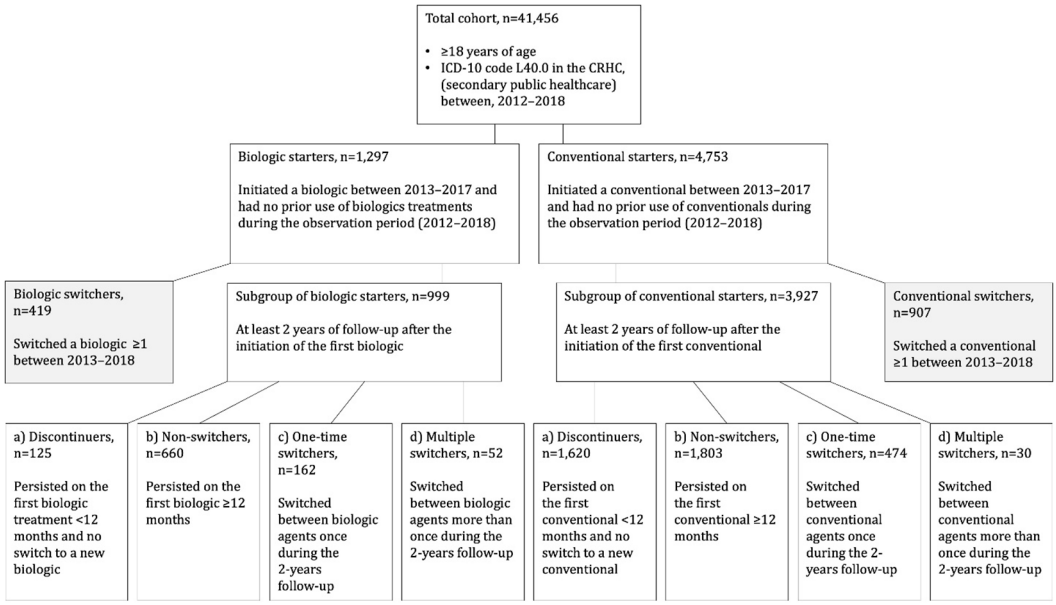

FIGURE 1
Patient flow. ICD-10, International Classification of Diseases, Tenth Revision.

and other secondary care excluding dermatology. Treatment switch was defined as the purchase of a new biologic/conventional drug (analyzed in the Anatomical Therapeutic Chemical Classification System (ATC) classes at the level of 7 digits) per time window.

Statistical analyses

Demographic characteristics and comorbidities were analyzed using descriptive statistics. Categorical variables were presented as the number of observations and proportions. Continuous variables were reported as mean with standard deviation (SD) and median with first (Q1) and third (Q3) quartiles.

The outcomes were illustrated by figures describing a moving average as a function of time from the index date. In addition, the outcomes were described by the number of events, accumulated person-years, and rate of events (number of events per person-years) before and after the index date. The rate of events was compared using the Poisson model.

The statistical analyses were conducted using R (version 4.1.3., http://www.r-project.org).

Results

Characteristics of biologic and conventional starters

During the observation period, the initial treatment was a biologic in 3.1% (n=1,297) of patients, and conventional in 11.5% (n=4,753) of patients (Figure 1). The baseline demographic characteristics and comorbidities for the main study groups are presented in Table 1. Biologic starters were slightly more often male (63.7%) than conventional starters (58.2%) and the mean age was younger for biologic starters (51.8 years; SD, 13.8 vs. 56.5 years; SD, 15.5). Immune-mediated inflammatory comorbidities, such as psoriatic arthropathies, rheumatoid arthritis, and inflammatory bowel diseases were more common in biologic compared with conventional starters, whereas other dermatological diseases were more common in conventional starters.

HCRU before and after the initiation or switch of a biologic

The mean annual number of contacts with a dermatologist decreased from 5.4 to 2.3 per person after the initiation of the first biologic (n=1,297) (Figure 2A). The mean annual number of both primary care (8.7 and 9.1 per person before and after the initiation, respectively) and other secondary care (3.9 and 4.1) contacts was higher after the initiation of the first biologic (Figure 2A). In all categories, the number of contacts peaked just before the initiation of biologic treatment (Supplementary Figure S1A).

A total of 419 patients (32.3%) switched biologic ≥1 time during the observation period. The peak in the contacts with a dermatologist was lower at the time of treatment switch than at the initiation of the first biologic (Supplementary Figure S2A, Supplementary Figure S1A), as was the difference between the mean number of contacts before (3.7 per person per year) and

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TABLE 1 Characterization of biologic (n=1,297) and conventional (n=4,753) starters.

	Biologic starters (n=1,297)	Conventional starters (n=4,753)
Sex, n (%)		
Female	471 (36.3)	1,986 (41.8)
Male	826 (63.7)	2,767 (58.2)
Age – continuous		
Mean (SD)	51.83 (13.84)	56.48 (15.51)
Median	52.58	57.88
Q1, Q3	41.80, 62.11	45.48, 68.16
Selected comorbidities, n (%) (based on ICD-10 codes from 2012–2018)		
Essential (primary) hypertension	226 (17.4)	960 (20.2)
Arthropathy	285 (22.0)	1,118 (23.5)
Distal interphalangeal psoriatic arthropathy	39 (3.0)	48 (1.0)
Arthropathic psoriasis	590 (45.5)	1,015 (21.4)
Dorsopathies	297 (22.9)	959 (20.2)
Acute upper respiratory infections	215 (16.6)	749 (15.8)
*Other dermatological diseases**	151 (11.6)	910 (19.1)
Type 2 diabetes mellitus	127 (9.8)	521 (11.0)
Osteoarthritis	132 (10.2)	539 (11.3)
Severe ischemic arrhythmias	61 (4.7)	323 (6.8)
Hypercholesterolemia	83 (6.4)	18 (0.4)
Influenza and pneumonia	69 (5.3)	235 (4.9)
Other lower respiratory infections	89 (6.9)	375 (7.9)
Cancer	33 (2.5)	293 (6.2)
Asthma	80 (6.2)	322 (6.8)
Major depressive disorder	109 (8.4)	351 (7.4)
Any mental disorder	222 (17.1)	844 (17.8)
Heart failure	24 (1.9)	91 (1.9)
Hemorrhagic or embolic stroke	13 (1.0)	110 (2.3)
Chronic obstructive pulmonary disease	29 (2.2)	144 (3.0)
Gout	23 (1.8)	119 (2.5)
Kidney diseases	13 (1.0)	44 (0.9)
Crohn's disease	35 (2.7)	56 (1.2)
Ulcerative colitis	27 (2.1)	66 (1.4)
Crohn's disease or ulcerative colitis	54 (4.2)	111 (2.3)
Rheumatoid arthritis	90 (6.9)	173 (3.6)

ICD-10, International Classification of Diseases, Tenth Revision; Q1, first quartile; Q3, third quartile; SD, standard deviation. *ICD-10 codes: L20–9, L30–9.

after (2.7) the treatment switch compared to the initiation of the first biologic (Figure 2A).

HCRU before and after the initiation or switch of a conventional

For the conventional starters (n=4,753), the mean annual number of contacts with a dermatologist was 3.3 per person before and 3.2 after the initiation of the first conventional, with a high, symmetric peak in contacts at the time of treatment initiation (Figure 2B; Supplementary Figure S1B). The mean annual number of both other secondary (3.1 and 3.9 per person before and after the index, respectively) and primary care contacts (10.4 and 13.6) increased after the initiation of the first conventional (Figure 2B).

A total of 907 (19%) patients switched ≥1 time among conventionals during the observation period. For these patients, the mean annual number of contacts with a dermatologist before the treatment switch was almost three times higher (9.2 vs 3.3 per person) than before the initiation of the first conventional (Figure 2B; Supplementary Figure S2B). After the conventional switch, the annual number of contacts with a dermatologist decreased to an annual mean of 4.2 per person.

HCRU in the subgroups of biologic starters

HCRU from one year before to two years after the initiation of the first biologic was analyzed in the subgroups of patients who had ≥2 years of follow-up (n=999) (Figure 1). A total of 66.1% (n=660) of patients persisted on the first biologic and 12.5% (n=125) discontinued the treatment during the 12 months following the treatment initiation. During the 2-year period after the initiation of the first biologic, 16.2% (n=162) patients switched a biologic once and 5.2% (n=52) more than once.

The cumulative number of healthcare contacts during the 2-year period was significantly lower for non-switchers compared to all other subgroups in all care categories excluding contacts with a dermatologist for patients who discontinued the treatment ($p<0.001$) (Figure 3A). In non-switchers, the mean number of annual contacts with a dermatologist in the year before the initiation of the first biologic was 7.4 per person, compared to 2.6 during the 2-year period after the initiation (n=660) (Figure 4A). In non-switchers, the mean annual number of other secondary care and primary care contacts also decreased after the treatment initiation.

For the discontinuers, the mean number of primary and other secondary care contacts was significantly higher than for any other subgroup during the 2-year period ($p<0.001$). The difference was observed before the initiation of the first biologic (Figure 4A). In discontinuers, but not in any other subgroup, Crohn´s disease (recorded in 5% of all secondary care visits) and rheumatoid arthritis (4%) appeared as one of the most common reasons for visits (Supplementary Table S2).

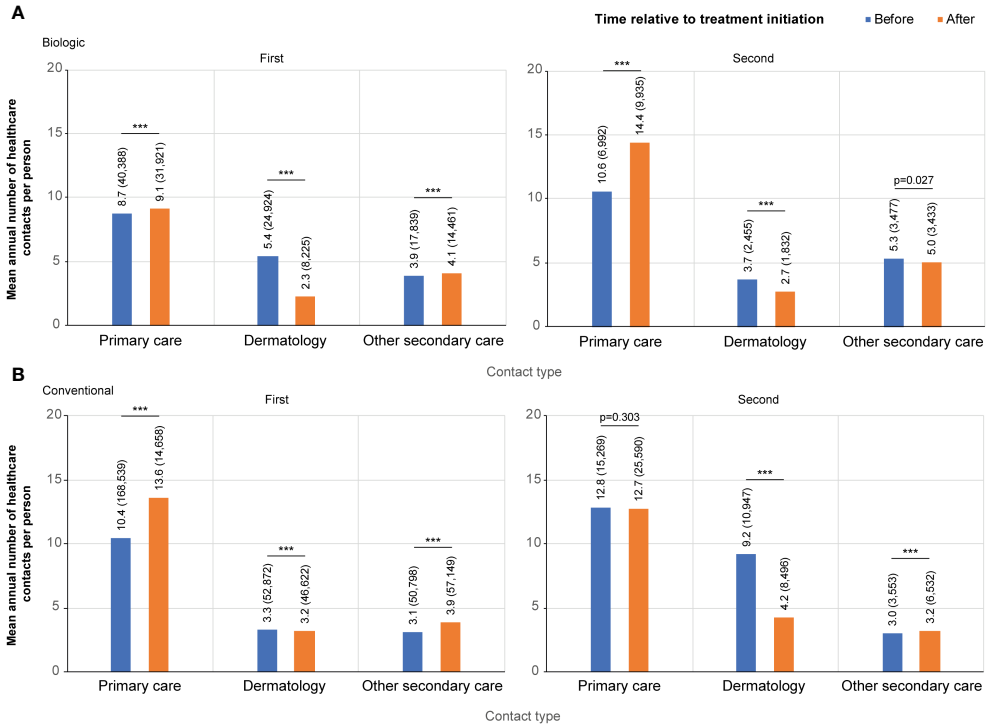

FIGURE 2
Contact rates per category before and after the initiation of the first and the second **(A)** biologic, and **(B)** conventional. Contact categories included: all primary care, dermatology, and other secondary care excluding dermatology. For the first biologic/conventional, the follow-up starts at January 1, 2012, and ends either when a patient switches to a second biologic or December 31, 2018, whichever occurred first (the index date is the date of the first drug initiation). For the second biologic/conventional, the follow-up starts from the initiation of a first biologic/conventional and ends when a patient switches to a third biologic, or on December 31, 2018, whichever occurred first (the index date is the date of the treatment switch).
*** p<0.001.

HCRU in the subgroups of conventional starters

Of the conventional starters who had ≥2 years of follow-up (n=3,927), 45.9% (n=1,803) persisted on the first conventional treatment and 41.3% (n=1,620) discontinued the treatment during the first year after the initiation (Figure 1). During the 2-year period after initiation of the first conventional, 12.1% (n=474) switched the treatment once, and only 30 (1%) switched more than once.

The cumulative number of contacts during the 2-year period after the initiation of the first conventional was significantly (p<0.001) different between all subgroups and care categories, excluding the discontinuers (n=1,620) and non-switchers (n=1,803) in primary care contacts (Figure 3B). In the non-switchers, the mean annual number of contacts with a dermatologist decreased after the initiation of the first conventional (6.0 and 3.4. per person before and after the initiation, respectively; n=1,803) whereas for patients switching once, it remained at a similar level (8.6 and 8.2; n=474) (Figure 4B).

Discussion

This study characterized the HCRU patterns in the population-based cohort of psoriasis patients using systemic treatments in Finland. The results showed a high overall HCRU burden consisting not only of contacts with a dermatologist, but also primary and other secondary care HCRU. A decrease in contacts with a dermatologist was observed after treatment initiation among patients who initiated a biologic, but not a conventional. Treatment switching correlated with steep peak in contacts with a dermatologist for conventional users, but not for those using a biologic treatment. Overall, primary and other secondary care contacts besides dermatology contacts did not decrease after the initiation or switch of either biologic or conventional treatments.

Previous studies have shown that the initiation of biologics is associated with a significant decrease in HCRU and associated costs in patients with moderate to severe psoriasis (19–21). Some of the first studies have suggested that the decrease in HCRU after the initiation of the biologics can even offset the higher prescription costs associated with biologics (19). However, most of the previous studies are based either on the US claims databases or small cohorts in Europe – nationally representative, population-based analyses are rare. In line with the previous findings, this study indicated a significant decrease in the mean annual number of contacts with a dermatologist in the period after (2.3 per person) compared to before the initiation of biologics (5.4). The observed decrease, specifically in the contacts with a dermatologist, likely reflects improved psoriasis control resulting in fewer hospitalizations and emergency room visits, as previously shown, but also suggests a need for less frequent control visits (21, 22).

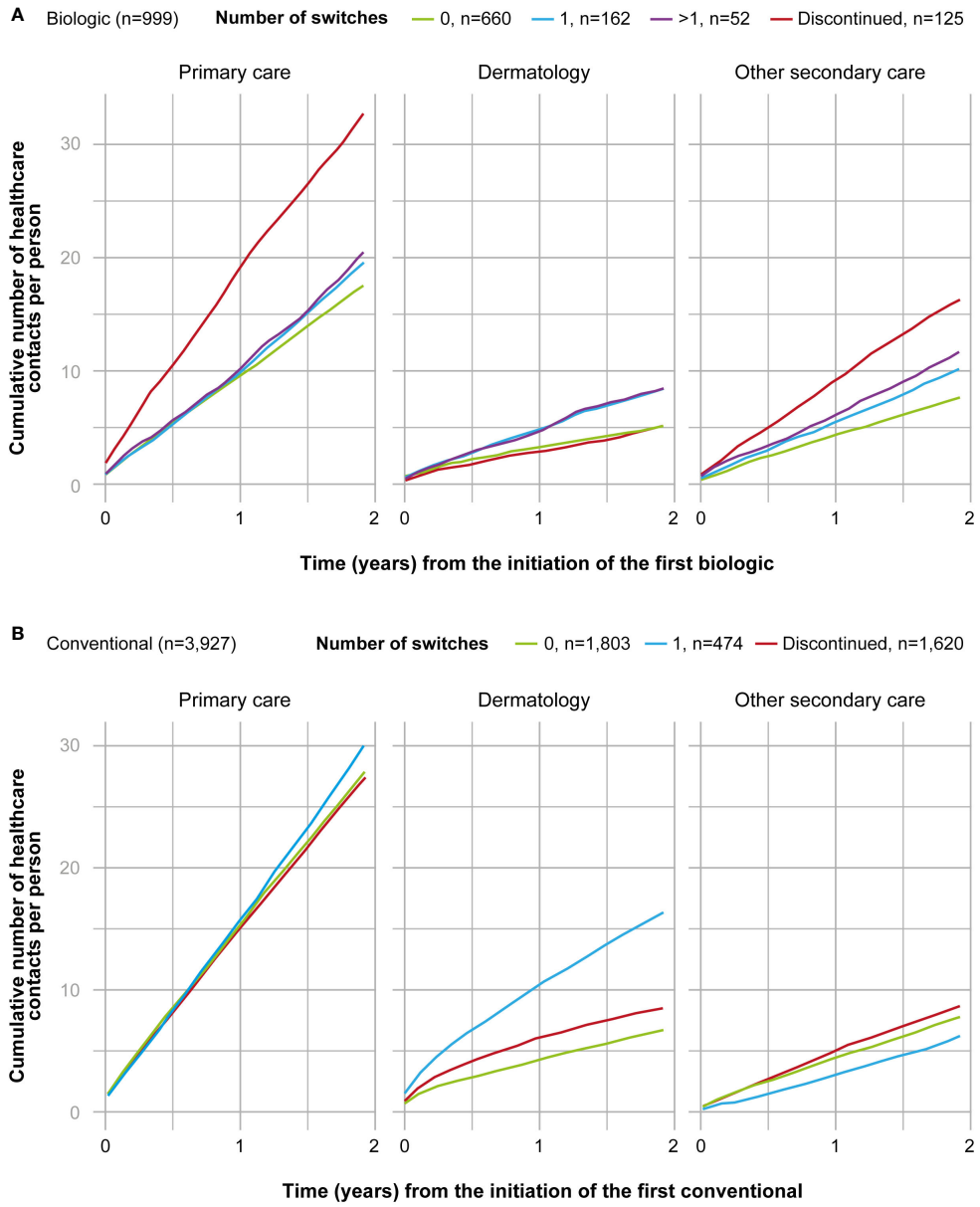

FIGURE 3
Cumulative number of healthcare contacts from the 2-year period after the initiation of the first **(A)** biologic (n=999), and **(B)** conventional (n=3,927) in different subgroups and by category (primary care, dermatology, secondary care excluding dermatology). Subgroups of biologic starters included patients who persisted on the first biologic ≥12 months (0, n=660); switched the biologic once during the 2-years period (1, n=162); switched the biologic more than once during 2-years period (>1, n=52); and patients who persisted on the first biologic <12 months (discontinued, n=125). Subgroups of conventional starters included patients who persisted on the first conventional <12 months (discontinued, n=1,620); persisted on the first conventional ≥12 months (0, n=1,803); and switched the conventional once during the 2-year period (1, n=474). Patients who switched conventional more than once during the 2-year period were excluded from the figure due to the small number (>1, n=30).

Interestingly, only a very slight decrease in the number of contacts with a dermatologist (3.3 before and 3.2 after the initiation, respectively) was observed in the conventional starters after the initiation of the first conventional. The mean number of contacts with a dermatologist after the treatment initiation was higher in the conventional starters compared to biologic starters, even though conventional starters likely suffer from less severe disease. According to the Finnish Current Care Guidelines for Psoriasis and the reimbursement criteria by the Social Insurance Institution of Finland, biologics can be used only for patients with severe psoriasis who have not responded or are intolerant to first-line systemic treatments or phototherapy (17). This is notable from a healthcare perspective in general, as a vast majority of systemic users are on conventional treatment, causing the most significant burden on healthcare providers (18).

Limited treatment persistence has been reported with biologics, with one-year persistence rates ranging from 30% to 70% in different studies (13, 14, 16, 23, 24). Although switching of biologic agents due to inefficacy or adverse effects can improve disease control, switching and discontinuing the treatment have

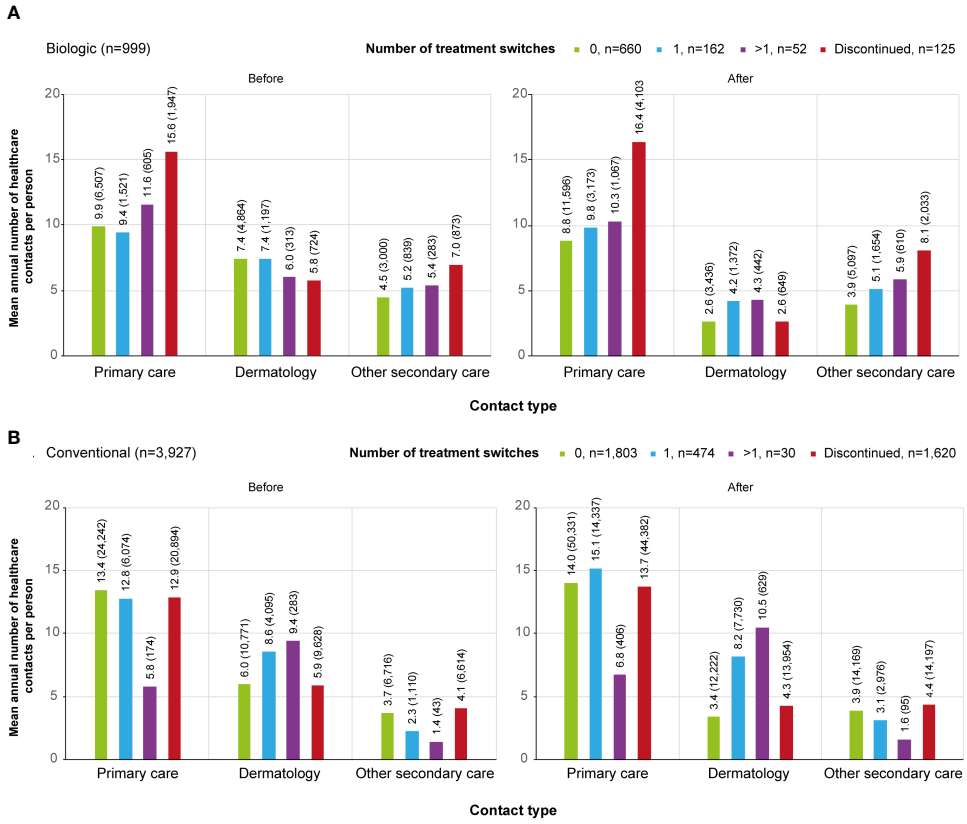

FIGURE 4
Contact rates by category (primary care, dermatology, secondary care excluding dermatology) before and after the initiation of the first **(A)** biologic / **(B)** conventional in different subgroups.. Subgroups were defined as follows, patients who: persisted on the first treatment ≥12 months (0, biologic n=660, conventional n=1,803); switched a biologic or conventional once during the 2-year period after the initiation of the first treatment (1, biologic n=162, conventional n=474); switched a biologic or conventional more than once during the 2-year period after the initiation of the first treatment (>1, biologic n=52, conventional n=30); continued the first treatment <12 months from the initiation and did not start a new medication within the medication group (discontinued, biologic n=125, conventional n=1,620).

been reported to be associated with a significant healthcare burden compared to continuing treatment on the same biologic (15). In this study, 21% of biologic and 13% conventional starters switched between agents, and 13% of biologic and 41% of conventional starters discontinued the treatment during the first two years after the initiation of their first biologic/conventional. Switching to the second biologic caused a smaller peak in the contacts with a dermatologist compared to the initiation of the first biologic, suggesting that the switch as such is not associated with a considerable HCRU burden.

Instead, there was a significant peak in contacts with a dermatologist before switching to the second conventional, and the 2-year cumulative numbers of contacts with a dermatologist were approximately 2.5 times higher for conventional switchers vs. non-switchers. These findings suggest that for the subgroup of conventional switchers, switching to a biologic instead of another conventional could be a potential option to decrease the burden to both patients and healthcare system.

Although the switch to the second biologic did not correspond with a peak in the average annual contacts with a dermatologist, the cumulative healthcare burden was significantly lower for biologic non-switchers than for switchers in all care categories studied, in line with previous findings (15, 16). The non-switchers were the only subgroup in which the average number of contacts decreased in all care categories including primary and other secondary care, suggesting that improved psoriasis control may have favorable effects on overall HCRU even with a relatively short timeframe.

Based on the HCRU pattern, biologic discontinuers seemed to differ from those persisting or switching treatment. The discontinuers had a higher number of primary and other secondary care contacts before the initiation of the biologic, suggesting a higher burden of comorbidities in these patients. In fact, previous studies have indicated that patients with a high comorbidity index and concomitant medications had an increased risk of biologic discontinuation (13, 25, 26). Another possible explanation is that among the discontinuers, biologics are more often used for another indication than psoriasis. This idea is supported by the finding that the number of contacts with a dermatologist was relatively low in the discontinuers, while other inflammatory diseases such as Crohn´s disease and rheumatoid arthritis appeared as one of the most common reasons for visits, specifically in biologic discontinuers.

The major strengths of this population-based study include utilization of nationwide healthcare registers providing a

representative picture of the patient population at a national level. The Finnish healthcare system allows all citizens equal access to tax-funded, high-quality public healthcare with an annual maximum limit on out-of-pocket costs, minimizing the selection bias in due to accessibility reasons. This is especially important regarding biologic treatments, for which the costs are globally one of the major factors limiting accessibility to patients.

Limitations of the study include a lack of detailed clinical information data and indication of biologics, as well as reasons for treatment discontinuation and switches. Another limitation is the fact that national registries used in this study are not quality registries per se, and therefore, lack disease-specific data such as Psoriasis Area and Severity Index. Incorporation of disease-specific structural parameters into registries would allow even more comprehensive analyses. In addition, the use of private and occupational healthcare is not recorded in the national health registers. Private care accounted for approximately 22% of all healthcare provided in Finland in 2020, thus the actual use of healthcare services is higher than what was reported here (27). This applies especially to primary care, whereas most of the secondary care is organized by public healthcare service providers in Finland. Analyses on systemic treatments were based on purchases of nationally reimbursed prescription medicines, and thus do not include drugs administered in hospitals, such as intravenous infliximab. Although the study design includes only a minimal bias in patient selection, and the results are thus expected to reflect moderate-to-severe psoriasis patients in general, it should be noted that healthcare systems and treatment practices may vary considerably between countries. Moreover, patients who start biologics have used conventional treatments before, since in Finland biologics are reimbursed only after use of conventionals. Therefore, from the analysis point of view, it is possible that patients that are conventional discontinuers are also contemplated in the biologic starters group, which brings some limitations for the conventional discontinuers analysis.

With the increasing number of treatment options available for psoriasis, identification of patients' individual needs and preferences and understanding of disease burden comprehensively become more important than ever. This study provides a nationwide real-world view on the HCRU in psoriasis patients using systemic treatments. The results strengthen previous evidence on the benefits of biologics in decreasing the HCRU and associated costs in psoriasis patients, however, the benefits reach beyond that. Less frequent healthcare visits have a positive impact on patients in terms of reduced days off from work, improved work productivity, and overall activity in psoriasis patients, decreasing the burden and indirect costs of the disease (13, 27–31). The results highlight the importance of thorough consideration of the most optimal treatment alternatives, considering the overall disease burden to patients and healthcare systems. This includes the repertoire of new biologics, and the possibility to switch, especially in patients not responding to the first conventional treatment.

Data availability statement

The datasets presented in this article are not readily available because according to Finnish legislation, access to individual-level data is restricted only to individuals named in the study permit. The study protocol is available upon request from the corresponding author.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article because the datasets presented in this article are not readily available (according to Finnish legislation, access to individual-level data is restricted only to individuals named in the study permit).

Author contributions

AV: Conceptualization, Data curation, Investigation, Methodology, Project administration, Validation, Visualization, Writing – original draft, Writing – review & editing. JM: Data curation, Investigation, Methodology, Validation, Visualization, Writing – review & editing, Conceptualization. JA: Conceptualization, Investigation, Methodology, Project administration, Writing – review & editing. RK: Conceptualization, Investigation, Methodology, Writing – review & editing. KT: Conceptualization, Investigation, Methodology, Writing – review & editing. LH: Conceptualization, Investigation, Methodology, Validation, Writing – review & editing.

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Conflict of interest

LH has received educational grants from AbbVie, Janssen-Cilag, LEO, Novartis, CSL Behring and Takeda; honoraria from AbbVie, Boehringer Ingelheim, Lilly, Novartis, Orion, Pfizer, and Sanofi Genzyme for consulting and/or speaking; and is an investigator for AbbVie and Amgen. AV and JM are employees of MedEngine Oy. RK and JA are employees of AbbVie and may or may not own AbbVie shares. KT has received educational grants from Sanofi Genzyme and honoraria from AbbVie, Bristol Myers Squibb, Janssen-Cilag, Leo, Novartis, Sanofi

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Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2024.1374829/full#supplementary-material

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Hepatitis-related adverse events associated with immune checkpoint inhibitors in cancer patients: an observational, retrospective, pharmacovigilance study using the FAERS database

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Background: Immune checkpoint inhibitors (ICIs), including anti-PD-1, anti-PD-L1 and anti-CTLA-4 antibodies, have become a standard treatment for multiple cancer types. However, ICIs can induce immune-related adverse events, with hepatitis-related adverse events (HRAEs) being of particular concern. Our objective is to identify and characterize HRAEs that exhibit a significant association with ICIs using real-world data.

Methods: In this observational and retrospective pharmacovigilance study, we extracted real-world adverse events reports from the FDA Adverse Event Reporting System database spanning from the first quarter of 2004 to the first quarter of 2023. We conducted both Frequentist and Bayesian methodologies in the framework of disproportionality analysis, which included the reporting odds ratios (ROR) and information components (IC) to explore the intricate relationship between ICIs and HRAEs.

Results: Through disproportionality analysis, we identified three categories of HRAEs as being significantly related with ICIs, including autoimmune hepatitis (634 cases, ROR 19.34 [95% CI 17.80–21.02]; IC025 2.43), immune-mediated hepatitis (546 cases, ROR 217.24 [189.95–248.45]; IC025 4.75), and hepatitis fulminant (80 cases, ROR 4.56 [3.65–5.70]; IC025 0.49). The median age of patients who report ICI-related HRAEs was 63 years (interquartile range [IQR] 53.8–72), with a fatal outcome observed in 24.9% (313/1,260) of these reports. Cases pertaining to skin cancer, lung cancer, and kidney cancer constituted the majority of these occurrences. Patients treated with anti-PD-1 or anti-PD-L1 antibodies exhibited a higher frequency of immune-mediated hepatitis in comparison to those undergoing anti-CTLA-4 monotherapy, with a ROR of 3.59 (95% CI 1.78–6.18). Moreover, the dual ICI therapy demonstrated higher reporting rates of ICI-related HRAEs compared to ICI monotherapy.

Conclusion: Our findings confirm that ICI treatment carries a significant risk of severe HRAEs, in particular autoimmune hepatitis, immune-mediated hepatitis, and hepatitis fulminant. Healthcare providers should exercise heightened vigilance regarding these risks when managing patients receiving ICIs.

KEYWORDS

immune checkpoint inhibitors, hepatitis, disproportionality analysis, pharmacovigilance study, FAERS database

1 Introduction

Since the elucidation of the role of immunological processes in tumorigenesis, multiple immune checkpoint inhibitors (ICIs) targeting immune checkpoint molecules have emerged as promising cancer immunotherapies (Galluzzi et al., 2020; Robert, 2020). These include inhibitors of cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed cell death 1 (PD-1), and programmed death ligand 1 (PD-L1) (de Miguel and Calvo, 2020; Bagchi et al., 2021). By blocking these immune checkpoint proteins, ICIs can enhance T cell-mediated anti-tumor immunity. Since ipilimumab, as the first CTLA-4 inhibitor, was approved by the US Food and Drug Administration (FDA) for advanced melanoma in 2011, the ICIs have revolutionized the treatment landscape across various malignancies and have become an intensely studied area of cancer research (Dall'Olio et al., 2022; Vafaei et al., 2022).

However, the expanding clinical utilization of ICI agents has revealed a broad range of immune-related adverse events (irAEs) (Martins et al., 2019). It has been demonstrated that irAEs are caused by excessive immune activation affecting multiple organs, particularly the skin, liver, endocrine system, and gastrointestinal tract (Thapa et al., 2019; Albandar et al., 2021). As a key site of drug metabolism, the liver is a frequently impacted organ during cancer immunotherapy and the hepatotoxicity resulting from ICIs treatment is typically classified as immune-mediated hepatitis (Ng et al., 2022). Hepatitis has been reported as the third most common toxicity (5%–10%) following the dermatologic (44%–68%) and gastrointestinal (35%–50%) irAEs (Tian et al., 2018; Wang et al., 2020). Hepatitis, which is an inflammation of the liver, can be induced by ICIs due to their impact on immune system tolerance and regulation. The occurrence of hepatitis in patients treated with ICIs ranges from mild elevations in liver enzymes to severe hepatotoxicity. This severe form can lead to significant risks, including the development of liver cancer in chronic cases. Several mechanisms were suggested for the association between ICI therapies and the development of hepatitis. One potential mechanism of ICI-induced liver toxicity is the direct effect on liver cells. The presence of PD-1 and PD-L1 on the normal tissues cells implies that the use of ICIs could activate the body's complement system against these non-cancerous "self" cells (Parlati et al., 2023). Another possible mechanism is the disturbance of immune homeostasis, characterized by the expansion of proinflammatory T helper cell subsets (Th1, Th17) and subsequent release of cytokine release (IL-2, IFN-γ, TNF-α) (Adams et al., 2010; Liu et al., 2023). In addition, ICI-mediated monocyte activation and inflammatory milieu generation may also contribute to immune-mediated hepatitis (Shojaie et al., 2021).

The pharmacovigilance studies on irAEs associated with ICIs treatment have identified several possible clinical toxicities to help guide medical practice and enhance patient care, as well as the hepatotoxicity with different ICIs (Salem et al., 2018; Gérard et al., 2021; Ma et al., 2021; Xu et al., 2023). The previous work identified various liver-related adverse events reported with different ICIs (Xu et al., 2023), but the studies focusing on association between ICI therapy and hepatitis-related adverse events (HRAEs) remain limited. Herein, in this observational, retrospective, pharmacovigilance study, we aim to utilize a disproportionality analysis, based on real-world adverse events reports from the FDA Adverse Event Reporting System (FAERS) database, to conduct a comprehensive assessment of HRAEs associated with ICIs and to provide a detailed description of the clinical features of reported cases pertaining to ICI-related HRAEs. The findings from this study will provide a valuable reference for healthcare providers to caution the risk of HRAEs when managing patients receiving ICIs.

2 Methods

2.1 Study design and data sources

This retrospective, observational pharmacovigilance study utilized disproportionality analysis of adverse drug reaction reports from the FAERS database. The FAERS database is a comprehensive, publicly accessible passive surveillance system incorporating global data on medication-related adverse events and errors submitted by healthcare professionals, patients, and pharmaceutical companies in the United States and worldwide (Ma et al., 2021; Feng et al., 2022). Our study encompassed all adverse event reports in FAERS ranging from the first quarter of 2004 (Q1 2004) to the first quarter of 2023 (Q1 2023). Relevant adverse event data was obtained using the immune checkpoint inhibitors, including CTLA4 inhibitors (ipilimumab and tremelimumab), PD-1 inhibitors (nivolumab, pembrolizumab, and cemiplimab), and PD-L1 inhibitors (atezolizumab, avelumab, and durvalumab), as the primary suspected (PS) drugs. Since the ICI-based combination therapies are usually used in the clinical settings, the dual ICI therapy (CTLA4 inhibitor and PD-1/PD-L1 inhibitors) and ICI combined with chemotherapy were also included in the analysis for the investigation of differences. All adverse events in FAERS are coded using the preferred terms (PTs) based on the Medical Dictionary for Regulatory Activities (MedDRA version 26.1).

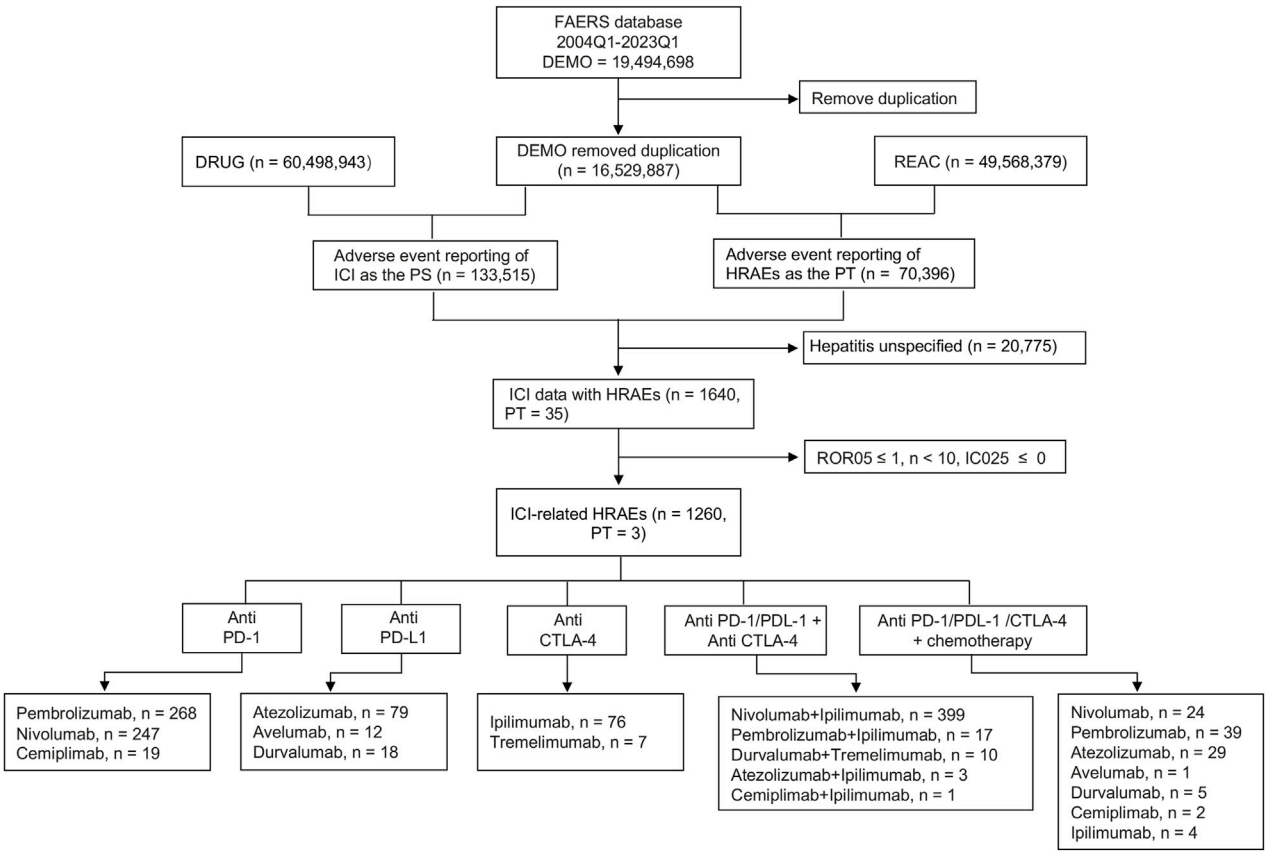

FIGURE 1
Flow chart showing the selection process of hepatitis-related adverse events for immune checkpoint inhibitors (ICIs) in the Food and Drug Administration Adverse Event Reporting System (FAERS). HRAEs, hepatitis-related adverse events; PTs, preferred terms; PS, primary suspected drugs; ROR05, the lower limit of 95% CI of reporting odds ratio (ROR); IC025, the lower limit of 95% CI of the information component (IC).

2.2 Data processing procedure

We exacted all quarterly data extract (QDE) data from the FAERS ranging from 2004Q1 to 2023Q1, which is available at: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. The files listed on this page contain raw data extracted from the FAERS database for the indicated time and we can choose the desired quarter to download for analysis. The QDE file contains diverse data, including demographics and administrative details (DEMO), drug information (DRUG), adverse events (REAC), patient outcomes (OUTC), reporting sources (RPSR), treatment timelines (THER), and dosage indications (INDI). All FAERS data is recorded in either ASCII or XML formats, the ASCII files were used as the data sources and imported into SAS software (version 9.4). To ensure data integrity and preclude duplication, a deduplication process recommended by the FDA was implemented based on two criteria: i. When the unique case identifier (CASEID) was identical, the most recent FDA receipt date (FDA_DT) was selected; ii. For reports with identical CASEID and FDA_DT, the higher PRIMARYID number (the unique identifier assigned to each report) was chosen (Giunchi et al., 2023).

Our initial inquiry focused on the occurrence of HRAEs in patients subjected to ICIs, as documented in the FAERS database. The comprehensive data processing methodology is demonstrated in Figure 1. Starting with a dataset containing 19,494,698 adverse event reports, we conducted a thorough deduplication process using the PRIMARYID and/or CASEID recorded in the DEMO files, ultimately obtaining 16,529,887 unique adverse event reports for analysis. Among these, there were 133,515 adverse event reports associated with the use of various ICI drugs and a cumulative total of 70,396 hepatitis adverse events were cataloged as PTs in the FAERS database. To ensure specificity in our analysis, cases involving non-specific HRAEs were excluded. Consequently, we obtained a refined dataset of the ICI drugs reporting HRAEs (1,640 cases, 35 PTs).

2.3 Signal mining

Disproportionality analysis was utilized in this study to evaluate reporting patterns of suspected ICI-related hepatitis adverse events compared to other drugs in the FAERS database. In order to improve the rigorousness of our analysis, both the Bayesian method and the frequency method were simultaneously applied in our study. Frequency methods demonstrate greater sensitivity compared to Bayesian analyses, whereas Bayesian methods exhibit higher specificity. (Shen et al., 2019). In the present study, disproportionality was quantified by the information component (IC, a method originally introduced through the Bayesian Confidence Propagation Neural Network) and reporting odds

ratio (ROR) (Shu et al., 2023; Trillenberg et al., 2023). The IC method can provide a conservative correlation measure and reduce the risk of highlighting spurious associations, especially for events with very low expected frequencies in large databases (Hou et al., 2014). The ROR allows to estimate the relative risk and identify abnormally higher than expected proportions of adverse event reporting, hence highlighting the risks associated with the use of specific drugs (Rothman et al., 2004). Specific formulas for calculating the IC and ROR along with their 95% confidence interval (CI) are shown below:

$$IC = Log_2\left(\frac{N_{observed}}{N_{expected}}\right)$$

$$N_{expected} = \frac{N_{drug} * N_{event}}{N_{total}}$$

where $N_{expected}$ is the number of hepatitis records expected for the ICI. $N_{observed}$ is the number of hepatitis records for the ICI. N_{drug} is the number of all adverse event reports associated with ICI agents. N_{event} is the number of hepatitis adverse events reported in the full database. N_{total} is the number of all adverse event reports for all drugs in the full database. The IC025 represents the lower boundary of the 95% credibility interval for the IC, which serves as a statistical measure. Traditionally, a positive value exceeding zero is considered the threshold for detecting signals. In our analysis, we also estimated the disproportionality of hepatitis adverse events among different ICI treatment strategies using the ROR along with its corresponding 95% confidence interval (95% CI). A lower limit of the 95% CI (ROR05) equal to or greater than 1 was deemed indicative of a positive signal.

$$ROR = \frac{N_{observed}}{N_{expected}}$$

In our study, preferred terms (PTs) of hepatitis adverse events with no fewer than ten cases (N > 10) that both meet the above two criteria (IC025 > 0 and ROR05 > 1) of disproportionality analysis were defined as ICI-related HRAEs.

2.4 Descriptive analysis

A comprehensive descriptive analysis was performed to summarize the clinical characteristics of FAERS reports documenting ICI-associated HRAEs. Variables analyzed included gender, country, outcome, FDA receipt date, immunotherapy regimen, report type, and other relevant clinical features. The association between ICI therapies and HRAEs was evaluated using both the IC and the ROR when the full database served as the comparator. However, IC cannot compare reporting between individual drugs (Bate et al., 1998; Norén et al., 2006; Norén et al., 2013). As a result, only the ROR was used when comparing individual drugs or drug classes to each other.

2.5 Statistical analysis

Samples with missing data were omitted from statistical analyses for each clinical characteristic. A p-value <0.05 was the threshold for statistical significance, with all statistical tests being two-tailed. We performed the statistical analyses and visualizations using R software (version 4.3, ggplot2 package), Microsoft Excel (version 16.65) and GraphPad Prism 9 (version 9.4.1). This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline (Von Elm et al., 2007).

3 Results

3.1 Identification of ICI-related HRAEs in the FAERS database

We firstly systematically tabulated the various categories of HRAEs and quantified their prevalence in the reports concerning the use of ICIs. The results revealed that autoimmune hepatitis (N = 634, 38.66%), immune-mediated hepatitis (N = 546, 33.29%), hepatitis acute (N = 85, 5.18%), hepatitis fulminant (N = 80, 4.88%), and hepatitis cholestatic (N = 65, 3.96%) emerged as the top five categories, displaying the highest frequency of reported cases. Subsequently, we conducted a disproportionality analysis, computing the ROR and IC for each PT associated with no fewer than ten cases within HRAEs. The full FAERS database served as the reference dataset for this analysis. Following stringent filtering based on predefined criteria for a positive signal, we identified distinctive HRAEs associated with various ICI treatment strategies, as depicted in Figure 2A. Finally, we designated three PTs (autoimmune hepatitis, immune-mediated hepatitis, and hepatitis fulminant) as ICI-related HRAEs, characterized by a statistically significant increase in reporting after ICI treatment, relative to their occurrence in the full database.

The utilization of ICIs was associated with an increased occurrence of autoimmune hepatitis, immune-mediated hepatitis, and hepatitis fulminant in comparison to their occurrence in the full database (Table 1). Specifically, the ROR05 for autoimmune hepatitis was 17.80, with an associated IC025 of 2.43. Similarly, immune-mediated hepatitis exhibited an ROR05 of 189.95 and an IC025 of 4.75, while hepatitis fulminant displayed an ROR05 of 3.65 and an IC025 of 0.49. Notably, immune-mediated hepatitis emerged as the ICI-related hepatitis adverse event with the most substantial ROR and IC signals across all contexts. Using the complete FAERS database as the reference, we recalculated the ROR and IC signals for ICI-related hepatitis adverse events. In an overarching analysis, all ICI treatment strategies exhibited a statistically significant association with the occurrence of ICI-related HRAEs, revealing an ROR of 23.6 (95% CI 22.3–25.1) (Figure 2B). Further delineating the nuances of ICI treatment strategies, we observed that ICI monotherapy exhibited similar ROR values. In contrast, the dual ICI therapy (combination ICI immunotherapy with anti-PD-(L)1 and anti-CTLA4) was notably associated to the highest ROR among the various treatment regimens, with an ROR of 41.3 (95% CI 37.5–45.4) (Figure 2B).

3.2 Descriptive analysis of cases with ICI-related HRAEs

Following a meticulous screening of the FAERS database, we identified a total of 1,260 cases exhibiting HRAEs related to the use

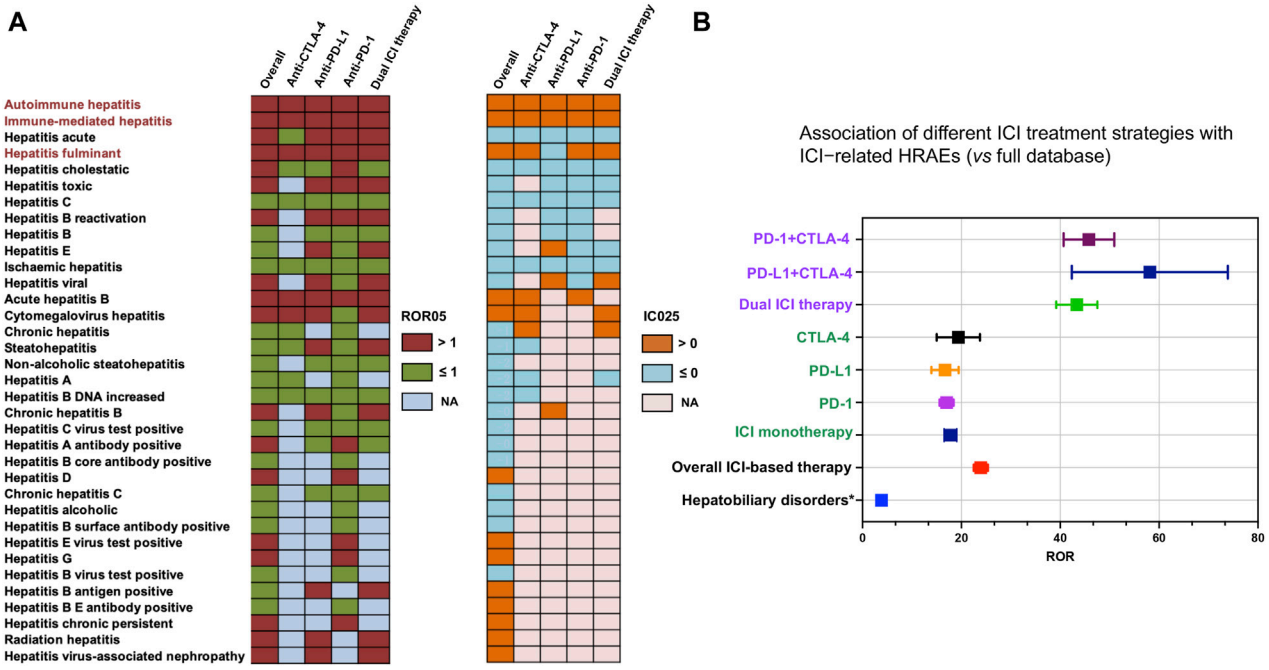

FIGURE 2
Scanning for ICI-related HRAEs based on the FAERS database. **(A)** The heatmap shows the ROR05 and IC025 for 35 hepatitis adverse events in the FAERS database under different ICI treatment strategies (including overall situation, dual ICI therapy, and ICI monotherapy). Hepatitis-related adverse events were identified and labeled with dark red color to meet the criteria including IC025 > 0, ROR05 > 1, and the number of cases occurring no less than 10. **(B)** The forest plot shows the ROR of hepatitis-related adverse events (considering the three categories of ICI-related HRAEs as one category of adverse events) under different ICI treatment strategies (including overall situation, dual ICI therapy, ICI monotherapy). * The overall hepatobiliary disorders caused by ICIs were used as a reference. HRAEs, hepatitis-related adverse events; ROR05, lower limit of 95% CI of reporting odds ratio. IC025, the lower limit of 95% CI of the information component (IC).

of ICIs. Subsequently, we conducted a comprehensive statistical analysis to describe the clinical characteristics, as summarized in Table 2. The median age of the involved patients was 63 years (interquartile range [IQR] 53.8–72) as indicated in 88 available cases. Most of the reported cases were male, constituting 57.2% of the total (N = 719). Furthermore, a significant proportion of these cases originated from the Americas, accounting for 34.6% (N = 435). Notably, the substantial majority of reports, approximately 87.8%, were submitted by healthcare professionals within the last 2 years (40.4%). Of the 1,260 cases, 24.9% (N = 313) experienced a fatal outcome, underscoring the severity of ICI-related HRAEs. A detailed analysis of ICI treatment strategies revealed that the majority of cases involved monotherapy with anti-PD-1 or anti-PD-L1 agents, constituting 51.0% (N = 641) of the total cases. Additionally, the dual ICI therapy was prominent, representing 34.2% (N = 430) of the cases. Among the cases experiencing ICI-related hepatitis adverse events, the indications for treatment predominantly encompassed skin cancer (37.4%, N = 470), followed by lung cancer (21.5%, N = 270), and kidney cancer (9.2%, N = 116) (Figure 3A).

We further explored the RORs of ICI-related HRAEs among different cancer indications by a disproportionality analysis. Compared to the uterus cancer as a reference (N = 11 cases, the lowest ROR in the groups), patients with liver cancer, skin cancer, bladder cancer, prostate cancer, stomach cancer, pancreases cancer, thymus cancer, brain cancer, and hematologic cancer have significant higher RORs, in particular liver cancer. When treated with ICI therapies, the patients with liver cancer have 23.78 times higher odds (ROR = 23.78 [12.24–46.20], $p < 0.0001$) of developing hepatitis, followed by patients with skin cancer (ROR = 4.01 [2.20–7.30], $p < 0.0001$).

We also explored whether the different ICI treatment strategies influence the occurrence of ICI-related HRAEs. Table 3 illustrates the associations of ICI-related HRAEs with various treatment regimens, including anti-CTLA-4 therapy, anti-PD-1 or anti-PD-L1 therapy, and dual ICI therapy in comparison to monotherapy. Patients treated with anti-PD-1 or anti-PD-L1 antibodies exhibited a high frequency of immune-mediated hepatitis in comparison to those undergoing anti-CTLA-4 monotherapy, with a ROR of 3.59 (95% CI 1.78–6.18). Moreover, the dual ICI therapy had a higher reporting rate of immune-mediated hepatitis compared to the ICI monotherapy, with an ROR of 2.74 (95% CI 2.30–7.56). In cases of autoimmune hepatitis and fulminant hepatitis, patients receiving dual ICI therapy were overrepresented compared to those on monotherapy, likely due to greater immune system activation. The RORs for autoimmune hepatitis and fulminant hepatitis were 2.46 (95% CI 2.09–7.31) and 1.74 (95% CI 1.06–4.81), respectively. However, no significant difference in reporting was observed between patients treated with anti-PD-1 or anti-PD-L1 monotherapy and those subjected to anti-CTLA-4 regarding these two adverse events (Table 3).

Further analysis of specific subclassification to individual ICI agents, we used ipilimumab, the only one CTLA-4 inhibitor, as the reference for the comparison. Table 4 shows the risk profile of

TABLE 1 Hepatitis adverse events reported with ICIs *versus* those reported in the full database from the FAERS, from 2004Q1 to 2023Q1.

	AEs reported for ICIs (n = 353,949)	AEs reported in full database (n = 49,568,379)	IC025	ROR05
Autoimmune hepatitis	634	4,566	2.43	17.80
Immune-mediated hepatitis	546	350	4.75	189.95
Hepatitis acute	85	5,213	−0.50	1.83
Hepatitis fulminant	80	2,439	0.49	3.65
Hepatitis cholestatic	65	4,702	−0.73	1.50
Hepatitis toxic	38	2,210	−0.42	1.73
Hepatitis C	32	11,234	−3.00	0.28
Hepatitis B reactivation	28	2,412	−0.98	1.11
Hepatitis B	19	5,132	−2.62	0.33
Hepatitis E	14	1,192	−0.97	0.96
Ischaemic hepatitis	10	1,055	−1.27	0.71
Hepatitis viral	10	641	−0.56	1.16
Acute hepatitis B	9	232	0.71	2.77
Cytomegalovirus hepatitis	8	300	0.19	1.84
Chronic hepatitis	6	681	−1.38	0.55
Steatohepatitis	6	393	−0.60	0.95
Non-alcoholic steatohepatitis	5	953	−2.12	0.30
Hepatitis A	5	753	−1.78	0.38
Hepatitis B DNA increased	5	676	−1.63	0.43
Chronic hepatitis B	5	218	−0.03	1.31
Hepatitis C virus test positive	4	642	−1.88	0.32
Hepatitis A antibody positive	4	177	−0.05	1.17
Hepatitis B core antibody positive	3	352	−1.43	0.38
Hepatitis D	3	53	1.20	2.46
Chronic hepatitis C	2	337	−1.95	0.21
Hepatitis alcoholic	2	284	−1.70	0.24
Hepatitis B surface antibody positive	2	282	−1.69	0.25
Hepatitis E virus test positive	2	38	1.08	1.77
Hepatitis G	2	5	3.37	10.79
Hepatitis B virus test positive	1	352	−3.01	0.06
Hepatitis B antigen positive	1	40	0.05	0.48
Hepatitis B E antibody positive	1	30	0.43	0.63
Hepatitis chronic persistent	1	15	1.32	1.22
Radiation hepatitis	1	14	1.41	1.31
Hepatitis virus-associated nephropathy	1	8	2.06	2.17

Data are n unless otherwise stated. ICIs, refer to any AEs, reported for treatment with nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, ipilimumab, or tremelimumab. The positive IC025 value (>0) and ROR05 (>1) are the traditional thresholds used in statistical signal detection with the FAERS., FAERS, the FDA, adverse event reporting system; ICIs, immune checkpoint inhibitors; IC, information component; ROR, reporting odds ratios; IC025, the lower end of a 95% credibility interval for the IC; ROR05, the lower limit of the 95% confidence interval for ROR.

TABLE 2 Clinical characteristics of patients with ICI-associated autoimmune hepatitis, immune-mediated hepatitis, or hepatitis fulminant from the FAERS database.

Clinical characteristics	Overall (n = 1,260)	Autoimmune hepatitis (n = 634*)	Immune-mediated hepatitis (n = 546*)	Hepatitis fulminant (n = 80*)
Reporting region				
Americas	435 (34.6%)	223 (35.2%)	206 (37.7%)	6 (7.5%)
Oceania	53 (4.2%)	31 (4.9%)	22 (4.0%)	0 (0.0%)
Africa	4 (0.3%)	3 (0.5%)	1 (0.2%)	0 (0.0%)
Europe	513 (40.8%)	285 (45.0%)	209 (38.3%)	21 (26.3%)
Asia	251 (20.0%)	90 (14.2%)	108 (19.8%)	53 (66.3%)
Missing	2 (0.2%)	2 (0.3%)	0 (0.0%)	0 (0.0%)
Reporters				
Healthcare professional	1,105 (87.8%)	529 (83.4%)	504 (92.3%)	73 (91.3%)
Non-health-care professional	149 (11.8%)	101 (15.9%)	42 (7.7%)	7 (8.8%)
Reporting year				
2011–2015	69 (5.5%)	67 (10.6%)	0 (0.0%)	2 (2.5%)
2016–2020	681 (54.1%)	422 (66.6%)	224 (41.0%)	37 (46.3%)
2021–2023Q1	508 (40.4%)	145 (22.9%)	322 (59.0%)	41 (51.3%)
Sex				
Male	719 (57.2%)	361 (56.9%)	302 (55.3%)	56 (70.0%)
Female	429 (34.1%)	224 (35.3%)	190 (34.8%)	17 (21.3%)
Missing	110 (8.7%)	49 (7.7%)	54 (9.9%)	7 (8.8%)
Age at onset, years	63 (53.75–72); n = 88	64 (55.25–71.5); n = 26	60 (52–72.5); n = 55	69 (60.5–70.5); n = 7
Drugs				
Monotherapy with anti-PD-1 or anti-PD-L1	643 (51.0%)	319 (50.3%)	282 (51.6%)	42 (52.5%)
Nivolumab	247 (19.6%)	139 (21.9%)	87 (15.9%)	21 (26.3%)
Pembrolizumab	268 (21.2%)	121 (19.1%)	134 (24.5%)	13 (16.3%)
Cemiplimab	19 (1.5%)	8 (1.3%)	10 (1.8%)	1 (1.3%)
Atezolizumab	79 (6.2%)	42 (6.6%)	34 (6.2%)	3 (3.8%)
Avelumab	12 (1.0%)	5 (0.8%)	7 (1.3%)	0 (0.0%)
Durvalumab	18 (1.4%)	4 (0.6%)	10 (1.8%)	4 (5.0%)
Monotherapy with anti-CTLA-4	83 (6.6%)	70 (11.0%)	10 (1.8%)	3 (3.8%)
Ipilimumab	76 (6.0%)	65 (10.3%)	8 (1.5%)	3 (3.8%)
Tremelimumab	7 (0.6%)	5 (0.8%)	2 (0.4%)	0 (0.0%)
Dual ICI therapy	430 (34.2%)	209 (33.0%)	199 (36.4%)	22 (27.5%)
Nivolumab plus ipilimumab	399 (31.7%)	197 (31.1%)	181 (33.2%)	21 (26.3%)
Pembrolizumab plus ipilimumab	17 (1.4%)	7 (1.1%)	10 (1.8%)	0 (0.0%)
Tremelimumab plus durvalumab	10 (0.8%)	3 (0.5%)	6 (1.1%)	1 (1.3%)
Atezolizumab plus Ipilimumab	3 (0.2%)	1 (0.2%)	2 (0.4%)	0 (0.0%)
Cemiplimab plus Ipilimumab	1 (0.1%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
ICIs plus chemotherapy	104 (8.3%)	36 (5.7%)	55 (10.1%)	13 (16.3%)
Outcome				
Death	313 (24.9%)	156 (24.6%)	100 (18.3%)	58 (72.5%)
Life-threatening	179 (14.2%)	104 (16.4%)	59 (10.8%)	17 (21.3%)
Hospitalization	758 (60.3%)	405 (63.9%)	302 (55.3%)	53 (66.3%)
Disability	33 (2.6%)	19 (3.0%)	14 (2.6%)	0 (0.0%)
Others	1,089 (86.6%)	530 (83.6%)	489 (89.6%)	71 (88.8%)
Missing	9 (0.7%)	9 (1.4%)	0 (0.0%)	0 (0.0%)

(Continued on following page)

TABLE 2 (*Continued*) Clinical characteristics of patients with ICI-associated autoimmune hepatitis, immune-mediated hepatitis, or hepatitis fulminant from the FAERS database.

Clinical characteristics	Overall (n = 1,260)	Autoimmune hepatitis (n = 634*)	Immune-mediated hepatitis (n = 546*)	Hepatitis fulminant (n = 80*)
Indication organ				
Skin	470 (37.4%)	277 (43.7%)	176 (32.2%)	18 (22.5%)
Lung	270 (21.5%)	127 (20.0%)	122 (22.3%)	21 (26.3%)
Kidney	116 (9.2%)	54 (8.5%)	51 (9.3%)	11 (13.8%)
Unspecified	88 (7.0%)	53 (8.4%)	32 (5.9%)	3 (3.8%)
Liver	45 (3.6%)	17 (2.7%)	26 (4.8%)	2 (2.5%)
Head and neck	35 (2.8%)	16 (2.5%)	14 (2.6%)	5 (6.3%)
Bladder	28 (2.2%)	12 (1.9%)	16 (2.9%)	0 (0.0%)
Stomach	28 (2.2%)	11 (1.7%)	13 (2.4%)	4 (5.0%)
Breast	21 (1.7%)	8 (1.3%)	13 (2.4%)	0 (0.0%)
Prostate	14 (1.1%)	4 (0.6%)	10 (1.8%)	0 (0.0%)
Uterus	11 (0.9%)	5 (0.8%)	5 (0.9%)	1 (1.3%)
Esophagus	10 (0.8%)	4 (0.6%)	2 (0.4%)	4 (5.0%)
Lymphoid	10 (0.8%)	3 (0.5%)	6 (1.1%)	1 (1.3%)
Ovary	9 (0.7%)	4 (0.6%)	4 (0.7%)	2 (2.5%)
Pleura	7 (0.6%)	2 (0.3%)	2 (0.4%)	3 (3.8%)
Pancreas	8 (0.6%)	5 (0.8%)	3 (0.5%)	0 (0.0%)
Brain	7 (0.6%)	4 (0.6%)	3 (0.5%)	0 (0.0%)
Colon	7 (0.6%)	1 (0.2%)	6 (1.1%)	0 (0.0%)
Hematologic	6 (0.5%)	3 (0.5%)	3 (0.5%)	0 (0.0%)
Cholecyst	5 (0.4%)	0 (0.0%)	5 (0.9%)	0 (0.0%)
Thymoma	4 (0.3%)	1 (0.2%)	3 (0.5%)	0 (0.0%)
Others	59 (4.7%)	23 (3.6%)	31 (5.7%)	5 (6.3%)

Data are n (%), or median (IQR; range); ICI, immune checkpoint inhibitor; FAERS, FDA, Adverse Event Reporting System. * One patient reported both autoimmune and immune-mediated hepatitis, and another patient reported a combination of autoimmune hepatitis and hepatitis fulminant.

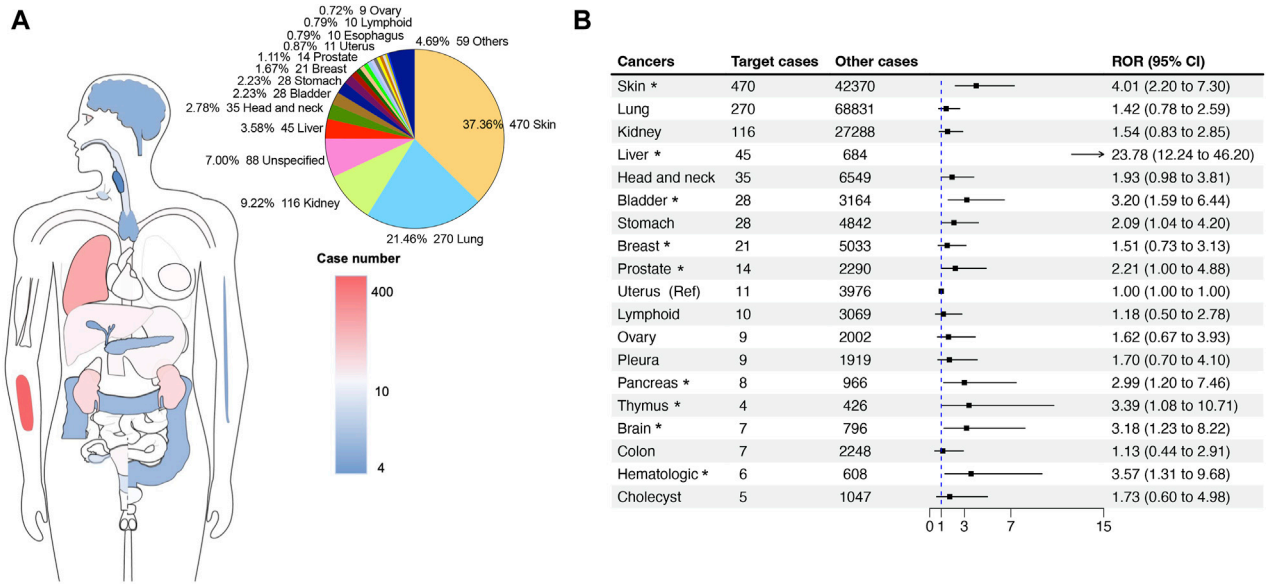

FIGURE 3
The site statistics for cancer occurrence in reports with hepatitis-related adverse events associated with ICIs. **(A)** The anatomical diagram of the patient's original cancer site and the number of cases. The pie chart on the right shows the proportional composition of the patient's cancer original sites. **(B)** The forest plot shows the ROR of ICI-related hepatitis adverse events among different cancer indications. The uterus cancer was used as a reference. * indicates a significant difference in comparison to uterus cancer.

HRAEs for different ICIs compared to the full FAERS database and specifically to ipilimumab. The analysis of ROR values against the full FAERS database shows a heightened risk of HRARs for all ICIs when compared to the overall database. This indicates a notable association of HRAE with these agents. Specifically compared to ipilimumab, nivolumab and pembrolizumab, along with atezolizumab and durvalumab, have a significant lower ROR, suggesting fewer risks of HRAE relative to ipilimumab. The

TABLE 3 Selected ICI-related hepatitis adverse events reported for ICIs *versus* the full database from the FAERS database, from 2004Q1 to 2023Q1.

	Cases reported with ICIs (N = 353,950)			Cases reported in the full database (N = 49,568,379)	ROR (95% CI) anti-PD-1 anti-PD-L1 vs. anti-CTLA-4 monotherapy	ROR (95% CI) dual ICIs vs. monotherapy	ROR (95% CI) ICIs vs. full database
	Anti-PD-1 or anti-PD-L1 Monotherapy; N = 268,517	Anti-CTLA-4 Monotherapy; N = 22,903	Dual ICI therapy; N = 62,530				
Autoimmune hepatitis	352 (0.13%)	63 (0.27%)	219 (0.35%)	5,200	0.48 (0.36–6.30)	2.46 (2.09–7.31)*	19.34 (17.80–21.02)*
Immune-mediated hepatitis	336 (0.13%)	8 (0.03%)	202 (0.32%)	896	3.59 (1.78–6.18)*	2.74 (2.30–7.56)*	217.24 (189.95–248.45)*
Hepatitis fulminant	54 (0.02%)	4 (0.02%)	22 (0.04%)	2,519	1.15 (0.42–3.31)	1.74 (1.06–4.81)*	4.56 (3.65–5.70)*

Data are n (%) unless otherwise stated. ICIs, refer to any AEs, reported for treatment with nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, ipilimumab, or tremelimumab. Anti-PD-1, or anti-PD-L1, monotherapy refers to any AEs, associated with any of the following five drugs only when used alone: nivolumab, pembrolizumab, atezolizumab, avelumab, or durvalumab. Anti-CTLA-4, monotherapy refers to any AEs, associated with ipilimumab or tremelimumab alone. Dual ICI, therapy refers to any AEs, reported with at least one anti-PD-1, or anti-PD-L1, drug combined with an anti-CTLA-4, drug. FAERS, FDA, adverse event reporting system; ICIs, immune checkpoint inhibitors; ROR, reporting odds ratio. * Significant over-reporting within immunotherapy subgroups.

RORs of cemiplimab and avelumab do not significantly deviate from that of ipilimumab, implying a similar risk profile for HRAE with these agents.

4 Discussion

Although the hepatotoxicity associated with different ICIs has been investigated (Xu et al., 2023), the study focusing more narrowly on HRAEs and the difference among different types of ICI-based therapies remains limited. By employing the full FAERS database as a reference dataset, our study presents the largest and most comprehensive clinical characterization of HRAEs that were highly associated to the treatment of ICIs through a rigorous disproportionality analysis.

ICIs have garnered widespread adoption in the management of various malignancies, including melanoma, lung cancer, renal cell carcinoma, and urothelial cancer (Postow et al., 2015; Shiravand et al., 2022). This adoption has stemmed from early clinical trials demonstrating substantial enhancements in clinical outcomes with ICI treatments. However, the adverse events associated with ICIs, including hepatitis, have emerged as a notably clinically significant complication. (Jiang et al., 2019). The link between hepatitis and liver cancer is well-established, with chronic hepatitis being a major risk factor for the development of hepatocellular carcinoma (HCC), the most prevalent type of liver cancer (Perz et al., 2006; Tu et al., 2017). For example, hepatitis B virus (HBV) acts as a potent liver carcinogen, primarily through mechanisms involving viral integration, chronic inflammation, and immune-mediated cellular damage (Song et al., 2019). While hepatitis was infrequently reported in the initial clinical trials involving ICI therapies, there has been a discernible increase in the number of published case reports and case series documenting hepatitis cases (Berti et al., 2021; Zhao et al., 2022). These case series have illuminated the diverse clinical presentations of hepatitis adverse events. Nevertheless, the comprehensive spectrum of ICI-related HRAEs remains elusive. In this study, we identify autoimmune hepatitis, immune-mediated hepatitis, and hepatitis fulminant as potential considerations for ICI-related HRAEs. These findings provide valuable insights for clinicians engaged in the management of cancer patients undergoing immunotherapies. Moreover, a substantial proportion of the ICI-related HRAE reports sourced from the FAERS database were concentrated within the past 2 years. This trend suggests that the increased reporting of adverse events over time is likely due to the growing use of ICIs, along with the their expanding range of indications.

Importantly, our study offers the most extensive clinical characterization of ICI-related HRAEs based on a comprehensive analysis of all collected cases within the FAERS database. To the best of our knowledge, this dataset of 1,260 patients represents the largest compilation of such cases to date. Our findings underscore the poor outcomes of ICI-associated HRAEs, with a substantial proportion of cases resulting in adverse outcomes. Specifically, 24.9% of cases were reported with fatal outcomes, while 14.2% were reported with life-threatening outcomes, emphasizing the severity of these events. It is also important to note that a higher risk of immune-related hepatitis is reported in real-world settings compared to clinical trials of ICIs as described by Z. Zhang et al (Zhang et al., 2022). The stringent

TABLE 4 The risk profile of hepatitis-related adverse events associated with different ICIs *versus* the FAERS full database.

	HRAE cases	All AE cases of ICIs	ROR (95% CI) vs. Ipilimumab	ROR (95% CI) vs. full database
Cemiplimab	22	9,906	1.54 (0.99–2.39)	38.51 (25.33–58.55)
Nivolumab	576	471,495	0.84 (0.71–1)*	22.55 (20.72–24.54)
Pembrolizumab	320	298,395	0.74 (0.62–0.89)*	19.21 (17.18–21.48)
Atezolizumab	111	104,568	0.73 (0.58–0.93)*	18.57 (15.4–22.39)
Avelumab	13	6,798	1.32 (0.75–2.32)	31.22 (18.11–53.83)
Durvalumab	38	43,278	0.61 (0.43–0.86)*	15.23 (11.07–20.95)
Ipilimumab	179	123,792	Ref (1.0)	25.5 (21.99–29.58)

Notes: FAERS, FDA, adverse event reporting system; ICIs, immune checkpoint inhibitors; ROR, reporting odds ratio; HRAE, hepatitis-related adverse event; AE, adverse event; CI, confidence interval. * Significant difference compared to Ipilimumab.

inclusion and exclusion criteria and the shorter exposure and study period in the clinical trials can be attributed to the discrepancy. Additionally, real-world populations include patients being treated in community settings who may not have the same degree of experience or vigilance for irAEs as academic centers participating in trials. Considering these factors, our study suggests that while clinical trials provide valuable insights into the efficacy and safety of anticancer therapies, real-world data is crucial for understanding the full spectrum of drug-related adverse events in the broader patient population.

Furthermore, we identified that ICI-related HRAEs were linked with various ICI treatments and a diverse range of cancer types. The patients with liver cancer receiving ICIs have the highest risk of developing hepatitis (ROR = 23.78 [12.24–46.20] due to several compounding factors. Primarily, the liver, already compromised by cancer, may have reduced functional reserve, making it more susceptible to further damage from the inflammatory and immune-mediated effects of ICIs (Sangro et al., 2020). Additionally, patients with liver cancer often have underlying chronic liver conditions such as cirrhosis or chronic hepatitis, which themselves are risk factors for increased liver inflammation (Shiani et al., 2017). The cumulative effect of a pre-existing hepatic disease, the burden of liver cancer, and the immune-modulating actions of ICIs likely contributes to this heightened risk, making management and monitoring of liver function particularly crucial in this patient group.

Additionally, the dual ICI therapy emerges as a prominent high-risk factor in comparison to monotherapy (ROR = 2.23, Figure 2B) due to the synergistic enhancement of immune activation. By simultaneously blocking two critical immune checkpoints, dual therapy leads to a more profound disinhibition of immune responses (Chu et al., 2023). This dual blockade not only enhances the efficacy against tumors but also increases the likelihood of breaking self-tolerance, leading to higher rates of autoimmune and inflammatory side effects, including hepatitis. These findings align with prior published case series that have similarly reported a heightened frequency of hepatitis incidents associated with the dual ICI therapies (Da et al., 2020; Ramos-Casals et al., 2020). We further reviewed the immune-related hepatitis events reported in the clinical trials (Weber et al., 2009; Robert et al., 2015; Long et al., 2017; Hodi et al., 2018; Yau et al., 2020; Boyer et al., 2021; Aamdal et al., 2022; Wolchok et al., 2022), the relative risk (RR) of dual ICI therapy (6.5%) *versus* monotherapy (3.8%) was 1.71, slightly lower compared to the ROR obtained from the real-world setting. The identification of patients at elevated risk for ICI-associated HRAEs is of paramount importance. Demographic profiles indicate that those most at risk typically include older adults, possibly with a history of liver disease or prior immune-related adverse events. These patients are often treated for cancers like melanoma, lung cancer, or renal cancer, which may inherently place them at a higher risk due to the nature of their treatment regimens. Enhanced monitoring of liver function parameters, including alkaline phosphatase, alanine transaminase, aspartate aminotransferase, and bilirubin, should be incorporated into clinical management of patients with all types of hepatitis. For those identified as having a particularly high risk of developing severe hepatitis, additional preventive and therapeutic measures should indeed be considered, including proactive management strategies, alternative therapeutic options, multidisciplinary team approach, and patient education and involvement. By incorporating these strategies, the goal is to not only monitor but actively prevent and manage ICI-induced hepatitis, thereby reducing the risk of fatal outcomes and improving overall patient safety. These recommendations advocate a more aggressive approach to managing patients at the highest risk, aligning with the severity of potential outcomes outlined in our findings.

Through the subgroup analysis, the data suggests that ICIs have a distinct profile of HRAEs when compared to the broader set of data from the FAERS database. Specifically, nivolumab and pembrolizumab, among others, show a higher risk of HRAEs compared to ipilimumab, which could imply a better safety profile in this aspect. It is probably due to the distinct mechanisms through which these pathways modulate the immune system. Anti-PD-1 and anti-PD-L1 agents act primarily by blocking the PD-1/PD-L1 pathway, a critical immune checkpoint that regulates T cell activity in peripheral tissues, including the liver (Singh et al., 2021). By inhibiting this pathway, these agents prevent PD-1 on T cells from engaging with PD-L1 on tumor cells and normal hepatocytes, which normally helps to maintain immune tolerance and prevent autoimmune responses. This leads to increased activation and proliferation of cytotoxic T cells within the liver, enhancing the likelihood of immune-mediated liver injury. In contrast, anti-CTLA-4 therapies primarily regulate immune responses at the level of initial T cell activation in lymph nodes

(Seidel et al., 2018). These findings were consistent with previous studies reporting that the incidence and severity of irAEs caused by CTLA-4 are lower for PD-1/PD-L1 inhibitors (Liu et al., 2021). However, it is crucial to consider the clinical context, including patient selection and the underlying mechanism of action of ICIs, which could influence the incidence and reporting of adverse events. Further investigation into these differences, perhaps through a stratified analysis of patient subgroups or a deeper mechanistic study, might provide more insight into the safety and monitoring strategies for these therapies.

While the precise mechanisms underlying ICI-associated HRAEs remain incompletely understood, it is imperative to recognize the pivotal role of the liver's unique immunological attributes in its pathogenesis. The liver holds a distinctive position due to its connection to the portal circulation, which serves as the primary conduit for detoxifying blood entering from the intestines and processing a multitude of antigen exposures (Crispe, 2014). As one of the primary mechanisms contributing to liver immunotolerance, hepatic non-parenchymal cells also express PD-L1, as well as $CD4^+$ Treg cells expressing CTLA-4 (Makarova-Rusher et al., 2015). It drives synergistically to shield the liver from autoimmune reactions triggered by antigens by suppressing the activity of effector T cells. However, with the administration of ICIs to disrupt these critical regulatory pathways, T cells may become excessively activated, breaching the liver's immune tolerance. This susceptibility to acute inflammatory responses subsequently precipitates hepatitis (Gudd and Possamai, 2022). Furthermore, the disruption of self-tolerance in the liver activates a variety of immune cells, contributing to the pathophysiological development of immune-mediated hepatitis (Gudd et al., 2021). Given the emergent nature of ICI-induced immune-mediated hepatitis, the cornerstone of treatment involves the prompt initiation of high-dose glucocorticoids (Darnell et al., 2020). Additionally, the consideration of other hepatoprotective agents, including isoglycyrrhizinate, bicyclol, or reduced glutathione, which are commonly used in patients with liver inflammation, may also be considered (Niu et al., 2021).

Our study also has several limitations that warrant consideration: firstly, the FAERS database is a global spontaneous reporting system, open to reports from healthcare professionals, consumers, pharmaceutical companies, and individuals who suspect potential adverse reactions. It introduces inherent selection biases, including variations in the ethnicity and geographical origin of reported cases. Consequently, we are unable to establish a definitive causal relationship between ICIs and ICI-related HRAEs. Moreover, the database does not facilitate the calculation of incidence rates for these identified ICI-related HRAEs, although the incidence of ICI-related HRAEs could be determined as approximately 3%–6% using the data from clinical trials. Secondly, the wide array of anticancer drugs, such as targeted therapy agents, chemotherapeutic drugs, and antibody drugs, presents a challenge in individually extracting all such drugs from the FAERS database. This intricacy can introduce a potential bias related to indications and increase the risk of false positive associations. Thirdly, although the patients with liver cancer were identified with the highest ROR of developing hepatitis when receiving ICI therapies, we cannot eliminate the influence of the disease state that may induce hepatitis. Finally, the three identified ICI-related HRAEs have not undergone clinical validation. The extremely increased ROR observed in FAERS for severe HRAEs might be influenced by the limitations of the FAERS database, particularly reporting biases and the absence of denominator data which would provide a more accurate risk assessment. Further research, including prospective cohort studies, case-control studies, and nested case-control studies, is essential to validate findings from the FAERS database and to accurately determine the risk profile of ICIs in relation to severe hepatitis. These studies would monitor patients from the initiation of ICI therapy, tracking the onset and progression of hepatitis and any subsequent development of liver disease. This approach allows for the collection of baseline liver function data, aiding in controlling for pre-existing liver conditions. Stratifying patients based on their hepatitis status before starting ICI treatment would enable comparisons between those with and without prior hepatitis. Such studies would provide richer patient background information, which is often inadequately captured in the FAERS database.

5 Conclusion

While it is recognized that hepatitis induced by ICIs is associated with the risk of liver cancer, significant uncertainties remain concerning the long-term effects and the precise mechanisms involved. Our study contributes to the existing body of evidence by providing a detailed analysis of hepatitis as an adverse event following ICI therapy, using a large, real-world dataset from the FAERS database. This real-world evidence is critical, as clinical trials often have stringent inclusion criteria and may not fully capture the breadth of adverse outcomes seen in a more diverse patient population. To further enhance understanding and management of ICI-induced hepatitis, additional research should focus on longitudinal studies to observe the long-term effects and progression of hepatitis in patients receiving ICIs, identifying precise mechanistic pathways through detailed molecular and cellular studies. Development of predictive biomarkers is also crucial to more effectively identify at-risk patients, thereby facilitating personalized treatment approaches. Additionally, comparative studies across different ICIs and treatment regimens could also provide valuable insights into risk profiles and guide safer treatment protocols. These focused areas of research are essential for developing targeted strategies to reduce the incidence and severity of hepatitis in patients treated with ICIs.

In conclusion, our study provides comprehensive real-world data that illuminate the prevalence and characteristics of ICI-related HRAEs, including autoimmune hepatitis, immune-mediated hepatitis, and hepatitis fulminant, reinforcing the need for heightened surveillance and management strategies in clinical practice. By documenting the variety and severity of hepatitis cases associated with different ICIs and treatment regimens, it adds depth to the clinical understanding necessary for optimizing patient care in oncology. Furthermore, the study underscores the potential for severe outcomes, including death, from ICI-induced hepatitis, which emphasizes the critical need for ongoing research and improved clinical protocols.

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.

Author contributions

ZF: Conceptualization, Data curation, Funding acquisition, Visualization, Writing–original draft, Writing–review and editing. JL: Conceptualization, Validation, Visualization, Writing–original draft, Writing–review and editing. CZ: Methodology, Software, Writing - original draft. HH: Methodology, Resources, Writing - original draft. SL: Methodology, Visualization, Writing–original draft. YZ: Validation, Writing–review and editing. RY: Supervision, Writing–review and editing.

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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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Anti-TNFα in inflammatory bowel disease: from originators to biosimilars

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The introduction of anti-tumor necrosis factor α (TNFα) biologics significantly innovated inflammatory bowel disease (IBD) treatment and increased medical costs. The recent expiration of patents of some anti-TNFα biologics (such as infliximab and adalimumab) facilitated the development of biosimilars. Comparable pharmacokinetic, efficacy, safety, and immunogenicity profiles between anti-TNFα originators and biosimilars were demonstrated in different studies. Anti-TNFα biosimilars hold promise for reducing the high cost of biologics and increasing patient access to biologics. In this review, we outline the current data on the use of anti-TNFα originators and biosimilars in patients with IBD, with a focus on the efficacy, safety, and immunogenicity profiles of infliximab and adalimumab biosimilars. The potential benefits, challenges, and future directions of anti-TNFα biosimilars are also discussed in the review.

KEYWORDS

biosimilars, originators, anti-TNFα, biologics, inflammatory bowel disease

1 Introduction

Inflammatory bowel disease (IBD) is a destructive, long-lasting, and immune-mediated disease, mainly including crohn's disease (CD) and ulcerative colitis (UC) (Jiang et al., 2022). Despite significant advances have been made in exploring the occurrence and development of IBD, the exact pathogenesis is yet unclear. Immune dysfunction, intestinal dysbiosis, genetic susceptibility alongside environmental triggers may contribute to the development of IBD (Abraham and Cho, 2009; Dang et al., 2023) (Figure 1). It's universally acknowledged that IBD is a global disease with high incidence and prevalence (Kaplan and Windsor, 2021). The chronic inflammation and remission-relapse pattern of IBD make patients experience chronic abdominal pain and repeated diarrhea, which exerts a significant impact on the quality of life (Chen et al., 2024). Available data indicated that the cumulative rates of hospitalization in CD and UC patients were 23%–49% and 9%–33% at 1 year; the 5-year hospitalization rates ranged between 44% to 54% and 18% to 54% for CD and UC, respectively. During the first 5 years after diagnosis, the cumulative rates for surgery were 5%–10% for UC and 10%–40% for CD. What should be noted is that the risk of developing colorectal cancer in patients with UC was two times higher than general population (Zhao et al., 2021). The high hospitalization and surgery rates, as well as high risk of developing cancers significantly increase medical costs for patients with IBD. In 2017, the global disability-adjusted life-years caused attributed to IBD was 1.85 million,

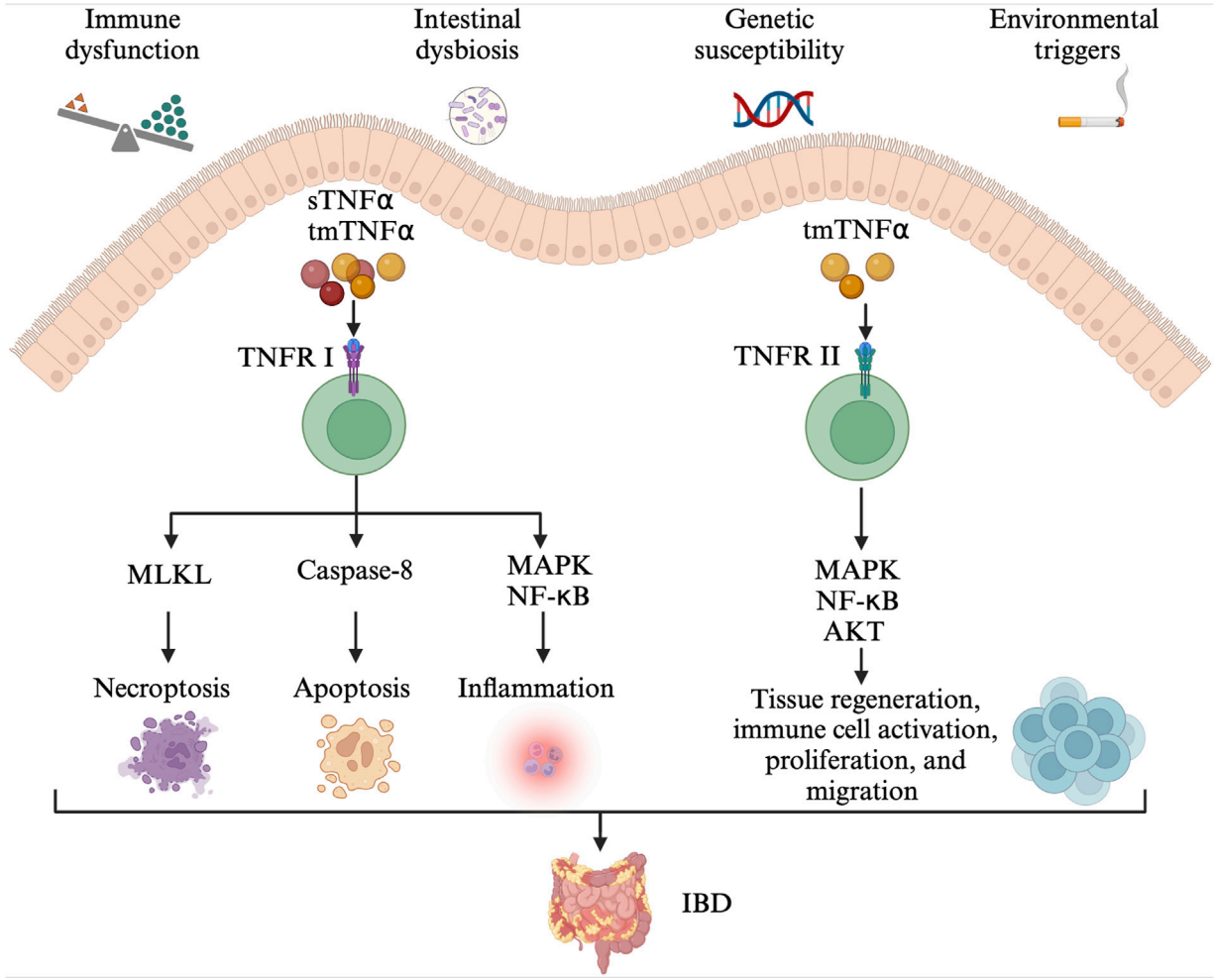

FIGURE 1
The pathogenesis of IBD. Immune dysfunction, intestinal dysbiosis, genetic susceptibility alongside environmental triggers contribute to the development of IBD. The tmTNFα and sTNFα bind with TNFRI, mediating the activation of pro-inflammatory (MAPK and NF-κB) signaling pathways, MLKL-dependent necroptosis, and caspase-8-dependent apoptosis. The TNFR2 signaling pathway is mainly activated by the tmTNF-α. The tmTNFα binds with TNFRII and activates MAPK, NF-κB, and AKT signaling pathways, involved in tissue regeneration, immune cell activation, migration, and proliferation. IBD: inflammatory bowel disease; tmTNFα: transmembrane TNFα; sTNFα: soluble TNFα; TNFRI: TNF receptor I; MAPK: mitogen-activated protein kinase; NF- NF-κB: nuclear factor kappa-B; MLKL: mixed-lineage kinase domain-like protein; TNFRII: TNF receptor II.

about 1.5 times as that in 1990 (1.25 million) (GBD, 2017 Inflammatory Bowel Disease Collaborators, 2020). Indeed, it poses a huge burden on global healthcare systems.

Available data indicated that the mean healthcare costs for CD and UC were $8,265 and $5,066 per patient-year in the United States in 2004, respectively (Kappelman et al., 2008). From 2007 to 2016, the direct healthcare costs for IBD (CD and UC) increased to $22,987, three times higher than non-IBD controls ($6,956) (Park et al., 2020). In Europe, the mean total healthcare costs for CD and UC rose from €2,548 and €1,524 per patient-year in 2003 to €3,500 and €2,000 in 2020, respectively (Odes et al., 2006; Zhao et al., 2021). In China, the mean direct care costs for IBD (CD and UC) are $7,944 per patient-year from 2018 to 2019 (Yu et al., 2021). In the initial stages, the major drivers of healthcare costs for IBD were hospital and surgery. However, with the rapid progress made in drug development, the main health costs have shifted to medication. The global IBD medication treatment market size is extremely large. The introduction of biologics innovated IBD treatment and thus accounted for the majority of healthcare expenditures. Available data showed that biologics accounted for €1,782 for CD and €286 for UC per patient-year in Europe (Burisch et al., 2020). Anti-tumor necrosis factor-α (anti-TNFα) is the first approved biologic agent for CD and UC (Buchner et al., 2021). Among these biologics available for IBD, the annual costs of anti-TNFα treatment are considerable, making up 64% and 31% of the total costs in CD and UC, respectively (van der Valk et al., 2014). Although some anti-TNFα biologics have been included in medical insurance, the financial burden of IBD, especially for anti-TNFα biologic drugs, is still heavy. The high price further limits the access to anti-TNFα biologic treatment in resource-limited settings.

TNFα is a pro-inflammatory cytokine and plays an important role in the pathophysiology of IBD (Figure 1) (Chen L. et al., 2020; Chen et al., 2021). TNFα exists in two forms, the transmembrane and soluble form. On the one hand, transmembrane TNFα (tmTNFα) and the soluble TNFα (sTNFα) can bind with TNF receptor I (TNFRI), mediating the activation of mitogen-activated

protein kinase (MAPK) and nuclear factor kappa-B (NF-κB) signaling pathways, and then, producing pro-inflammatory cytokines, cell adhesion molecules and synthetase nitric oxide (Wang and Shen, 2022). The binding between them also can activate caspase-8-dependent and mixed-lineage kinase domain-like protein (MLKL) death signaling pathways, involved in apoptosis and necroptosis, respectively (Jang et al., 2021). On the other hand, the binding of tmTNFα with TNF receptor II (TNFRII) can also activate MAPK, NF-κB, and AKT signaling pathways, causing tissue regeneration, immune cell activation, migration, and proliferation (Levin et al., 2016; Zeng et al., 2023). As a result, severe intestinal inflammation and mucosal barrier injury occur. In order to prevent its pro-inflammatory process, monoclonal antibodies to TNFα including infliximab, adalimumab, golimumab, and certolizumab have been developed and approved for CD and/or UC treatment (Leone et al., 2023). They may exert their therapeutic effects in the induction and maintenance of disease remission by inducing $CD4^+$ T cell apoptosis and/or promoting the differentiation from monocytes to M2-type wound-healing macrophages (Levin et al., 2016).

Despite anti-TNFα biologics show favorable therapeutic effects in achieving clinical, endoscopic, and histologic remission in IBD, the annual costs are really high (Jiang et al., 2023). The expiration of patents of some anti-TNFα biologics has further facilitated the development of biosimilar agents. Biosimilars potentially reduce the high costs of biologics and increase patient access to biologics due to the stiff competition in the pharmaceutical market and extrapolation across indications (Fiorino and Danese, 2014). In this review, we briefly introduce the drug utilization, effectiveness, and safety of the most used anti-TNFα originators (infliximab and adalimumab), and elaborate on the efficacy and safety of these biosimilars in IBD. Furthermore, we also evaluate the efficacy and safety of the switches from originators to biosimilars, and discuss the benefits, challenges, and future directions of biosimilars in IBD.

2 The use of anti-TNFα originators in IBD

2.1 What are anti-TNFα originators

Anti-TNFα originators, discussed in this review, are the two anti-TNFα biologicals. Although biologicals comprise various groups of medicines, such as monoclonal antibodies, vaccines, growth factors, immune modulators, and medicines derived from human blood. Our review mainly discusses the two anti-TNFα monoclonal antibodies (infliximab and adalimumab). Anti-TNFα monoclonal antibodies are purified from human or mouse living systems, completely different from small molecules that are produced by chemical synthesis or purified from plants (Buchner et al., 2021). Anti-TNFα originators are a diverse group of original, independent research and development new drugs with pharmaceutical patents, usually used as licensed reference products (Kang et al., 2023). Anti-TNFα originators follow a complex and long process for regulatory approval, including drug screening and optimization (structure, pharmacologic action, and biological activity), preclinical studies (pharmacokinetics, pharmacodynamics, and toxicology *in vitro* and *in vivo* studies), clinical studies (I–III randomized clinical trials), marketing approval, and post-marketing research (IV clinical trial), which significantly increases the time and money costs. Besides, the manufacturing costs of anti-TNFα originators are very high. Available data indicated that the cost to develop a new biological agent is about $2.0 billion, significantly higher than the production costs of biosimilars ($100–250 million) (Zheng et al., 2017).

2.2 Infliximab

Infliximab, a human-mouse chimeric anti-TNFα monoclonal IgG1 antibody, is the first biologic approved for CD by the United States Food and Drug Administration (FDA) in 1998. It binds with TNFα and prevents the binding between TNFα and TNFR (Knight et al., 1993). Until now, it has been approved for various indications including CD, UC, rheumatoid arthritis (RA), psoriasis, and others. The famous ACCENT I randomized trial of 573 moderate to severe CD patients showed that infliximab can induce disease response at week 2 in 58% (335/573) of patients. At week 30, the clinical remission rates were higher in the infliximab maintenance group (5 mg/kg infliximab and 10 mg/kg infliximab), compared with the placebo group (39% vs. 21%, 45% vs. 21%, respectively). The maintenance treatment efficacy of infliximab was also claimed at week 54. At week 54, the proportion of patients who discontinued corticosteroid treatment in the infliximab maintenance group was 2.22 times higher than that of the placebo group (29% vs. 9%). Besides, patients in the infliximab maintenance group also presented lower mean Crohn's Disease Activity Index (CDAI) and higher mean inflammatory bowel disease questionnaire (IBDQ) scores (Hanauer et al., 2002). Recently, a network meta-analysis of 25 clinical trials and 8,720 CD patients claimed that infliximab had optimal efficacy in the induction of clinical remission in patients with luminal CD (Barberio et al., 2023). The excellent therapeutic effects of infliximab were also confirmed in another ACCENT II trial of 306 fistulizing CD patients. In comparison with the placebo group (19%), 36% of patients with infliximab treatment had a total absence of fistulas at week 54 (Sands et al., 2004). As for the safety of infliximab, the FDA label indicated that the risk of serious adverse events (SAEs) including serious infections and malignancy increased in the infliximab treatment group, although SAE rates were similar between the infliximab treatment arm and the placebo arm in another study (Sands et al., 2004; Food and Drug Administration, 2021). In a word, infliximab treatment is effective and safe in inducing and maintaining disease remission in moderate to severe CD.

In UC, the Active Ulcerative Colitis Trials 1 and 2 (ACT 1 and ACT 2) of 364 moderate to severe UC patients revealed that infliximab therapy can induce clinical remission and mucosal healing as early as week 8, and maintain effective during week 54 (Rutgeerts et al., 2005). As for patients with steroid-refractory acute severe ulcerative colitis (ASUC), infliximab outperformed cyclosporine in achieving endoscopic remission at day 98 (73% vs. 25%) (Laharie et al., 2021). Moreover, infliximab was also claimed to be an effective salvage treatment for patients with tacrolimus-refractory ASUC (Yamamoto et al., 2010). It was also proven to be safe in treating UC with regard to similar rates of

adverse events (AEs), infections, and acute infusion reactions (Rutgeerts et al., 2005). It should be noted that infliximab is a chimeric antibody, implying a higher possibility of formation of antibodies to infliximab. As a result, the risk of experiencing infusion reactions and even loss of efficacy may increase (Su and Lichtenstein, 2003). Concomitant immunosuppressive therapy or changing antibody structure may mitigate immunogenic responses (Su and Lichtenstein, 2003). Indeed, the introduction of infliximab innovated IBD therapy and became the mainstay of treatment for refractory IBD. Further studies on other anti-TNFα biologics are therefore encouraged.

2.3 Adalimumab

Adalimumab is also an anti-TNFα monoclonal IgG1 antibody, but it is different from infliximab regarding antibody structure (Tracey et al., 2008). It is a fully human, recombinant monoclonal antibody with lower immunogenicity and a larger antigen-antibody interface (Tracey et al., 2008; Hu et al., 2013; Kennedy et al., 2019). The CLASSIC-I trial of 299 moderate to severe CD patients (naive to anti-TNFα antagonists) claimed that the adalimumab 160/80 treatment (160 mg at week 0 and 80 mg at week 2) was more effective than placebo in inducing clinical remission (36% vs. 12%) (Hanauer et al., 2006). One year later, the CLASSIC II trial further demonstrated its significant efficacy and safety in maintaining clinical remission during week 56. In comparison with the placebo group, the adalimumab treatment group (40 mg every other week) presented higher remission rates (79% vs. 44%), greater mean decreases of CDAI scores (197.7 vs. 119.6), and higher IBDQ scores (Sandborn et al., 2007). In the same year, the better therapeutic effects of adalimumab were also found in those CD patients previously exposed to anti-TNFα therapy. This finding suggested that adalimumab could be an additional treatment option for those who lost response to and/or were intolerant to infliximab. Besides, patients receiving adalimumab were more likely to achieve corticosteroid-free remission and fistula remission than the placebo group (Colombel et al., 2007). Recently, the CREOLE study further evaluated the efficacy of adalimumab in CD patients with symptomatic small bowel stricture (SSBS) and proved its excellent effects in patients with SSBS due to CD. Treatment with adalimumab can make 53% of patients free of surgery 4 years after initiation (Bouhnik et al., 2018). A large meta-analysis of 31 clinical trials recommended adalimumab as second-line therapy for patients who were intolerant to infliximab (Singh et al., 2021).

As for moderate to severe UC patients, a multicenter study of 576 patients suggested that the clinical remission rates at week 8 in the adalimumab subcutaneous injection regimen arm (160 mg at week 0 and 80 mg at week 2) were one time higher than that in the placebo group (18.5% vs. 9.2%) (Reinisch et al., 2011). At week 52, 17.3% of patients in the adalimumab group maintained clinical remission, compared with 8.5% of patients in the placebo group. Moreover, more patients with adalimumab therapy achieved sustained mucosal healing (at week 8 and week 52), and sustained corticosteroid-free remission (at week 32 and 52) than the placebo group (18.5% vs. 10.6%, and 10.0% vs. 1.4%, respectively) (Sandborn et al., 2012). Even in those patients with a history of anti-TNFα therapy, the adalimumab treatment group was more likely to maintain sustained clinical response at week 8, and week 52 than the placebo group, providing an alternative therapeutic option to patients who experienced infliximab failure (Sandborn et al., 2012). A cost-effectiveness analysis from the United Kingdom further claimed that the total costs (including costs of drug acquisition and administration, direct and indirect healthcare costs) and biologic costs for adalimumab was lower than infliximab (£194,764.73 vs. £206,065.90, and £10,289.40 vs. £19,285.37, respectively). And patients on adalimumab incurred slightly higher quality-adjusted life years (QALYs) than those on infliximab treatment (13.872 vs. 13.788) (Wilson et al., 2018). Caution needs to be taken when interpreting these results, because different study designs, different standards of treatment response, and different ethnicities are used in various studies. Collectively, adalimumab is an effective and well-tolerated biologic drug for moderate to severe CD and UC patients. It also became the efficacy benchmark of its category and the reference product for bioequivalence studies.

3 The use of anti-TNFα biosimilars in IBD

3.1 What are anti-TNFα biosimilars

Biosimilars are biological products that are similar in terms of quality, safety, and efficacy to an already licensed reference product (World Health Organization, 2022). Therefore, the anti-TNFα biosimilars are a group of monoclonal antibodies that contain a version of the active pharmaceutical ingredient and associated molecules of already licensed original biologics (originators) (Blandizzi et al., 2017; World Health Organization, 2022). Anti-TNFα biosimilars are different from generic medicines in terms of the drug substance. The former contains similar active ingredients, while the latter has identical active ingredients (Blandizzi et al., 2017). Moreover, given the relatively high molecular weight, complicated three-dimensional protein structure, and complex posttranslational modification, the structural sameness and bioequivalence evaluation approaches used in generic medicines is not applicable to biosimilars. Firstly, researchers should characterize the quality attributes of the reference product, and make direct head-to-head comparison between the licensed reference product and the biosimilar in terms of structural and functional similarity (*in vivo* and *in vitro*). Then, the clinical pharmacologic comparability assessment (pharmacokinetic modeling, pharmacodynamic modeling and immunogenicity) is carried out in one or more indications (if possible). Then, the comparative clinical trials (safety, efficacy, and immunogenicity profiles) are performed in one or more sensitive populations (if possible) (Lyman et al., 2018; World Health Organization, 2022) (Figure 2).

The regulatory process for approval of anti-TNFα biosimilars is speedier and easier in comparison with originators. The core evidence to support regulatory approval for anti-TNFα biosimilars is obtained from manufacturing and preclinical data. While the marketing approval for originators depends more on extensive clinical data. Besides, extrapolation across indications further accelerates the regulatory approval process of anti-TNFα

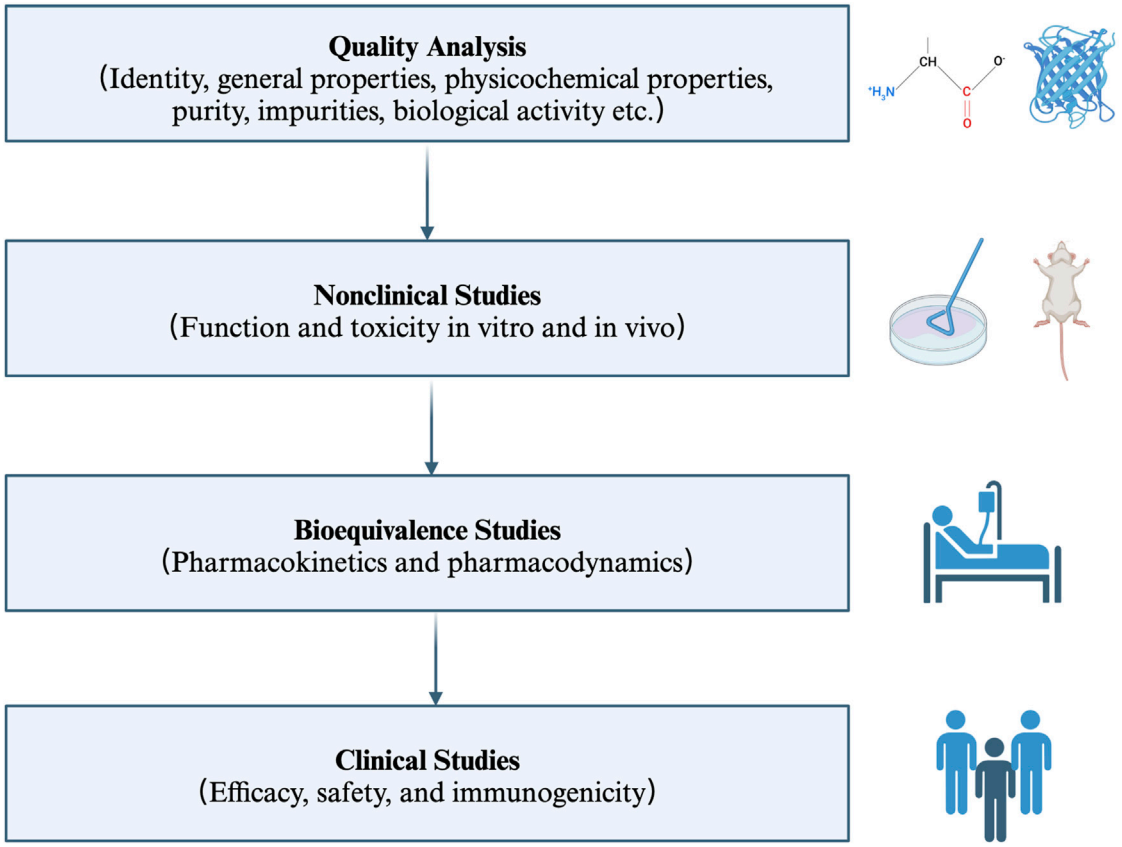

FIGURE 2
Key principles for the licensing of biosimilars by WHO. The regulatory and approval pathway for biosimilars includes four steps. Firstly, characterize the quality attributes of the biosimilar and the reference product. Secondly, evaluate the pharmaco-toxicological activity of the biosimilar and the reference product *in vitro* and *in vivo*; Thirdly, investigate the pharmacokinetic and pharmacodynamic profiles in healthy volunteers; Fourthly, assess the efficacy, safety, and immunogenicity profiles in one or more indications. WHO: World Health Organization.

biosimilars. Once clinical bioequivalence is fulfilled in one condition, this biosimilar may be approved for other indications for which the reference product has been approved, without the need for repeating clinical trials across different indications. This process is called extrapolation (Lyman et al., 2018). Most clinical equivalence studies of anti-TNFα biosimilars have been conducted in patients with RA and/or those with plaque psoriasis, rarely in patients with IBD (Ben-Horin et al., 2016). Collectively, anti-TNFα biosimilars follow an accelerated process for marketing approval.

The biosimilar, Omnitrope, was approved by the European Medicines Agency (EMA) for patients with growth hormone deficiency in April 2006 (Fuhr et al., 2010). It is the first biosimilar approved for patients. Seven years later, biosimilars of infliximab, Remsima and Inflectra (CT-P13) got approval for CD or UC in September 2013. They two have become the first monoclonal antibody biosimilar approved by the EMA. In 2016, Inflectra was firstly approved by the FDA for patients with IBD. One year later, the biosimilar of adalimumab, Amjevita (ABP 501) was approved for patients with IBD. In recent 10 years, several other biosimilars of infliximab such as Flixabi (SB2) and Zessly (PF-06438179/GP1111) (Table 1), and biosimilars of adalimumab including Imraldi (SB5), Cyltezo (BI 695501), Halimatoz (GP 2017), and Idacio (MSB11022) have been approved for patients with IBD, significantly expanding the treatment options for patients (Generics and Biosimilars Initiative, 2023a; Generics and Biosimilars Initiative, 2023b) (Table 2). In this part, we mainly discuss the most studied biosimilars of infliximab (Supplementary Table S1) and biosimilars of adalimumab in IBD (Supplementary Table S2).

3.2 Biosimilars of infliximab in IBD

3.2.1 CT-P13

CT-P13 is the first approved biosimilar of infliximab used in immune-mediated diseases including RA, ankylosing spondylitis (AS), psoriasis, CD, and UC (Parigi et al., 2021). Two clinical head-to-head studies, the PLANETRA study, and PLANETAS study, demonstrated that CT-P13 (intravenous, IV formulation) was non-inferior to infliximab originator in terms of clinical efficacy and safety. Moreover, comparable pharmacokinetic and immunogenicity profiles have also been claimed in the two studies (Park et al., 2013; Yoo et al., 2013). Therefore, CT-P13 was approved for CD and UC based on extrapolation. The PROSIT-BIO cohort study of 547 patients with IBD firstly suggested that 73.7% of anti-TNF naïve patients with CT-P13 treatment could achieve clinical response at week 24, which was comparable with

TABLE 1 Approval status of infliximab biosimilars.

Originator	INN	Trade name	Manufacturer name	Approval status
Infliximab	ABP 710	Avsola	Amgen, United States	FDA: December 2019; Canada: March 2020
Infliximab	BOW015	Infimab	Epirus Biopharmaceuticals, United States	India: September 2014
Infliximab	CMAB008	Ting Lei	Mabpharm, China	NMPA: July 2021
Infliximab	CT-P13	Remsima	Celltrion, South Korea	EMA: September 2013 (IV), September 2019 (SC); Japan: July 2014; South Korea: July 2012; Canada: January 2014 (IV), January 2021 (SC)
Infliximab	CT-P13	Inflectra	Pfizer (Hospira), United States	FDA: April 2016; Canada: January 2014; Australia: August 2015
Infliximab	CT-P13	Saixi	Celltrion, South Korea	NMPA: June 2023
Infliximab	CT-P13	Flammegis	Celltrion, South Korea	Russia: July 2015
Infliximab	CT-P13	Infliximab biosimilar 1	Celltrion, South Korea/Nippon Kayaku, Japan	Japan: July 2014
Infliximab	GB242	Jian Jiayou	Genor Biopharma, China	NMPA: February 2022
Infliximab	HS626	Baite An	BioRay, China	NMPA: September 2021
Infliximab	N/A	Infliximab biosimilar 3	Pfizer Japan	Japan: July 2018
Infliximab	NI-071	Infliximab biosimilar 2	Nichi-Iko Pharmaceutical, Japan	Japan: September 2017
Infliximab	PF-06438179	Ixifi	Pfizer, United States	FDA: December 2017; Canada: December 2021
Infliximab	PF-06438179/	Zessly	Sandoz, Switzerland	EMA: May 2018
Infliximab	SB2	Flixabi	Samsung Bioepis, South Korea	EMA: May 2016
Infliximab	SB2	Renflexis	Samsung Bioepis, South Korea; Merck, United States	FDA: April 2017; South Korea: December 2015; Australia: November 2016, Canada: December 2017

Abbreviations: INN, International non-proprietary names; EMA, European Medicines Agency; IV, intravenous; SC, subcutaneous; FDA, Food and Drug Administration; NMPA, National Medical Products Administration.

infliximab therapy (Fiorino et al., 2017). Following head-to-head comparison between infliximab and CT-P13 was conducted in 220 patients with active CD. The week 6 clinical response rates (a decrease of 70 points or more in CDAI, CDAI-70) were similar between the infliximab treatment group and the CT-P13 therapy group (74.3% vs. 69.4%). Furthermore, the two groups also showed comparable clinical remission rates and steroid-free remission rates at week 30. No significant differences in mean C reactive protein (CRP) concentrations, mean fecal calprotectin (FC) levels, pharmacokinetic, and pharmacodynamic profiles (C_{max} and C_{trough}) were observed between the two groups at every visit (Ye et al., 2019). Another comparative equivalence cohort study of 5050 infliximab naïve CD patients further proved the therapeutic equivalence between CT-P13 and infliximab (Meyer et al., 2019). Recently, a subcutaneous (SC) formulation of CT-P13 (CT-P13 SC) was developed for immune-mediated diseases. Although CT-P13 SC has its inherent shortcomings in comparison with the IV formulation of CT-P13 (CT-P13 IV), such as slower absorption, inadequate bioavailability, and lower initial peak concentrations, it shows its superiority in convenience, easy access, and time-saving (Bittner et al., 2018). It was claimed to be non-inferior to CT-P13 IV in patients with RA and IBD (Reinisch et al., 2019; Schreiber et al., 2021). An open-label, randomized, phase 1 study of 53 active CD and 78 active UC evaluated the efficacy and safety profiles of CT-P13 SC and suggested that the clinical response rates (86.8% vs. 74.4%, at week 30), clinical remission rates (60.5% vs. 38.5%, at week 30), and mucosal healing rates (47.7% vs. 30.8%, at week 22) were not significantly different between the CT-P13 SC group and the CT-P13 IV group. Besides, no differences in safety (treatment-emergent adverse events, TEAEs, 57.6% vs. 49.2%) and pharmacokinetics (C_{trough} 21.45 μg/mL vs. C_{trough} 2.93 μg/mL, at week 22) were found between the two arms, despite CT-P13 SC group showed numerically higher C_{trough} during week 6 to week 54 (Schreiber et al., 2021). CT-P13 SC indeed provides an additional alternative for IBD patients. It holds the promise of reducing medical visit-associated costs, optimizing medical resources, and reducing the burden on the healthcare systems. It is also an important step towards patient empowerment and medication self-management in IBD treatment.

What should be noted is that switching from originator infliximab to biosimilar CT-P13 was also claimed to be safe and tolerated (Schmitz et al., 2018; Ye et al., 2019; Haifer et al., 2021). At week 54, the clinical response rates and clinical remission rates were similar between the continued treatment group and the switching treatment group (Ye et al., 2019). These results were in accord with similar findings by the pivotal NOR-SWITCH study that switching from infliximab to CT-P13 IV was not inferior to continued

TABLE 2 Approval status of adalimumab biosimilars.

Originator	INN	Trade name	Manufacturer name	Approval status
Adalimumab	ABP 501	Amjevita	Amgen, United States	FDA: September 2016
Adalimumab	ABP 501	Amgevita	Amgen, United States	EMA: 21 March 2017; Canada: November 2020; Australia: October 2017
Adalimumab	ABP 501	Solymbic	Amgen, United States	EMA: March 2017, withdrawn on March 2019
Adalimumab	ABP 501	Adalimumab biosimilar 2	Daiichi Sankyo, Japan/Amgen, United States	Japan: January 2021
Adalimumab	AVT02	Hukyndra	Alvotech, Iceland/Stada Artnimettel, Germany	EMA: November 2021
Adalimumab	AVT02	Libmyris	Alvotech, Iceland/Stada Artnimettel, Germany	EMA: November 2021
Adalimumab	AVT02	Simlandi	Alvotech, Iceland/Teva, Israel	FDA: February 2024; Canada: January 2022
Adalimumab	BAT1406	QLETLI	Bio-Thera, China	NMPA: October 2019
Adalimumab	BCD-057	Dalibra	Biocad, Russia	Russia: February 2019
Adalimumab	BI 695501	Cyltezo	Boehringer Ingelheim, Germany	FDA: August 2017; EMA: November 2017, withdrawn on January 2019
Adalimumab	CHS-1420	Yusimry	Coherus Biosciences, United States	FDA: December 2021
Adalimumab	CT-P17	Yuflyma	Celltrion, South Korea	EMA: February 2021; Canada: December 2021
Adalimumab	FKB327	Hulio	Mylan/Fujifilm Kyowa Kirin Biologics, United States	FDA: July 2020; EMA: September 2018; Canada: November 2020; Japan: June 2020
Adalimumab	GP2017	Hyrimoz	Sandoz, Switzerland	FDA: October 2018; EMA: July 2018; Canada: November 2020
Adalimumab	GP2017	Halimatoz	Sandoz, Switzerland	EMA: July 2018, withdrawn on January 2021
Adalimumab	GP2017	Hefiya	Sandoz, Switzerland	EMA: July 2018
Adalimumab	HLX03	Yuan Handa	Shanghai Henlius Biotech, China	NMPA: December 2020
Adalimumab	HS 016	Jianning An	BioRay, China	NMPA: December 2019
Adalimumab	IBI-303	Sulinno	Innovent, China	NMPA: September 2020
Adalimumab	LBAL	adalimumab biosimilar 3	LG Life Sciences, South Korea; Mochida Pharmaceutica, Japan	Japan: March 2021
Adalimumab	MSB11022	Idacio	Fresenius Kabi, Germany	FDA: December 2022; EMA: April 2019; Canada: October 2020
Adalimumab	MSB11022	Kromeya	Fresenius Kabi, Germany	EMA: April 2019, withdrawn on December 2019
Adalimumab	N/A	Mabura	Hetero Drugs, India	India: January 2018
Adalimumab	N/A	Adfrar	Torrent Pharmaceuticals, India	India: January 2016
Adalimumab	N/A	Cadalimab	Zydus Cadila, India	India: August 2020
Adalimumab	PF-06410293	Abrilada	Pfizer, United States	FDA: November 2019; Canada: June 2021
Adalimumab	PF-06410293	Amsparity	Pfizer, United States	EMA: February 2020
Adalimumab	SB5	Hadlima	Samsung Bioepis, South Korea	FDA: July 2019; Canada: May 2018; Australia: January 2018; South Korea: September 2017
Adalimumab	SB5	Imraldi	Samsung Bioepis, South Korea	EMA: August 2017
Adalimumab	SCT630	Jianrun An	SinoCellTech, China	NMPA: June 2023
Adalimumab	TQ-Z2301	Bowei Tai	Chiatai Tianqing, China	NMPA: January 2022
Adalimumab	UBP1211	Maikang Jun	Shanghai Junshi Biosciences, China	NMPA: March 2022
Adalimumab	ZRC3197	Exemptia	Zydus Cadila, India	India: September 2014

Abbreviations: INN, International non-proprietary names; FDA, Food and Drug Administration; EMA, European Medicines Agency; NMPA, National Medical Products Administration.

treatment with infliximab in patients with immune-mediated diseases including CD, UC, RA, and others (Jørgensen et al., 2017). The two groups presented similar disease worsening rates during 54-week follow-up (26% vs. 30%). Moreover, they also claimed no notable differences in trough drug concentrations in the two groups (Jørgensen et al., 2017). Comparable serum drug concentrations between the maintenance and the switching treatment group were also demonstrated in the SECURE study (Strik et al., 2018). Switching from originator infliximab to CT-P13 SC is also safe and tolerated (Smith et al., 2022). Concerns regarding safety and immunogenicity arose when we made a non-medical switch from originators to biosimilars. The NOR-SWITCH extension study of 380 patients with immune-mediated disease revealed that treatment switching did not increase the incidence of anti-drug antibodies (ADAbs) and AEs during 78-week follow-up (Goll et al., 2019). Several studies also demonstrated no differences in safety and immunogenicity between the maintenance and the switching treatment group (Jørgensen et al., 2017; Strik et al., 2018; Meyer et al., 2019; Ye et al., 2019). However, a contrary result that CT-P13 was inferior to infliximab was showed in another study (Chaparro et al., 2019). Chaparro et al. (Chaparro et al., 2019) claimed that switching treatment increased the risk of disease relapse in patients with IBD. Cautions need to be made when we interpret these results. Various definitions of disease relapse, disease remission, clinical remission, and disease worse were set in different studies. What's more, the time for switching treatment from originators to biosimilars was also different, bringing additional hurdles to explain these findings. Further studies should be taken to elucidate these uncertainties.

3.2.2 SB2

SB2 is the second infliximab biosimilar approved for CD and UC. One phase I study and another phase III clinical trial demonstrated its equivalence of pharmacokinetics, efficacy, and safety with originator infliximab in healthy volunteers and patients with RA, paving the way to SB2 approval in RA and other immune-mediated diseases (Shin et al., 2015; Choe et al., 2017). As for IBD, a prospective observational study assessed its efficacy and safety in 276 patients with IBD (136 CD and 140 UC). 57.3% of infliximab naïve patients can achieve steroid-free remission after an 8-week SB2 treatment, which is similar to the effectiveness of infliximab and CT-P13 (Macaluso et al., 2021b). One aspect should be taken into consideration is that previous anti-TNF treatment may decrease the efficacy of SB2 in IBD. In comparison with anti-TNF-naïve cases, patients who were previously exposed to anti-TNF presented lower steroid-free remission rates (66.1% vs. 40.0%) (Macaluso et al., 2021b). Another real-life study of 85 patients with IBD further verified its efficacy and immunogenicity. No significant differences in clinical remission rates, FC levels, and corticosteroid-free rates have been found after switching from infliximab to SB2 treatment (at a mean time of 329 days). Switching treatment also did not increase the risk of developing ADAbs and SAEs during a mean 135-day follow-up (Massimi et al., 2021). The long-term effectiveness, safety, and immunogenicity were further investigated by a German research. During an 80-week follow-up, the changes in the Harvey-Bradshaw Index (HBI) and partial Mayo Score (PMS) were not significant after switching treatment. Furthermore, about 72% of patients persisted in SB2 therapy at week 78, indicating that this switch was well tolerated (Fischer et al., 2021). The safety profile of SB2 in IBD varies between different studies. Some studies did not record any SAEs, while some other studies claimed that about 7.6%–20.7% of patients might suffer from SAEs (Fiorino et al., 2017; Fischer et al., 2021; Massimi et al., 2021; Bouhnik et al., 2023). The inconsistency in follow-up time might partly explain the difference in SAEs.

A single switch from infliximab to SB2 is claimed to be safe and tolerated in patients with IBD. Multiple switches from originators to CT-P13 to SB2 are still demonstrated to be safe and effective. An observational study evaluated the effects and pharmacokinetics of the first switch (from CT-P13 to SB2) and the second switch (from infliximab to CT-P13 to SB2) in 186 patients with IBD. No significant changes in CRP, HBI, or Simple Clinical Colitis Activity Index were found upon the first and second switches. Similar median C_{trough} was recorded in pre-switch, early, and 1-year post-switch (4.9 μg/mL vs. 5.5 μg/mL vs. 5.3 μg/mL). Moreover, switching treatment did not exert a negative influence on disease response, given the comparable response rates during the 1-year follow-up (91% vs. 92% vs. 95%) (Luber et al., 2021). Another prospective multicenter cohort study of 176 patients with IBD further provided convincing evidence of efficacy and safety for multiple switches from originators to different biosimilars. The first switch (from CT-P13 to SB2) and the second switch (from infliximab to CT-P13 to SB2) showed comparable clinical remission rates at 12 months after switching treatment. Besides, 62.5% of the first switch group and 72.2% of the second switch group presented low FC levels (<250 mg/kg). It is worth noting that only the first switch group reported infusion reactions (3/80, 3.8%), suggesting multiple switches did not increase the risk of AEs (Hanzel et al., 2022). As aforementioned, the risk of increased immunogenicity is one of the core concerns when we make multiple switches. Available data demonstrated that no new ADAbs were developed after multiple switches (Hanzel et al., 2022). Although SB2 was claimed to be safe and effective in several studies, the clinical equivalence of SB2 in IBD is mostly proven in real-world studies, indicating a pressing need to conduct randomized, head-to-head, parallel clinical trials. Furthermore, few studies evaluated the efficacy of SB2 in achieving higher therapeutic goals, such as endoscopic mucosal healing and histologic remission. More studies are warranted to fill this gap.

3.2.3 PF-06438179/GP1111

PF-06438179/GP1111 is another biosimilar of infliximab, which was approved for immune-mediated diseases by the FDA in 2017 and by the EMA in 2018 (Generics and Biosimilars Initiative, 2023a; Generics and Biosimilars Initiative, 2023b). One phase I clinical study evaluated the pharmacokinetics and immunogenicity of PF-06438179/GP1111 in 151 healthy subjects. The PF-06438179/GP1111 group showed great similarities in serum concentration-time profiles and ADAb response rates to the infliximab group (Palaparthy et al., 2018). The equivalent safety and efficacy of PF-06438179/GP1111 was demonstrated in a large randomized controlled trial of 650 patients with moderate to severe active RA (Cohen et al., 2018b). There are no significant differences in the American College of Rheumatology (ACR)-20, ACR-50, and ACR-70 response rates between the PF-06438179/

GP1111 treatment group and the infliximab treatment group. Comparable Disease Activity Score (DAS) remission rates, and the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) remission rates were also claimed in this study. Besides, the PF-06438179/GP1111 arm showed similar all-cause TEAEs, incidence of ADAbs, and median C_{trough} concentrations to the infliximab arm. When we made a non-medical switch from originator infliximab to PF-06438179/GP1111, efficacy was also well sustained in terms of ACR20, ACR50 and ACR70 response rates (Cohen et al., 2018b). This result indicated that single switch from a originator to PF-06438179/GP1111 was acceptable. Therefore, the strong equivalence of PF-06438179/GP1111 to infliximab with regard to efficacy, pharmacokinetics, and safety allowed the approval of it in the treatment of IBD, which is based on the concept of extrapolation. However, data on the efficacy and safety profiles in patients with IBD are very limited. A retrospective real-life study of 87 pediatric IBD patients assessed the efficacy of several biosimilars including CT-P13, SB2 and PF-06438179/GP1111, and demonstrated their favorable effectiveness in induction and maintenance of disease remission. Another single-center observational study reported that switching from SB2 to PF-06438179/GP1111 and re-switching from PF-06438179/GP1111 to SB2 were effective and tolerated (Macaluso et al., 2023). One point should be noted is that this study only included ten patients with IBD and followed up 16–28 weeks. The small sample size and short length of follow-up may limit the strength of conclusions. Further large, multicenter, long-term, prospective studies are needed. Moreover, head-to-head parallel studies are also warranted to provide more clinical evidence and clarify the exact role in the treatment of IBD, thus building confidence in the use of PF-06438179/GP1111 in IBD.

3.2.4 Others

ABP 710, a biosimilar of infliximab, was approved for CD, UC, RA, AS, psoriasis, and psoriasis arthritis by the FDA in 2019 (Generics and Biosimilars Initiative, 2023b). It presented physicochemical, pharmacodynamic, and pharmacokinetic similarities to originator infliximab based on the analytical study and phase I clinical study (Chow et al., 2020; Saleem et al., 2020). Comparable efficacy, safety, and immunogenicity profiles were also demonstrated in the comparative clinical trial of RA. The ABP 710 group showed similar ACR-20 response rates (at week 22) to the infliximab arm (68.1% vs. 59.1%). Besides, there are also no clinically meaningful differences between the two arms in AEs (51.8% vs. 49.6%) and incidence of ADAbs (57.1% vs. 60.0%) (Genovese et al., 2020). No new safety signals have been reported. Other agents including NI-071, BOW015, GB242, CMAB008, etc. have also been approved by different countries. One network meta-analysis including seven randomized controlled trials of RA demonstrated that treatment of NI-071 was more probable to gain therapeutic success (the ACR-20 response rate), compared with ABP 710, CT-P13, PF-06438179/GP1111, and SB2 (Lee and Song, 2023). BOW015, GB242, and CMAB008 were claimed to be comparable to infliximab in terms of bioavailability, safety, and immunogenicity in three phase I clinical studies (Lambert et al., 2016; An et al., 2019; Zhang et al., 2019). Non-inferiority studies of these agents were all conducted in patients with RA. The ACR-20 response rates of the GB242 group and CMAB008 at week 30 were highly similar to that of the infliximab group (62.54% vs. 56.89%, and 57.6% vs. 62.2%, respectively). No clinically meaningful differences in safety, immunogenicity, and pharmacokinetics were found (Liu et al., 2022; Ye et al., 2023). However, studies on the above agents in IBD are still in the preliminary stages, no randomized studies and real-world data were reported. Further efforts should be made to facilitate clinical equivalence study in IBD.

3.3 Biosimilars of adalimumab in IBD

3.3.1 ABP 501

ABP 501, the first biosimilar of adalimumab, was approved for various diseases including RA, CD, UC, AS, and others by the FDA in 2016 and by the EMA in 2017(Generics and Biosimilars Initiative, 2023a; Generics and Biosimilars Initiative, 2023b). The analytical and functional characterization studies suggested that ABP 501 and adalimumab had great similarity in identity, general properties, physicochemical properties, purity and impurities, and inhibition effect on TNFα activities. The equivalent pharmacokinetics, similar safety profiles, and comparable immunogenicity of ABP 501 and adalimumab were further confirmed in a phase I study (Kaur et al., 2017). Based on the similar structures, functions, and pharmacokinetics between ABP 501 and adalimumab, further clinical equivalence studies were conducted. Comparable efficacy, safety, and immunogenicity between ABP501 and adalimumab were first demonstrated in patients with moderate to severe plaque psoriasis and then confirmed in cases with moderate to severe RA (Cohen et al., 2017; Papp et al., 2017). Following studies in IBD further claimed its favorable efficacy and safety. An observational study demonstrated that about 56% of CD patients could gain clinical remission upon ABP 501 treatment, with no new safety signals detected. Besides, the mean HBI scores (4.7 vs. 6.1) and CRP values (6.2 mg/L vs. 14.9 mg/L) at week 12 were numerically lower compared with the baseline values (Ribaldone et al., 2020). A three-arm propensity score-weighted analysis further compared the therapeutic effects and safety profiles of adalimumab and its biosimilars (ABP501 and SB5) in 86 CD and 69 UC patients. The three arms showed no significant differences in steroid-free clinical remission rates at induction stages (40.0% vs. 50.0% vs. 58.7%, at week 8) and maintenance stages (49.1% vs. 54.5% vs. 59.0%, at week 32). What should be noted is that superior efficacy was achieved by patients with CD compared with those with UC. The clinical response rate at week 8, and steroid-free clinical remission rates at weeks 8 and 32 were significantly higher in CD than in UC (Barberio et al., 2021). This is in accordance with the findings that adalimumab, infliximab, and its biosimilar were more effective in CD than UC, without no differences in safety and tolerability (Barberio et al., 2020). Underlying mechanisms are needed to be revealed.

ABP 501 seems to be as effective and tolerated as adalimumab in patients with IBD, thus providing an additional option for IBD patients who are naïve to or previously exposed to adalimumab. Switching from adalimumab to ABP 501 might be a cost-effective therapy for those patients. Available data indicated that there were no significant changes in HBI scores and CRP levels after switching from adalimumab to ABP 501 (Ribaldone et al., 2020). Similarly,

Cingolani et al. (Cingolani et al., 2021) enrolled 55 IBD patients with switching treatment (adalimumab to ABP 501) and followed up for 6 months. In comparison with sustained therapy (adalimumab), switching treatment did not exert negative effects on HBI scores, PMS scores, and FC levels. There were still 76.3% of patients in remission after switching (Cingolani et al., 2021). Recently, the ADA-SWICTH study provided complementary data on disease relapse and safety profiles after switching treatment in patients with IBD (Casanova et al., 2023). Comparable relapse rates at 6 months (3% vs. 3%), 12 months (6% vs. 6%), and 24 months (26% vs. 12%) between switch treatment and sustained treatment group were recorded. The switching treatment group presented a numerally lower risk of suffering from endoscopic and/or radiologic activity compared with the other group (3% vs. 10%). Besides, this study also reported similar AEs between the two arms (6% vs. 5%), which further increased the confidence of physicians in the use of adalimumab biosimilars in clinical practice (Casanova et al., 2023). More valuable data were provided by the SPOSAB study. In this study, 85.5% of patients (adalimumab naïve) could gain clinical remission and 75.3% of patients could achieve a steroid-free remission after a 12-week ABP501 treatment. No efficacy difference was found between anti-TNFs-naïve patients and those previously exposed to anti-TNFs. However, inconsistent findings were reported by Cingolani et al. (2022). Better therapeutic effects of ABP 501 were achieved in anti-TNF-naïve patients, compared with anti-TNF-experienced ones (Cingolani et al., 2022). Different identifications of therapeutic effects in different studies may explain this inconsistency. One note in particular is that the incidence rates of SAEs were significantly lower in the switching therapy group. Thus, the lower incidence rates of SAEs might partly account for the finding that patients receiving switching therapy (adalimumab to ABP501) were more likely to persist in ABP 501 treatment, in comparison with those adalimumab-naïve patients (Macaluso et al., 2021a). Besides, no negative impacts of ABP 501 treatment on health-related quality of life were recorded, whether for the ABP 501 initiators or the adalimumab-ABP 501 switchers. More than 98% of physicians and patients expressed their satisfaction on ABP 501 treatment (Jin et al., 2024). Indeed, ABP 501 is truly effective and well-tolerated in IBD. However, data on immunogenicity, long-term efficacy, and long-term safety of ABP 501 in IBD are limited, suggesting a need to fill this gap. Cost-benefit analyses based on medical insurance of different countries are also warranted. Furthermore, in the "precision medicine" era, identifying suitable patients who will benefit most from ABP 501 is an essential prerequisite in the precision treatment of IBD. Therefore, exploring reliable biomarkers for predicting therapeutic response to ABP 501 is also needed.

3.3.2 SB5

SB5 is another biosimilar of adalimumab, approved by the EMA in 2017 and the FDA in 2019(Generics and Biosimilars Initiative, 2023a; Generics and Biosimilars Initiative, 2023b). The clinical equivalence study was firstly conducted in a large phase III randomized study of 542 patients with moderate to severe RA. The ACR20, ACR50, and ACR70 response rates were equivalent between the SB5 treatment group and the adalimumab treatment group. No significant differences in the incidence of TEAEs, development of ADAbs, and pharmacokinetics were reported in this study (Weinblatt et al., 2018). By extrapolation, the approval was extended to IBD, axial spondylarthritis, and psoriasis arthritis (Müller-Ladner et al., 2023).

Lukas et al. (2020) firstly provided the real-life study that directly compared the efficacy, safety, pharmacokinetic, and immunogenicity profiles between the originator and SB5. 93 IBD patients received switch treatment (from adalimumab to SB5) and the other 93 patients still received originator adalimumab therapy. The two groups did not show any significant changes at week 10 with regard to HBI scores, PMS scores, CRP levels, and FC concentrations. They also claimed no notable differences in trough drug concentrations (13.0 μg/mL vs. 13.7 μg/mL) and the incidence of ADAbs (2% vs. 2%) between the two arms at week 10. However, the follow-up time was only 10 weeks, too short to evaluate the long-term safety profiles. Further study conducted by Barberio et al. (2021) provided additional information on the long-term efficacy and safety profiles in patients with IBD. They compared the effectiveness and safety profiles of SB5 and adalimumab at weeks 8 and 48. The rates of steroid-free clinical remission at the two time points were 58.7% and 59.0%, which were comparable to the rates of adalimumab (40% and 49.1%, respectively). Similar clinical response rates at weeks 8 and 48 were also collected in this study (Barberio et al., 2021). Data on the 1-year performance of SB5 in patients with IBD were further reported by a UK study. They divided patients into two arms, the SB5-switch group and the SB5-start group (adalimumab naïve), and followed up at a median time of 13.7 months and 8.3 months, respectively. SB5 showed comparable effectiveness to adalimumab given similar 1-year drug persistence rates (62.5% vs. 50.89%) (Chen et al., 2019; Derikx et al., 2021). Switching treatment also did not worsen the biochemical remission rates, fecal biomarker remission rates, and clinical remission rates at weeks 26 and 52. Besides, there were also no differences in the median C_{trough} concentrations at weeks 0, 26, and 52 after switching treatment (10.1 μg/mL vs. 11.6 μg/mL vs. 7.8 μg/mL). This is consistent with the other two studies reporting stable trough drug concentrations after switching from adalimumab to SB5 (Lukas et al., 2020; Tapete et al., 2022).

About 19.9% of patients in the SB5-switch cohort and 17.3% of patients in the SB5-start cohort reported AEs, respectively. The most common AE in the SB5-switch cohort was injection-site pain (66.7%), which lead to a double-switch treatment (from adalimumab to SB5 to ABP 501) in these patients. Therefore, this study provided the first data on the double-switch treatment. Median trough concentrations were stable during the first and the second switch treatment, suggesting that multiple switches might work in cases intolerant to SB5 (Derikx et al., 2021). Similarly, switching from adalimumab to ABP 501 to SB5 was also tolerated (Ribaldone et al., 2021). It did not impair the efficacy and increase the risk of AEs in patients with IBD. Given that injection-site pain negatively affected treatment persistence, solutions to help relieve injection-site pain were designed. A citrate-free and high concentration of SB5 (SB5-HC) was claimed to be associated with less injection site pain (Ahn et al., 2022). Besides, injection technique training and psychological interventions are also important to alleviate pain. Overall, SB5 is effective and safe in IBD, though this conclusion was based on post-marketing evidence. Healthcare professionals and patients expressed their concerns about its efficacy and safety, causing some negative effects on the market share of SB5. Therefore,

further randomized controlled clinical trials may help build confidence and increase the uptake of SB5. Moreover, some studies did not perform dose optimization in a standardized manner and evaluate endoscopic/histological healing after dose optimization, which might cause potential selection bias.

3.3.3 BI 695501

BI 695501 is another biosimilar of adalimumab (Wynne et al., 2016). The regulatory approval of BI 695501 was granted in Europe and the United States in 2017 based on the "totality of the evidence" (Generics and Biosimilars Initiative, 2023a; Generics and Biosimilars Initiative, 2023b). The bioequivalence, comparable safety, and similar immunogenicity of BI 695501 to adalimumab were first demonstrated in a phase I study of 327 healthy volunteers in 2016 (Wynne et al., 2016). Two years later, the efficacy data were primarily obtained in patients with RA (Cohen et al., 2018a). This study suggested the non-inferiority of BI 695501 to originator adalimumab in terms of efficacy, safety, and immunogenicity. Switching from adalimumab to BI 695501 was not associated with lower efficacy, increased incidence of AEs, and elevated levels of ADAbs (Cohen et al., 2018a). By extrapolation, the approval was extended to other indications including CD, UC, AS, psoriasis, and others.

Clinical data on BI 695501 in patients with IBD were limited. One large, multicenter, randomized, double-blind, phase 3 study including 147 moderately to severely active CD patients divided patients into two groups, the BI 695501 group and the adalimumab group (Hanauer et al., 2021). The two groups showed similarities in clinical response rates (90% vs. 94% at week 4, and 81% vs. 82% at week 24), clinical remission rates (68% vs. 75% at week 24), and AE rates (63% vs. 56% at week 24). Besides, this VOLTAIRE-CD study also evaluated the feasibility of switching from adalimumab to BI 695501. No negative impacts of switching treatment on efficacy and AEs were claimed. Patients in the switch group presented a similar degree of reduction in CDAI scores and a similar incidence of TEAEs to those in the BI 695501 sustained group (Hanauer et al., 2021). Likewise, the VOLTAIRE-X study of 238 patients with chronic plaque psoriasis further demonstrated that switching back and forth from adalimumab to BI 695501 was safe, effective, and tolerated (Menter et al., 2022). This study provided direct evidence for the interchangeability of BI 695501. Thus, BI 695501 (Cyltezo) became the first FDA-approved interchangeable biosimilar to adalimumab (Kay et al., 2024). This indicated that pharmacists can substitute the biosimilar for its originator without the permission of the prescribing healthcare professionals (Alvarez et al., 2020). The "interchangeable" logo may greatly increase the uptake of Cyltezo. More treatment options are thus provided for patients who need repeated therapy during the overall disease course. However, the paucity of safety and immunogenicity data on IBD highlighted the need to conduct real-world studies in the future. Besides, evaluating the long-term outcomes of BI 695501 on the basis of interchangeability designation in different diseases is also warranted.

3.3.4 GP2017

GP2017 is the fourth adalimumab biosimilar approved by the EMA and the third one approved by the FDA in 2018 (Generics and Biosimilars Initiative, 2023a; Generics and Biosimilars Initiative, 2023b). The equivalent efficacy, safety, and immunogenicity between GP2017 and adalimumab were demonstrated in a phase III randomized study of 465 patients with plaque psoriasis. This study also demonstrated that multiple switches between adalimumab and GP2017 did not impair the disease outcomes and affect the safety and immunogenicity profiles (Blauvelt et al., 2018). The following study in patients with moderate to severe active RA further confirmed the non-inferiority of GP2017 to adalimumab in terms of efficacy, safety, and immunogenicity (Wiland et al., 2020). GP2017 was approved for IBD through extrapolation of indications.

Real-life data on the efficacy of GP2017 in IBD were provided by an Italy study (Mocci et al., 2022). This study retrospectively analyzed the clinical data of 134 patients with IBD. Among these patients, 62 patients received GP2017 treatment while the others received adalimumab therapy. Similar clinical remission rates and clinical response rates were reported regardless of whether they were naïve to biologics or not. 82.3% of patients in the GP2017 group and 75.0% of patients in the adalimumab group achieved clinical remission at a median follow-up time of 12 months. No clinically meaningful differences in the rates of treatment optimization and surgery, as well as the incidence of AEs were suggested. More importantly, GP2017 showed better effects in achieving mucosal healing than adalimumab. The mucosal healing rate in the GP2017 group was about 1.5 times as that in the adalimumab group (89.2% vs. 60.2%). Recently, another real-world retrospective study evaluated the impacts of switching treatment in IBD patients (Vernero et al., 2023). Switching from adalimumab to GP2017 did not increase the clinical disease activity and interfere the treatment persistence. Patients who were previously exposed to infliximab were at a higher risk of needing dose optimization of GP 2017 (Vernero et al., 2023). However, the retrospective design cannot prove the causal association and control the potential confounding factors. Well-designed, well-paired, prospective studies might add useful information. A prospective observational study of 50 IBD patients further proved the favorable efficacy and safety profiles of GP2017. 75.0% of patients obtained remission or partial response after 12-week treatment of GP2017. A median decrease of CDAI and Mayo score was 140.5 and 4.0. respectively (Wasserbauer et al., 2022). This study also had limitations, including a lack of reference product control, a short follow-up time, and a small sample size. Recently, a cross-sectional, questionnaire-based study assessed the subjective efficacy of switching treatment in 179 IBD patients (Sarlós et al., 2023). Patients with GP2017 switching treatment reported better efficacy of GP2017 than adalimumab. However, they also complained of a higher incidence of new AEs (1.79 per patient) that did not occur during adalimumab treatment. Most of these patients also expressed their willingness to switch back to adalimumab if possible (Sarlós et al., 2023). Such a contradiction may be partly explained by the "nocebo" effect, an unfavorable therapeutic effect of a medical therapy that is not caused by pharmacological effects and is related to patients' high expectations on it (Colloca et al., 2019).

Overall, GP2017 is as effective and safe as adalimumab in patients with IBD. However, there is relatively limited data on the pharmacokinetics and immunogenicity of GP2017 in IBD. Little is known about the drug concentrations and ADAb levels after switching treatment. More prospective studies are also needed to evaluate the performance of multiple switches between adalimumab and GP2017 in patients with IBD.

3.3.5 Others

Biosimilars of adalimumab including FKB327, MSB11022, AVT02, PF-06410293, CHS-1420, CT-P17, and others were also approved for treatment of CD and UC (Generics and Biosimilars Initiative, 2023b; Generics and Biosimilars Initiative, 2023a). However, most clinical evidence was obtained from patients with RA and plaque psoriasis. There were relatively limited efficacy and safety data on them in IBD. FKB327 treatment showed high efficacy in inducing and maintaining disease remission or partial response at week 12 (18/22, 81.8%), which was comparable to the effectiveness of GP2017 (21/27, 75.0%) (Wasserbauer et al., 2022). A large, multicenter, observational study of 533 IBD patients evaluated the efficacy and safety profiles of four biosimilars of adalimumab (SB5, APB501, GP2017, and MSB11022). Available data indicated that 81.8% of patients with MSB11022 could achieve clinical remission, similar to SB5 (75.2%), APB501 (78.3%), and GP2017 (77.5%). MSB11022 also showed similarities in steroid-free remission rates and mucosal healing rates to the other three biosimilars. No new safety concerns were identified in MSB11022 (Tursi et al., 2023). However, the data must be viewed critically because the patients included in the MSB11022 group were only 11, which may weaken the strength of the evidence. Another Italy study of 143 IBD patients further compared the efficacy and safety of the four biosimilars (SB5, APB501, GP2017, and MSB11022) after switching from adalimumab. No significant differences in remission maintenance rates between the four biosimilars were claimed (Tursi et al., 2022). However, the sample size of the MSB11022 group was still too small (3 patients), which suggested a need to conduct a larger study of MSB11022. There are few studies on the roles of AVT02, PF-06410293, CHS-1420, and CT-P17 in patients with IBD. One phase IV clinical trial (NCT05913817) is currently evaluating the effectiveness, safety, and tolerability of AVT02 in patients who switch from low-concentration adalimumab to AVT02 (Clinical Trials.gov, 2024). CD and UC patients are included in this study. Most studies focused on healthy subjects and plaque psoriasis patients. More real-world studies in patients with IBD are therefore needed.

4 The benefits of biosimilars

Based on extrapolation, biosimilars of anti-TNFα were approved for a variety of immune-mediated diseases including CD and UC. Biosimilars showed strong bioequivalence and similar efficacy results, as well as comparable safety and immunogenicity profiles to originators. In the absence of high-quality evidence from randomized controlled trials, healthcare professionals always relied on real-life data to support their use in clinical settings. Even so, many physicians and patients still choose biosimilars, based on the following reasons.

4.1 Cost-saving

The most important benefit of using biosimilars is the cost savings. Available data suggested that biologics accounted for 77% of prescription drug spending in 2017 and made up 92% of spending growth from 2006 to 2017 under Medicare Part B (Dickson and Kent, 2021). According to the U.S. Generic and Biosimilar Medicines Savings Report 2023 provided by the Association for Accessible Medicines, the cumulative cost savings of biosimilars from 2015 to 2022 in the United States were $23.6 billion, which will increase to $130 billion in 2025. What should be noted is that biosimilars of infliximab accounted for the most of savings ($3.3 billion), indicating a pivotal role of infliximab biosimilars in cost savings (Association for Accessible Medicines, 2023).

It is universally acknowledged that the introduction of biosimilars greatly decreased medical spending. Take infliximab biosimilars for example, both the list price and net price of infliximab increased at a rate of 6% from 2007 to 2013. The introduction of its biosimilars decreased the net price to a mean of −13.6% in 2019 (San-Juan-Rodriguez et al., 2019). Furthermore, the cost savings resulting from the introduction of infliximab biosimilars in the United States were $21 million from 2015 to 2019 under Medicare Part B (Dickson and Kent, 2021). As for adalimumab originator (Humira), the list price increased from 2013 to 2020 continuously ($2,784 in 2020 vs. $1,153 in 2013), which caused a huge burden on public and private payers. However, the 2023 list price for the biosimilar of adalimumab (Amjevita) was only $1,558, a 44% discount from the 2020 list price of Humira (Dickson et al., 2023). This may hold promise for slowing prescription drug spending growth to some extent. In Europe, the cumulative cost savings of Remsima in 2014 were €25.79~€77.37 million over a 1-year time horizon in Germany, the United Kingdom, Italy, the Netherlands, and Belgium (Jha et al., 2015). In the United Kingdom, Italy, France, and Germany, using of CT-P13 over 5 years brought greater savings (€233~€433.5 million) for RA patients and payers. It was estimated that the potential cost savings were enough to cover biosimilar treatment for another 7,500 more patients with RA (Dörner et al., 2016). What should be noted is that changing prices of originators and biosimilars made it very challenging to do a real cost benefit evaluation of biosimilars. Researchers should do financial analysis based on the actual status. A recent report demonstrated that the median biosimilar treatment costs per patient-month in the United States in 2020 were $8,987, lower than originators ($11,503). Similar findings were also reported in Germany ($932 vs. $1,285) and Switzerland ($1,351 vs. $1,801) (Carl et al., 2022). Biosimilars have relatively lower prices than originators. Price negotiation and demand-side measures were carried out to facilitate market entry and market share. As a result, the entry of biosimilars further drove stiff competition between pharmaceutical companies. Manufacturers then reduced the price of originators to gain market share. Based on data from 2020, the introduction of the first and the second biosimilars of infliximab markedly decreased the volume-weighted average price per defined daily dose by 13.6% and 26.4% in Europe, respectively (Car et al., 2023). In the United States, market entry of biosimilars of infliximab decreased the average sales price of originators by 58%. Based on data from 2022, biosimilars were claimed to reduce the growth rate of total autoimmune disease spending by 41% (Association for Accessible Medicines, 2023). Collectively, biosimilars hold promise for curbing the prescription drug spending growth and lowering government expenditures.

4.2 Increase patient access to biologics

The high price of originator biologics substantially limited patient access to them. Many patients, especially those low-income patients, cannot afford the high costs of biologics. Biosimilars showed their superiority in prices and thus

attracted more attention from patients. Besides, government and healthcare managers proposed relevant policies to promote biosimilar use and increase their uptake. In Europe, market entry of biosimilars significantly increased the utilization of infliximab and adalimumab by an average of 88.9% and 22.4%, respectively (Car et al., 2023). Biosimilars have been used in 5.8 billion days of patient therapy over the last 10 years in Europe, increasing patient treatment days significantly (IQVIA Institute, 2023a). According to the U.S. Generic and Biosimilar Medicines Savings Report 2023, the cumulative patient treatment days were 694 million days since 2015, which made more than 344 million incremental days of patient therapy (Association for Accessible Medicines, 2023). These data indicated that biosimilars expand access to biologic treatment and healthcare. As it is known to us, inadequate or inappropriate treatment may aggravate disease progression, especially in IBD patients with severe disease (Zeng et al., 2023). Biosimilars provide an additional option for these patients, making it possible for patients to receive biologic treatment earlier and receive dose optimization more easily. As a result, the disease prognosis might be improved and natural history might be changed.

5 The challenges and obstacles of biosimilars

Although biosimilars are cost-saving, the market share of biosimilars varies across different countries (IQVIA Institute, 2023b). Available data suggested that the uptake for biosimilars of infliximab was lowest in the United States, with the highest uptake for bevacizumab biosimilars (36% vs. 3%) in 1 year after their entry into the market. In general, Germany has the highest market share of biosimilars, followed by the United States and Switzerland (Carl et al., 2022). However, the adoption of infliximab biosimilars increased to 44% 6 years after market entry in the United States (IQVIA Institute, 2023a). This difference in the market share of biosimilars might partly explained by different policies for market entry, reimbursement, and drug pricing negotiation across different countries.

The extensive patent protections and complex patent litigation on originators became the major threat to market entry of biosimilars. Even though biosimilars can get approval, patent infringement damages discourage them from entering the market. Take Humira for example, AbbVie company registered more than 160 patents on Humira which do not expire until 2037, though the core compound patent expired 7 years ago (Kvien et al., 2022). The tough situation made biosimilar companies have to sign settlement agreements and make major concessions. Otherwise, huge compensation and legal costs might be paid.

As for reimbursement, take the United States for example, drugs with lower average sales prices bring a lower reimbursement for insurers, pharmacy benefit managers (PBMs), government, wholesalers, and retailers. As a result, they prefer to choose high-priced originators, in order to receive higher rebates, thus hindering market penetration of low-priced biosimilars. Besides, some manufacturers proposed unique contracting mechanisms including rebate traps. It means that insurers, PBMs, and clinicians should return the rebates they got from prescribing originators if patients start to use biosimilars (Dean et al., 2021). Moreover, lack of and/or delayed coverage further delayed the adoption rates of biosimilars. Medicare, Medicaid, and commercial insurance are unwilling to cover the costs of biosimilars due to the great rebates offered by originator manufacturers. In 2023, Medicare price negotiation was launched in the United States. Although biosimilars were not included in the list, it will make an impact on biosimilars to some extent.

Interchangeability is another obstacle to biosimilars. Due to the rigorous standards set in the United States, the number of interchangeable biosimilars was relatively small. Pharmacists cannot substitute the biosimilar for its originator automatically, further resulting in a lower market share of biosimilars. What should be noted is that interchangeability is not permitted in many other countries, suggesting a need to analyze biosimilar issues based on national conditions.

In China, the coverage of commercial insurance is significantly lower than in other developed countries (Xu et al., 2021). Some biosimilars were not only not covered by basic medical insurance, but also not covered by commercial insurance, which further decreased the accessibility and affordability of biosimilars. Besides, the drug price negotiation mechanism of China is also different from other countries. The United States carried out independent pricing. Manufacturers, insurers, and PBMs fix the price by pricing negotiation. While in China, the drug price is based on manufacturing costs and clinical values. The National Healthcare Security Administration directly negotiated with manufacturers and fixed prices. Most manufacturers want to increase their market share at the expense of decreased drug prices. However, the biosimilar market in China is frail. And sales of biosimilars are not satisfactory, which always leads to failure in biosimilar pricing negotiation. A vicious circle developed. Therefore, more incentive programs are needed in China.

In addition to the above policies, the prescription inertia of physicians and low patient acceptance are also important obstacles to increasing market share. Healthcare professionals are willing to prescribe brand drugs that are used frequently, given that they are good at using them and dealing with side reactions caused by these drugs. Besides, the efficacy and safety of biosimilars are still a major concern, although they were proven to have comparable efficacy and safety to originators. Moreover, more concerns about therapeutic responses and side reactions were raised when making switching treatments, especially in patients in disease remission.

The above challenges and obstacles indeed hinder the development of biosimilars. A collaboration between government agencies, state legislators, manufacturers, insurance companies, healthcare professionals, and patients is encouraged.

6 The future of biosimilars in IBD

Biosimilars do play a key role in the treatment of IBD. With the expiration of patents of some anti-TNFα biologics, an increasing number of anti-TNFα biosimilars entered the market. The equivalent efficacy, safety, and immunogenicity profiles between biosimilars and originators were validated in several clinical trials. However, most clinical trials were not conducted in patients with IBD, resulting in some concerns about the efficacy and safety in IBD.

This further discouraged the market share of biosimilars in IBD treatment, suggesting a pressing need to design more studies to confirm their roles in IBD patients. With an increasing number of alternative biosimilars for IBD patients, more efforts should also be put into the investigation of efficacy and immunogenicity profiles of multiple successive switches between originators and biosimilars. Besides, from the perspectives of pharmacoeconomics and health economics, cost-effectiveness analyses of biosimilars are also warranted.

In the era of precision medicine, precision diagnosis and precision treatment hold the key to disease management. Given that IBD is a progressive disease, tailoring an individualized and precise therapeutic plan within the window of opportunity is highly crucial. Combined analysis of clinical, genetic, epigenetic, serological, histological, and fecal markers may assist physicians in predicting therapeutic response and selecting a suitable drug for individuals (Chen P. et al., 2020; Chen et al., 2023; Yueying et al., 2023). Thus, exploring predictive markers and establishing predictive models of anti-TNFα biosimilars seems to be necessary. Identifying molecular markers for therapeutic drug monitoring will also be helpful in the precision monitoring of biosimilars. To achieve the therapeutic goal for IBD, "treat-to-target," determining the optimal switching time for IBD patients is also of great importance. Switching too early may cause disease flare, while switching too late may increase the medical costs of patients. Moreover, more importance should be attached to ADAbs and drug concentrations. ADAbs are closely correlated with adverse reactions and therapeutic failures. Available assay techniques for ADAb detection and drug concentration assessment include enzyme-linked immunosorbent assay, fluid phase radioimmunoassay, homogeneous mobility shift assay, and others (Soubières and Poullis, 2016; Strand et al., 2020). The sensitivity and specificity of them vary greatly. The lack of a gold standard assay, undefined threshold values, and undetermined detection time points make it difficult to interpret immunogenicity results. Therefore, it is definitely a pressing need to identify a gold standard assay, and a universally acknowledged threshold value and detection time point for biosimilar treatment. What's more, the challenge remains to differentiate ADAbs from biologics themselves or other endogenous antibodies, which further limits their clinical application (Strand et al., 2020). More importantly, designing biosimilars with comfortable routes of administration (such as subcutaneous administration), high concentration, and reduced immunogenicity also became a matter of prime importance.

The European Union (EU) and the United States have established a comparatively perfect regulatory framework for biosimilar discovery, approval, and supervision. However, the study on anti-TNFα biosimilars in China is in the preliminary stages. Relevant laws and regulations are not very sound. Dynamically assessing and revising cost-containment and use restriction policies is the essential prerequisite for ensuring a competitive and sustainable market for biosimilar competition. More efforts are also needed to accelerate the discovery and approval processes of biosimilars. Patient empowerment and medication self-management will be the future medical model. Thus, education and training must be provided to build their confidence in using biosimilars. A close collaboration between government agencies, state legislators, manufacturers, insurance companies, healthcare professionals, and IBD patients is also needed, which holds the key to boosting the development of biosimilars.

Author contributions

ZZ: Visualization, Writing–original draft, Writing–review and editing. HL: Visualization, Writing–original draft, Writing–review and editing. MJ: Writing–review and editing. JY: Writing–review and editing. XL: Writing–review and editing. YJ: Writing–review and editing. LY: Supervision, Writing–review and editing. HZ: Supervision, Writing–review and editing.

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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

Supplementary material

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A systematic review and meta-analysis of the efficacy and safety of iguratimod in the treatment of inflammatory arthritis and degenerative arthritis

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Objective: To assess the efficacy and safety of iguratimod (IGU) in the treatment of inflammatory arthritis and degenerative arthritis.

Methods: Initially, randomized controlled trials (RCTs) on using IGU in treating inflammatory arthritis and degenerative arthritis were systematically gathered from various databases up to February 2024. Subsequently, two researchers independently screened the literature, extracted data, assessed the risk of bias in included studies, and conducted a meta-analysis using RevMan 5.4 software.

Results: Fifty-four RCTs involving three inflammatory arthritis were included, including ankylosing spondylitis (AS), osteoarthritis (OA), and rheumatoid arthritis (RA). For AS, the meta-analysis results showed that IGU may decrease BASDAI (SMD −1.68 [−2.32, −1.03], $P < 0.00001$) and BASFI (WMD −1.29 [−1.47, −1.11], $P < 0.00001$); IGU may also decrease inflammatory factor [ESR: (WMD −10.33 [−14.96, −5.70], $P < 0.0001$); CRP: (WMD −10.11 [−14.55, −5.66], $P < 0.00001$); TNF-α: (WMD −6.22 [−7.97, −4.47], $P < 0.00001$)]. For OA, the meta-analysis results showed that IGU may decrease VAS (WMD −2.20 [−2.38, −2.01], $P < 0.00001$) and WOMAC (WMD −7.27 [−12.31, −2.24], $P = 0.005$); IGU may also decrease IL-6 (WMD −8.72 [−10.00, −7.45], $P < 0.00001$). For RA, the meta-analysis results showed that IGU may improve RA remission rate [ACR20: (RR 1.18 [1.02, 1.35], $P = 0.02$); ACR50: (RR 1.32 [1.05, 1.64], $P = 0.02$); ACR70: (RR 1.44 [1.02, 2.04], $P = 0.04$)] and decrease DAS28 (WMD −0.92 [−1.20, −0.63], $P < 0.00001$); IGU may also decrease inflammatory factors [CRP:

(SMD −1.36 [−1.75, −0.96], $P < 0.00001$); ESR: (WMD −9.09 [−11.80, −6.38], $P < 0.00001$); RF: (SMD −1.21 [−1.69, −0.73], $P < 0.00001$)]. Regarding safety, adding IGU will not increase the incidence of adverse events.

Conclusion: IGU might emerge as a promising and secure therapeutic modality for addressing AS, OA, and RA.

Systematic Review Registration: Identifier PROSPERO: CRD42021289249

KEYWORDS

inflammatory arthritis, iguratimod, systematic review, meta-analysis, degenerative arthritis

1 Introduction

Arthritis encompasses various joint diseases and is associated with factors such as degenerative diseases and autoimmunity. Its hallmark features include chronic inflammation in one or more joints, often leading to pain and frequently resulting in disability. Primary clinical symptoms encompass joint pain, swelling, stiffness, and restricted mobility (Venetsanopoulou et al., 2023; Di Matteo et al., 2023). Epidemiological evidence indicates that arthritis is most prevalent among females, with an increasing incidence with age. Moreover, the prevalence of arthritis of different etiologies varies across populations (Syed et al., 2023; Katz and Bartels, 2024). Current research suggests the existence of over 100 distinct forms of arthritis, with osteoarthritis (OA) and rheumatoid arthritis (RA) being the most common; other types mainly involve arthritis linked to autoimmune diseases (Clark, 2023; Messina et al., 2023). Despite varying etiologies, these diseases are characterized by joint inflammation, resulting in pain and limited mobility (Messina et al., 2023). Presently, treatments for arthritis, both pharmacological and non-pharmacological, primarily address the progression of joint pain and the resolution of joint inflammation, especially with a common foundation in pain management (Marín et al., 2023). Osteoarthritis, a degenerative joint disease, is increasingly prevalent with the aging population (Gulati et al., 2023). According to the World Health Organization (WHO), there are over 400 million osteoarthritis patients globally (Minnig et al., 2024). In Asia, one in every six individuals is expected to develop OA at some stage (Minnig et al., 2024). Epidemiological investigations reveal that this growth is, in part, due to the rapid increase in the elderly and obese populations, resulting in a rise in osteoarthritis incidence (Wei et al., 2023; Scheuing et al., 2023; Perruccio et al., 2024). Rheumatoid arthritis (RA), characterized by primary synovial inflammation, is a chronic, disabling, autoimmune disease that can occur at any age, with a disability rate of up to 61.3% for a disease duration ≥1 year, significantly impacting patients' physical function and quality of life (Lau, 2023; Burmester and Pope, 2017). Apart from joint pain, swelling, and restricted mobility, 40% of patients may also experience extra-articular manifestations (EAMs), among which interstitial lung disease (ILD) is a common EAM in RA and a pivotal factor contributing to the high mortality rate associated with RA (Gravallese and Firestein, 2023). RA remains challenging to cure currently; nevertheless, standardized diagnostic and therapeutic interventions can achieve optimal treatment outcomes. However, without consistent treatment, it may lead to joint deformities and functional loss (Gravallese and Firestein, 2023). Other forms of arthritis are also linked to inflammation and pain, posing significant burdens on patients, yet effective treatments addressing the root causes are still lacking.

Currently, the primary objective of arthritis treatment is to alleviate joint pain caused by arthritis inflammation, daily joint wear and tear, and muscle strains (Juma et al., 2023). Existing medications for managing arthritis encompass analgesics, steroids, non-steroidal anti-inflammatory drugs (NSAIDs), and biologic/targeted therapies aimed at alleviating severe pain and inflammation symptoms (Harmalkar et al., 2024). However, these medications entail numerous side effects that hinder their sustained ability to mitigate disease symptoms and progression over prolonged use. For instance, NSAIDs are linked to severe gastrointestinal complications and inadequate pain relief post-treatment, while biologic/targeted therapies present risks of immune disruption and adverse cardiovascular events (Di Matteo et al., 2023; Mohapatra et al., 2023; Taylor, 2023). Consequently, the treatment landscape for arthritis has evolved towards comprehensive management and therapy, with alternative modalities gradually becoming integral components of this holistic approach to management and treatment (Brown et al., 2024; Sarzi-Puttini et al., 2023). Disease-modifying antirheumatic drugs (DMARDs) serve as principal therapeutics for RA, and the emergence of novel conventional synthetic DMARDs (csDMARDs) and biologic/targeted DMARDs (b/tsDMARDs) in recent years has heralded groundbreaking advancements in the treatment of RA and RA-ILD (Brown et al., 2024; Sarzi-Puttini et al., 2023).

Iguratimod (IGU), regarded as a new type of csDMARDs, exhibits a diverse mechanism of action with comprehensive immune-regulatory effects (Ito, 2016). Studies indicate that IGU can modulate the immune balance mediated by T cells and associated inflammatory factors by regulating the quantities of helper T cells (e.g., Th1 and Th17), follicular helper T (Tfh) cells, and regulatory T (Treg) cells. Additionally, IGU can inhibit the differentiation of B cells into plasma cells, thereby suppressing the production of autoantibodies (Liu et al., 2021). In recent years, massive randomized controlled trials have been published, so there is an urgent need to summarize the efficacy and safety of IGU in treating inflammatory arthritis. This study provides future clinicians with better evidence for clinical practice, and it also offers more details for future clinical trial design by conducting a comprehensive systematic review and meta-analysis of these RCTs.

2 Materials and methods

2.1 Protocol

This systematic review and meta-analysis were conducted strictly in accordance with the protocol registered in PROSPERO

(CRD42021289249) and PRISMA guidelines (see Supplementary Materials). There were not any significant deviations from the protocol.

2.2 Literature retrieval strategy

Chinese databases [VIP Database, China National Knowledge Infrastructure (CNKI), Wanfang Database and SINOMED] and English databases (Embase, PubMed, Medline Complete, Web of Science, Cochrane Library and ClinicalTrials.gov) were used for searching literature on IGU for the treatment of inflammatory arthritis. The retrieval period spans from the inception date to 1 February 2024. The search strategy is shown in Supplementary Table S1.

2.3 Search criteria

2.3.1 Inclusion criteria

1) Participants: Patients diagnosed with any type of inflammatory arthritis and degenerative arthritis by accepted criteria. 2) Intervention methods: The therapeutic approach in the experimental group involved the utilization of IGU, with unrestricted parameters in terms of dosage, formulation, and administration method. 3) Control: The therapeutic regimen in the control group encompassed interventions that did not include IGU, such as placebos and conventional therapies. 4) Outcomes: Disease-related therapeutic efficacy indicators, inflammation markers, and IGU-related adverse events. 5) Study design: randomized controlled trials (RCTs).

2.3.2 Exclusion criteria

1) Duplicate articles; 2) observational studies; 3) reviews, case reports, animal experiments, etc. ; 4) retracted articles.

2.4 Literature screening and data extraction

Initially, a preliminary literature search was conducted based on titles, abstracts, and keywords to select relevant literature initially. Subsequently, further literature inclusion was performed following established search criteria. Details regarding the study, including basic information, grouping methods, baseline conditions, treatment protocols, duration, and outcome measures, were extracted using predefined data extraction forms (Deeks et al., 2020a). Two researchers independently executed this process, with results cross-checked and any discrepancies resolved through discussion involving the entire team.

2.5 Risk of bias assessments

The quality assessment was conducted using the risk of bias assessment tools for RCTs recommended in the Cochrane Handbook (Deeks et al., 2020b). Each study was evaluated based on criteria, including random sequence generation, allocation concealment, blinding, attrition, and selective reporting risks. Two researchers independently performed bias risk assessments, with any inconsistencies resolved through discussion involving all researchers.

2.6 Data synthesis

Statistical analyses were performed using RevMan 5.4 software (Deeks et al., 2020c). Relative risk (RR) was utilized as the effect measure for dichotomous variables, while weighted mean difference (WMD) and standard mean difference (SMD) were employed for continuous variables. A 95% confidence interval (CI) was set for all analyses. Heterogeneity among results was assessed using the chi-square test, and if heterogeneity was minimal ($P > 0.1$, $I^2 < 50\%$), a fixed-effect model was employed for analysis; otherwise, a random-effects model was utilized.

3 Results

3.1 Literature search results

A total of 1,833 initial relevant articles were identified in this study, out of which 1,759 were excluded for mismeeting the research type and content criteria. Following a thorough review of the full texts, and based on the inclusion and exclusion criteria as well as the completeness of the literature information, 18 articles were excluded for not being RCTs (Gu et al., 2020; Guifeng and Yasong, 2014; He et al., 2015; Huang and Ma, 2018; Man and Yongxin, 2020; Lin, 2016; Luo et al., 2019; Luo et al., 2018; Meng et al., 2016a; Okamura et al., 2015; Shang et al., 2019; Suto et al., 2019; Wang et al., 2017; Wang et al., 2018; Wang, 2017; Xu et al., 2021; Yoshioka et al., 2016; Zhu et al., 2016). Consequently, 56 articles were included for quantitative and qualitative analysis (Li X. et al., 2021; Bai et al., 2021; Lin YP. et al., 2019; Xu BJ. et al., 2019; Zeng et al., 2016; Li Y. et al., 2021; Yuan et al., 2020; Pang et al., 2020; Zhang, 2022; Zeng et al., 2019; Zhang et al., 2023; Han et al., 2023; Wu et al., 2022; Lü et al., 2008; Hara et al., 2007; Mo and Ma, 2015; Xiong and Guanghui, 2020; Yan et al., 2022; Yi et al., 2022; Deng JX The effect of, 2017; Tian et al., 2020; Fan et al., 2020; Xie et al., 2018; Lianju et al., 2019; Zhao and Hao, 2018; Ma et al., 2019; Zhao et al., 2016; Meng et al., 2017; Xia et al., 2016; Lu, 2014; Qi et al., 2019; Zhao et al., 2017; Hu, 2014; Chen et al., 2018; Xia et al., 2020; Tian and Tao, 2017; Xu et al., 2017; Shi et al., 2015; Wang et al., 2019; Hara et al., 2014; Ishiguro et al., 2013; RAO et al., 2014; Xu et al., 2015; Bi, 2019; Sun and Li, 2022; Yan and Wang, 2018; Meng et al., 2016b; Duan et al., 2015; Xiaong et al., 2015; Lu et al., 2009; Ju et al., 2020; Meng et al., 2015; Li et al., 2016; Li and Huang, 2020; Mo et al., 2018; Shi et al., 2023). The literature screening process and results are shown in Figure 1.

3.2 Description of included trials

Two articles (Xia et al., 2016; Lu, 2014) originating from the same RCT were catalogued by Xia et al. (2016), Lu (2014). Similarly, two articles (Hara et al., 2014; Ishiguro et al., 2013) derived from the same RCT were documented by Hara et al. (2014), Ishiguro et al. (2013). Consequently, the 56 records pertain to 54 RCTs. In some randomized controlled trials with two experimental groups, the control group was divided into two equal portions to match them, each representing half of the population and labelled as Group A and Group B. Detailed characteristics of the studies are presented in Supplementary Information, Supplementary Table S2.

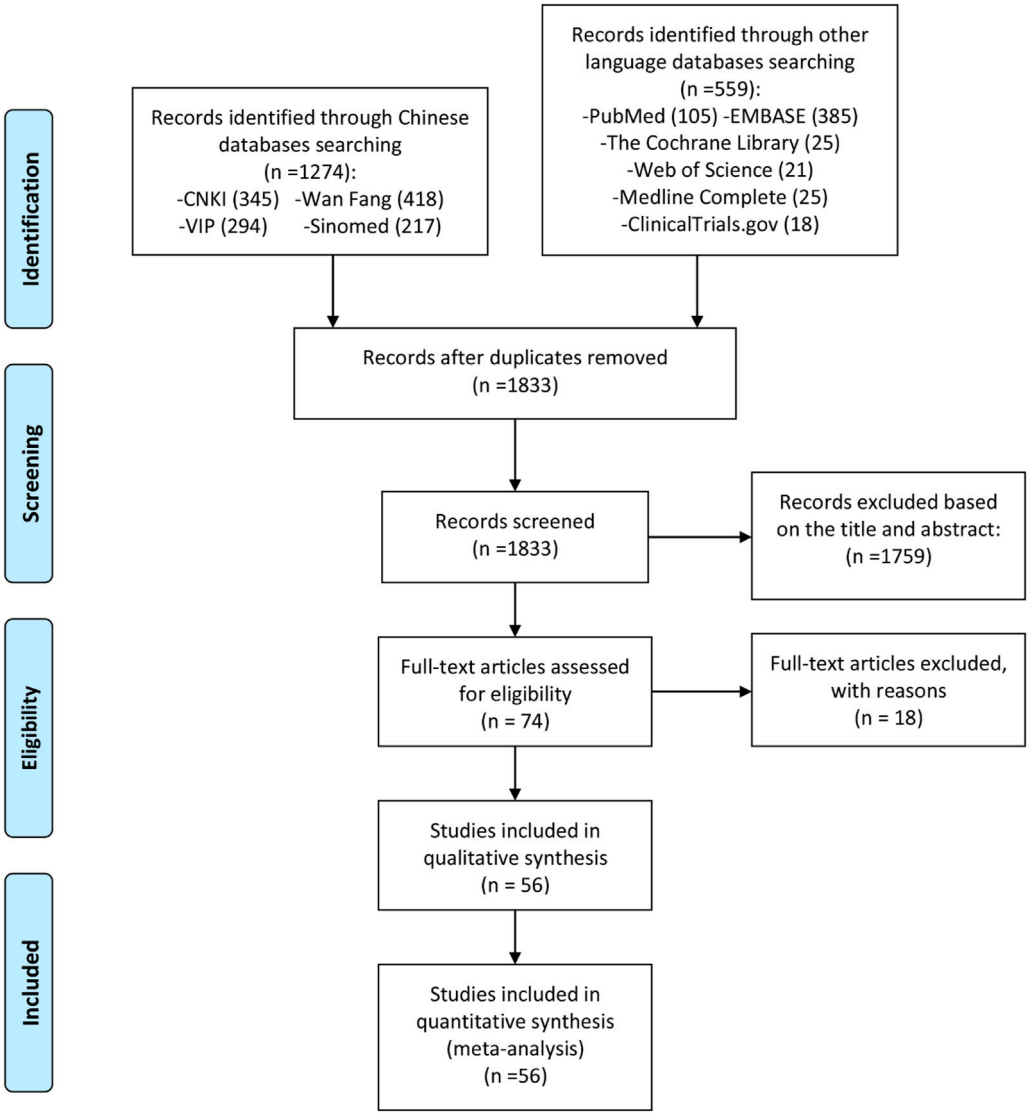

FIGURE 1
Flowchart of clinical literature searching and results screening.

3.3 Risk of bias assessments

The graph and summary of bias risk are shown in Figures 2, 3, respectively.

3.4 The outcomes of IGU in the treatment of AS

3.4.1 The bath ankylosing spondylitis disease activity index (BASDAI)

There are seven RCTs reporting BASDAI in their publication. The included studies showed high heterogeneity; thus, a random effects model was utilized. The IGU groups showed significantly lower BASDAI scores compared to the control groups (SMD −1.68 [−2.32, −1.03], $P < 0.00001$, Figure 4).

3.4.2 Bath ankylosing spondylitis functional index (BASFI)

Four RCTs reported BASFI in their manuscripts. The heterogeneity test showed low heterogeneity, a fixed effects model was used. The IGU group had a significantly lower BASFI score compared to the control group (WMD −1.29 [−1.47, −1.11], $P < 0.00001$) (Figure 5).

3.4.3 Inflammatory factor

The inflammatory factors focused on in this part of the study include erythrocyte sedimentation rates (ESRs), C-reactive protein (CRP) levels, and tumor necrosis factor- α (TNF-α) levels. Here, six RCTs reported ESRs. High heterogeneity was observed, and a random effects model was used. The IGU group had significantly lower ESRs compared to the control group (WMD −10.33 [−14.96, −5.70], $P < 0.0001$, Figure 6).

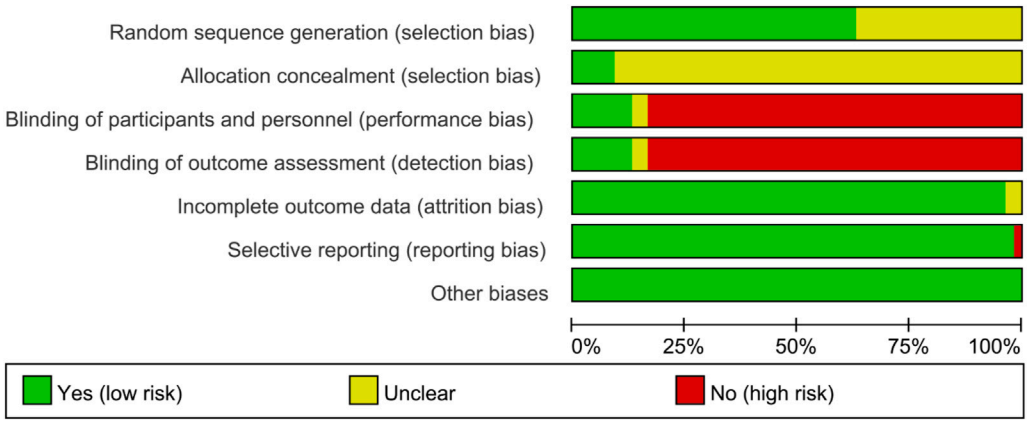

FIGURE 2
Risk of bias graph.

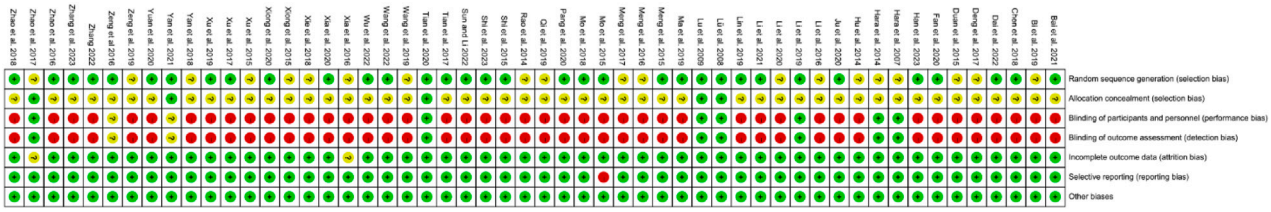

FIGURE 3
Risk of bias summary.

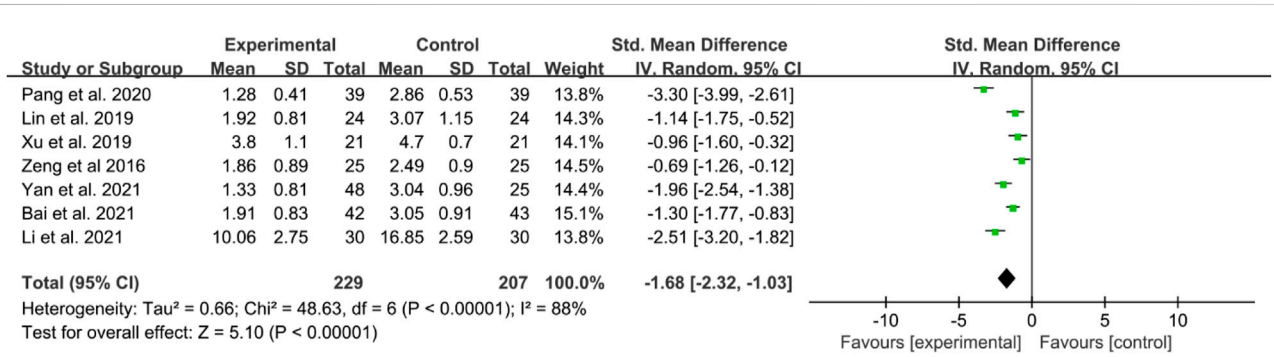

FIGURE 4
The results of BASDAI.

Seven RCTs reported CRP levels. The heterogeneity test indicated high heterogeneity, thus, a random effects model was utilized. The results demonstrated that IGU significantly decreased CRP levels compared to the control group (WMD −10.11 [−14.55, −5.66], $P < 0.00001$, Figure 7).

Four RCTs reported TNF-α levels. Significant heterogeneity was detected, and a random effects model was applied. The results indicated that TNF-α levels were significantly lower in the IGU group compared to the control group (WMD −6.22 [−7.97, −4.47], $P < 0.00001$, Figure 8).

3.4.4 Adverse events

Eight RCTs reported adverse events. In these RCTs, Bai et al. reported that the main adverse events were rash, abnormal liver function, and gastrointestinal reactions in 2021 (Bai et al., 2021). Lin et al. also found that in the IGU group, two cases of upper abdominal discomfort and one case of oral ulcers were observed; in contrast, the control group experienced three cases of upper abdominal discomfort, five cases of liver function abnormalities, two cases of oral ulcers, two cases of anemia, and one case of leukopenia; some patients in both groups experienced two or more adverse reactions

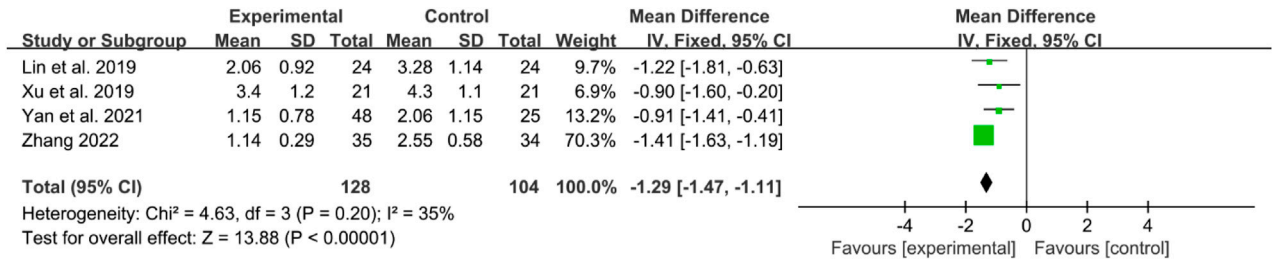

FIGURE 5
The results of BASFI.

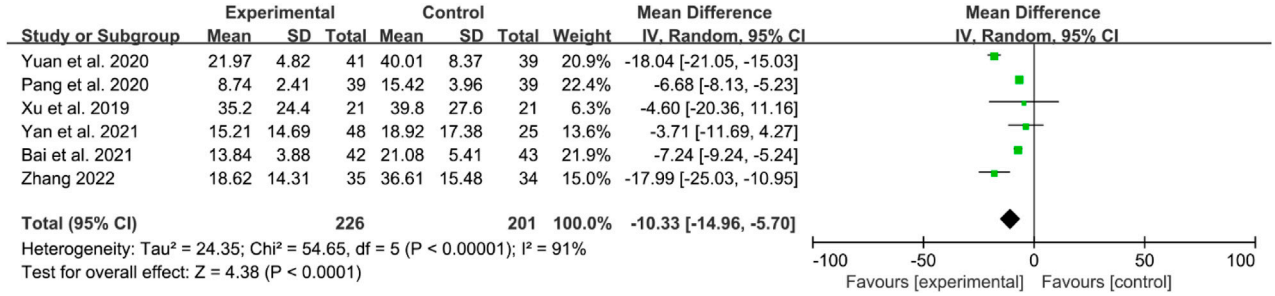

FIGURE 6
The results of ESRs.

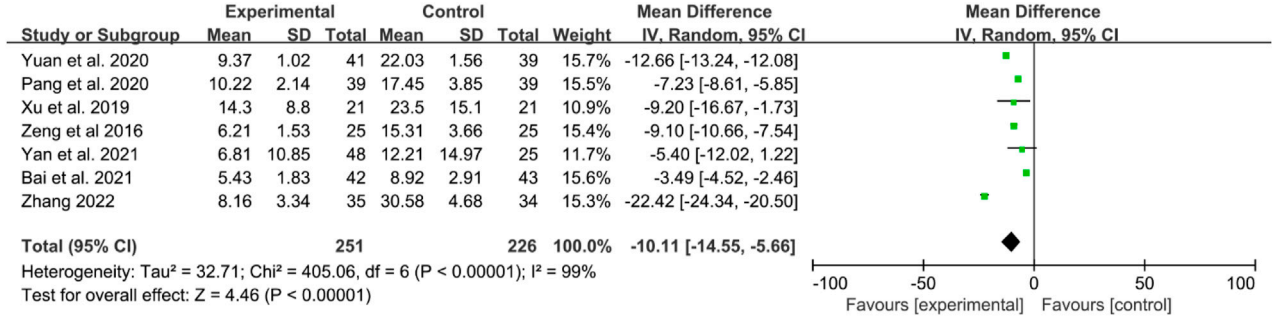

FIGURE 7
The results of CRP.

(Lin Y. P. et al., 2019). Xu et al. reported gastrointestinal discomfort and liver function abnormalities as adverse effects (Xu B. J. et al., 2019), and Zeng et al. mainly presented gastrointestinal reactions, leukopenia, and abnormal liver function (Zeng et al., 2016). Yan et al. primarily reported gastrointestinal discomfort (Li Y. et al., 2021), while Yuan et al. showed leukopenia, oral ulcers, nausea and vomiting, diarrhea, and abnormal liver function (Yuan et al., 2020). Pang et al. briefly reported gastrointestinal reactions, abnormal liver function and rash (Pang et al., 2020). Zhang mainly showed abnormal liver and kidney function, decreased leukocytosis, and gastrointestinal discomfort (Zhang, 2022).

The incidence rates of these adverse events were combined for meta-analysis. The heterogeneity test indicated low heterogeneity, suggesting that a fixed effects model was appropriate for analysis. The meta-analysis indicated that the incidence of adverse events in the IGU group was lower [RR 0.63 (0.24, 0.96), P = 0.03, Figure 9].

3.5 The outcomes of IGU in the treatment of OA

3.5.1 Visual analog scale (VAS)

Two RCTs reported the VAS scores of OA. The heterogeneity test indicated low heterogeneity, suggesting that a fixed effects model was appropriate for analysis. The meta-analysis revealed that the

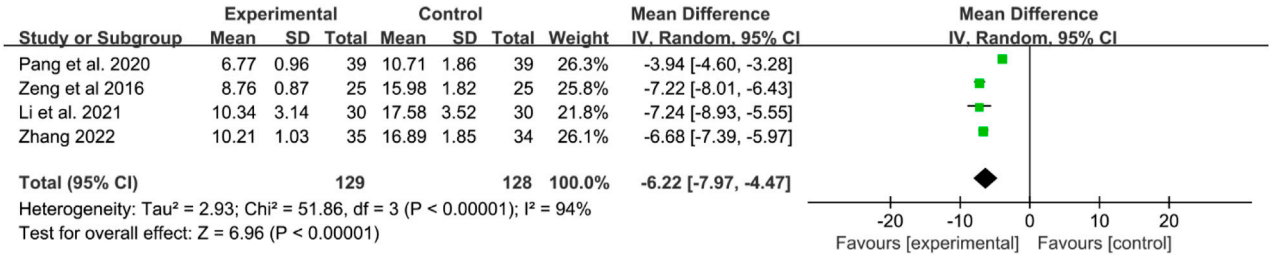

FIGURE 8
The results of TNF-α

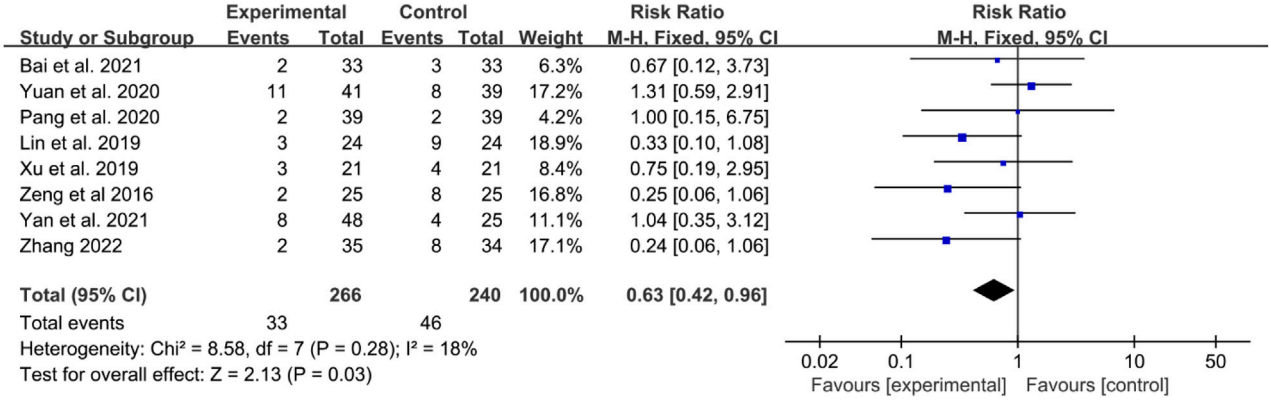

FIGURE 9
Adverse events.

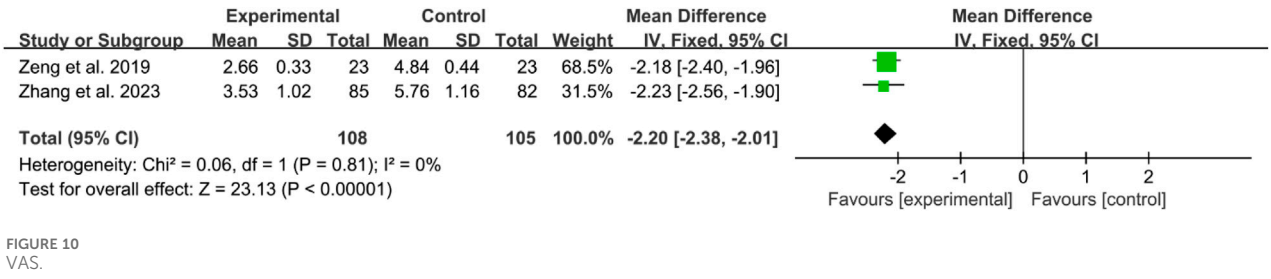

FIGURE 10
VAS.

VAS in IGU group was lower (WMD −2.20 [−2.38, −2.01], $p < 0.00001$, Figure 10).

3.5.2 The Western Ontario and McMaster universities osteoarthritis index (WOMAC)

Two RCTs reported WOMAC. The heterogeneity test indicated high heterogeneity, suggesting that a random effects model was appropriate for analysis. The meta-analysis indicated that the WOMAC in the IGU group was lower (WMD −7.27 [−12.31, −2.24], $P = 0.005$, Figure 11).

3.5.3 Inflammation factors

The inflammatory factors in this part of the study include TNF-α and interleukin (IL)-6.

Two RCTs reported TNF-α. The heterogeneity test indicated high heterogeneity, suggesting that a random effects model was appropriate for analysis. The meta-analysis indicated that the difference in TNF-α between the two groups was of no statistical significance (WMD −9.21 [−20.89, 2.47], $P = 0.12$, Figure 12).

Two RCTs reported IL-6. The heterogeneity test indicated high heterogeneity, suggesting that a random effects model was

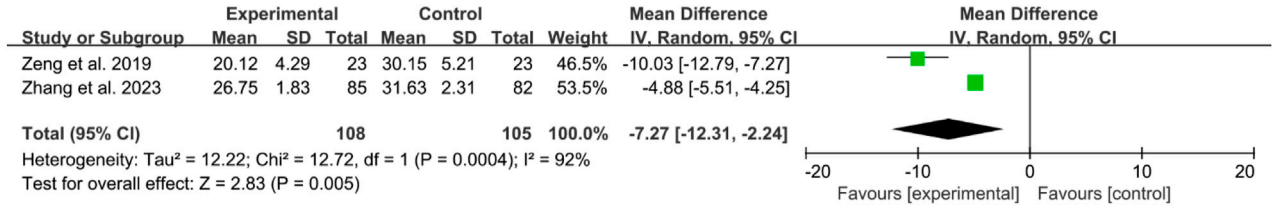

FIGURE 11
WOMAC.

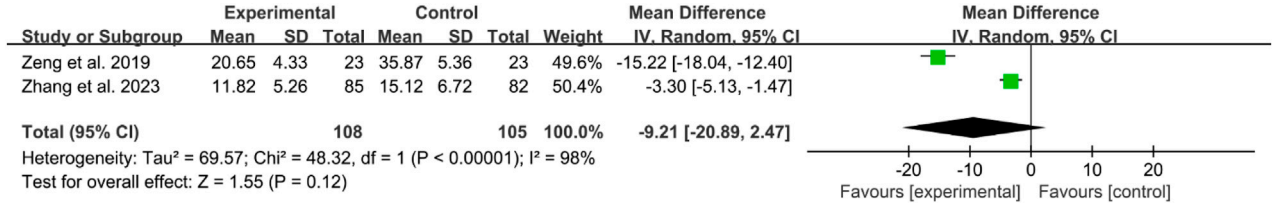

FIGURE 12
TNF-α.

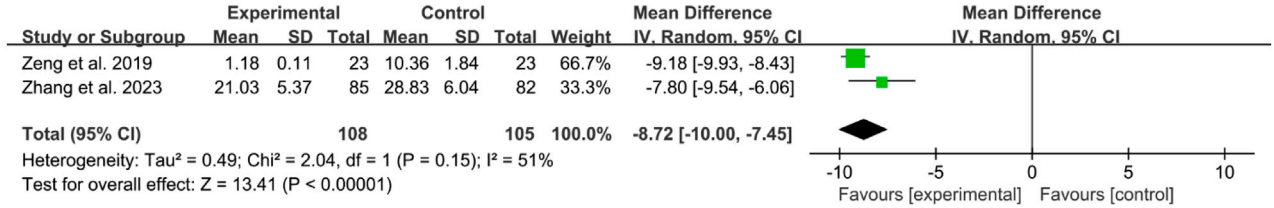

FIGURE 13
IL-6.

appropriate for analysis. The meta-analysis indicated that the WOMAC in IGU group was lower (WMD −8.72 [−10.00, −7.45], $P < 0.00001$, Figure 13).

3.5.4 Adverse events

In the RCT conducted by Zeng et al. in 2019, the IGU group exhibited 1 case of mild abdominal discomfort post-treatment. In contrast, the control group experienced 1 case of gastrointestinal reaction and 1 case of rash (Zeng et al., 2019). In the study by Zhang et al. (2023), it was discovered that both groups of patients did not experience any drug-related adverse reactions, indicating that the medication is relatively safe.

3.6 The outcomes of IGU in the treatment of RA

3.6.1 RA remission rate

American College of Rheumatology (ACR)20, ACR50 and ACR70 were used to represent RA remission rate.

For ACR20, the heterogeneity test indicated high heterogeneity, suggesting that a random effects model was appropriate for analysis. The meta-analysis findings indicate that the ACR20 in the IGU group is higher than the control group (RR 1.18 [1.02, 1.35], $P = 0.02$, Figure 14).

For ACR50, the heterogeneity test indicated high heterogeneity, suggesting that a random effects model was appropriate for analysis. The meta-analysis findings indicate that the ACR50 in the IGU group is higher than the control group (RR 1.32 [1.05, 1.64], $P = 0.02$, Figure 15).

For ACR70, the heterogeneity test indicated high heterogeneity, suggesting that a random effects model was appropriate for analysis. The meta-analysis findings indicate that the ACR70 in the IGU group is higher than the control group (RR 1.44 [1.02, 2.04], $P = 0.04$, Figure 16).

3.6.2 Disease activity score 28 (DAS28)

Twenty-four RCTs reported DAS28. The heterogeneity test indicated high heterogeneity, suggesting that a random effects model was appropriate for analysis. The meta-analysis findings

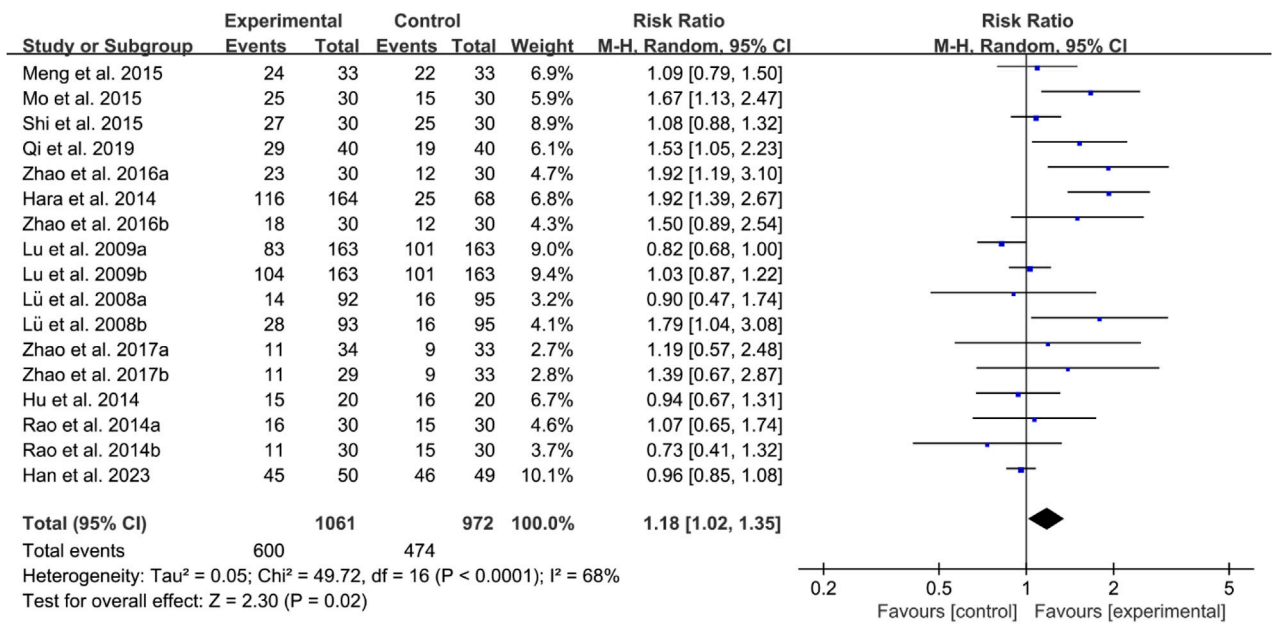

FIGURE 14
ACR20.

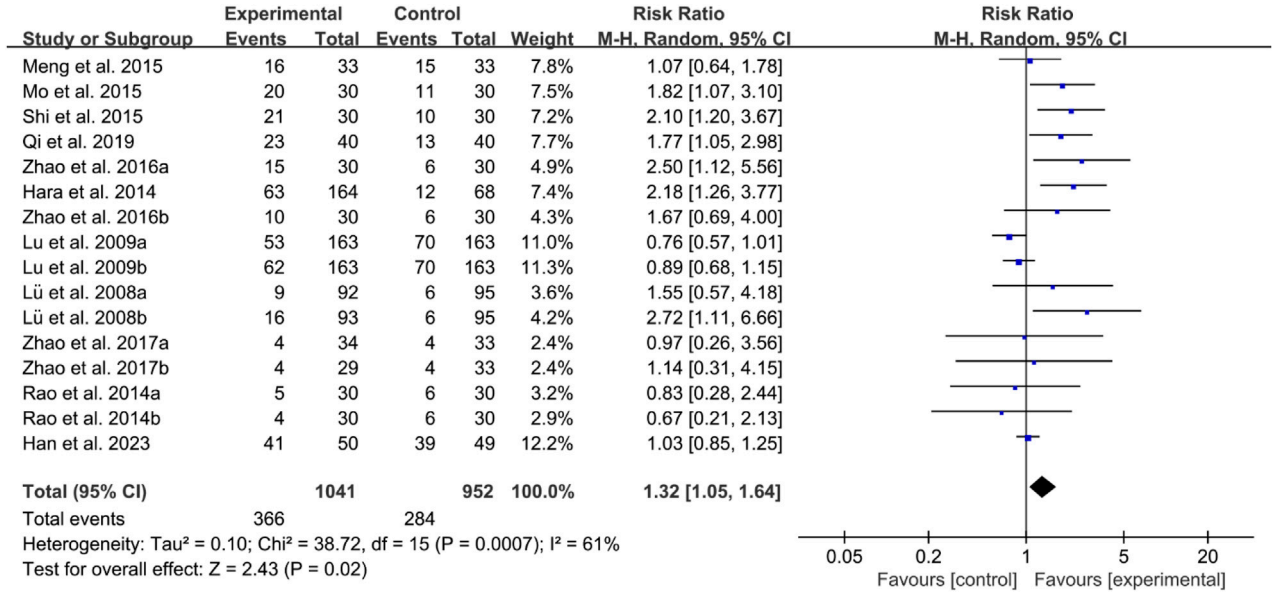

FIGURE 15
ACR50.

indicate that the DAS28 in IGU group is lower than control group (WMD −0.92 [−1.20, −0.63], $P < 0.00001$, Figure 17).

3.6.3 Inflammatory factor

Inflammatory factors focused in this section include CRP, ESR and rheumatoid factor (RF).

For CRP, the heterogeneity test indicated high heterogeneity, suggesting that a random effects model was appropriate for analysis. The meta-analysis findings indicate that the CRP in the IGU group is higher than the control group (SMD −1.36 [−1.75, −0.96], $P < 0.00001$, Figure 18).

For ESR, the heterogeneity test indicated high heterogeneity, suggesting that a random effects model was appropriate for analysis. The meta-analysis findings indicate that the ESR in the IGU group is higher than the control group (WMD −9.09 [−11.80, −6.38], $P < 0.00001$, Figure 19).

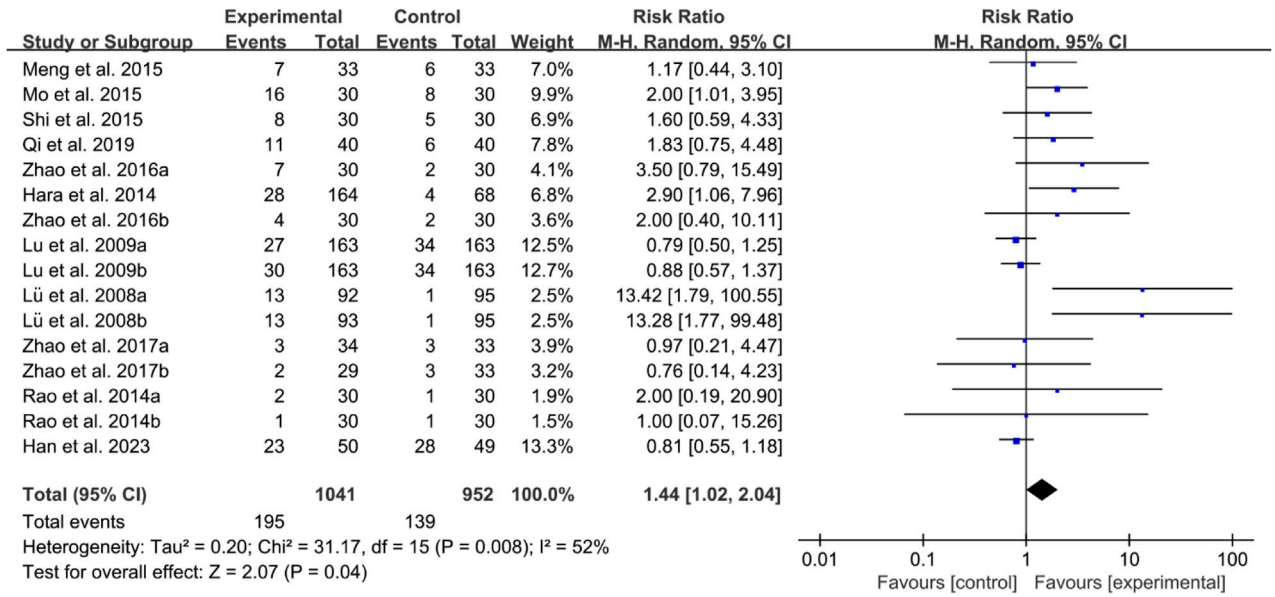

FIGURE 16
ACR70.

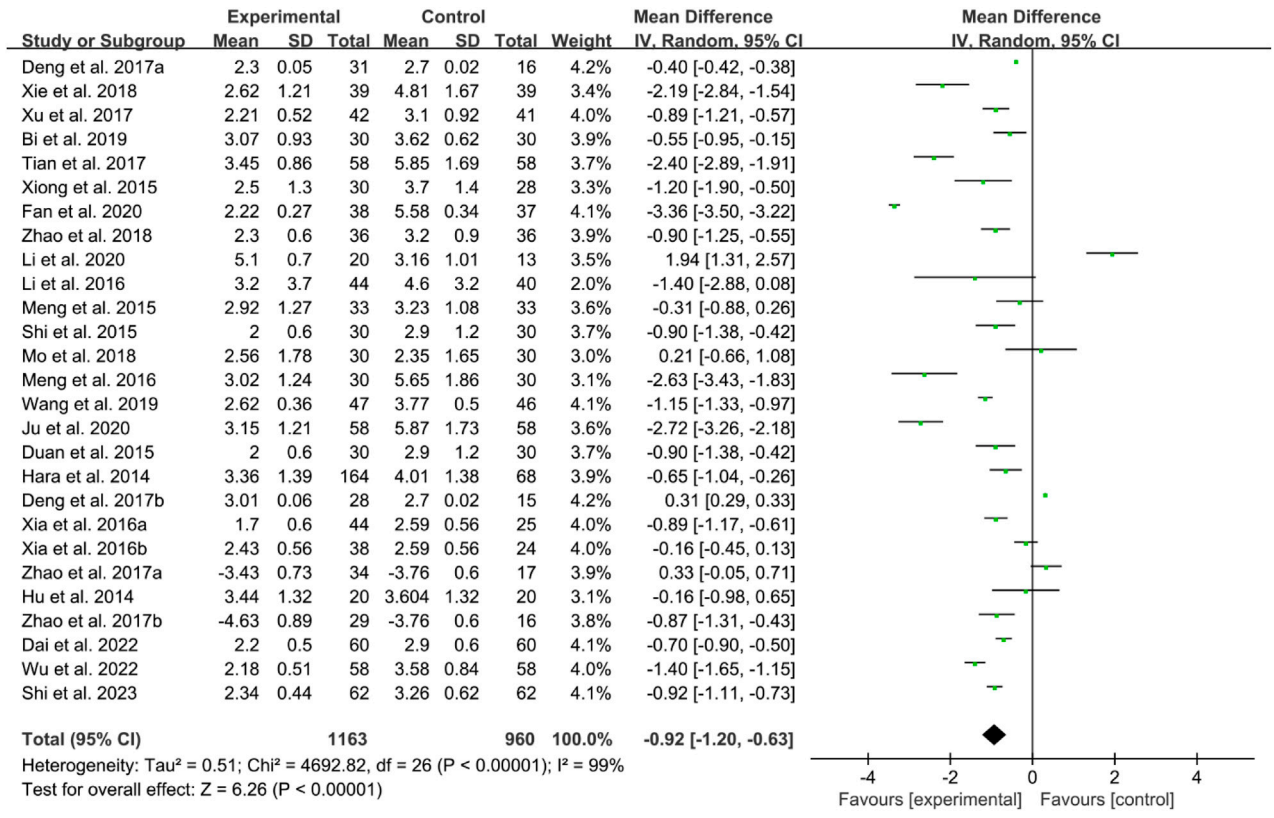

FIGURE 17
DAS28.

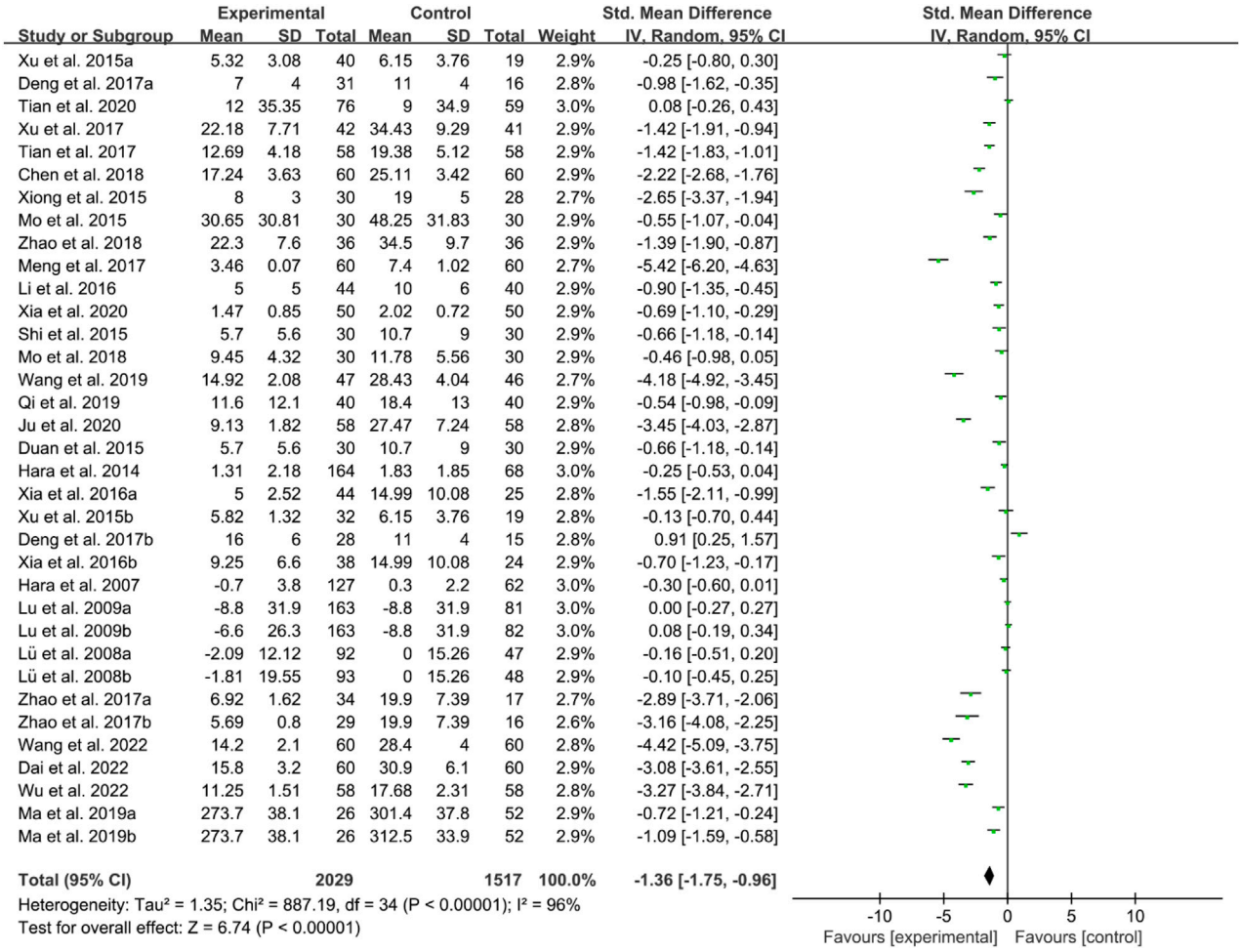

FIGURE 18
CRP.

For RF, the heterogeneity test indicated high heterogeneity, suggesting that a random effects model was appropriate for analysis. The meta-analysis findings indicate that the RF in the IGU group is higher than the control group (SMD −1.21 [−1.69, −0.73], $P < 0.00001$, Figure 20).

3.6.4 Adverse events

Thirty-five RCTs reported adverse events. The heterogeneity test indicated low heterogeneity with $P < 0.0001$ and $I^2 = 51\%$, suggesting that a fixed effects model was appropriate for analysis. The meta-analysis showed that the incidence of adverse events between the two groups was of no statistical significance (RR 1.06 [0.92, 1.23], $P = 0.40$, Figure 21).

4 Discussion

4.1 The molecular mechanism of IGU in treating inflammatory arthritis

IGU is a novel DMARD that offers anti-inflammatory, antifibrotic, anti-resorptive, immunomodulatory, and bone metabolism-regulating effects (Shen et al., 2024; Zeng et al., 2023; Zou et al., 2023). As research on IGU has advanced in recent years, its therapeutic applications have broadened. Current evidence indicates that IGU provides significant immunomodulatory benefits and comprehensive bone protection, balancing efficacy and safety, making it well-suited for combination therapy and long-term maintenance in the treatment of rheumatoid arthritis (Hu et al., 2024; Sun et al., 2023; Long et al., 2023). Compared to traditional DMARDs, IGU has been shown to reduce rheumatoid factor significantly and anti-CCP antibody levels, effectively preventing bone destruction and reducing the risk of disability and deformity associated with arthritis (Hu et al., 2024; Sun et al., 2023; Long et al., 2023).

Regarding its anti-inflammatory effect, IGU exerts its anti-inflammatory effects by inhibiting the proliferation of inflammatory cells and reducing the release of pro-inflammatory cytokines, thereby mediating key anti-inflammatory signaling pathways (Figure 22). Specifically, IGU at lower concentrations primarily inhibits the migration of fibroblast-like synoviocytes (FLS), with higher concentrations leading to the suppression of FLS proliferation and even inducing apoptosis. In animal models of RA, OA and AS, IGU significantly reduces the expression of pro-

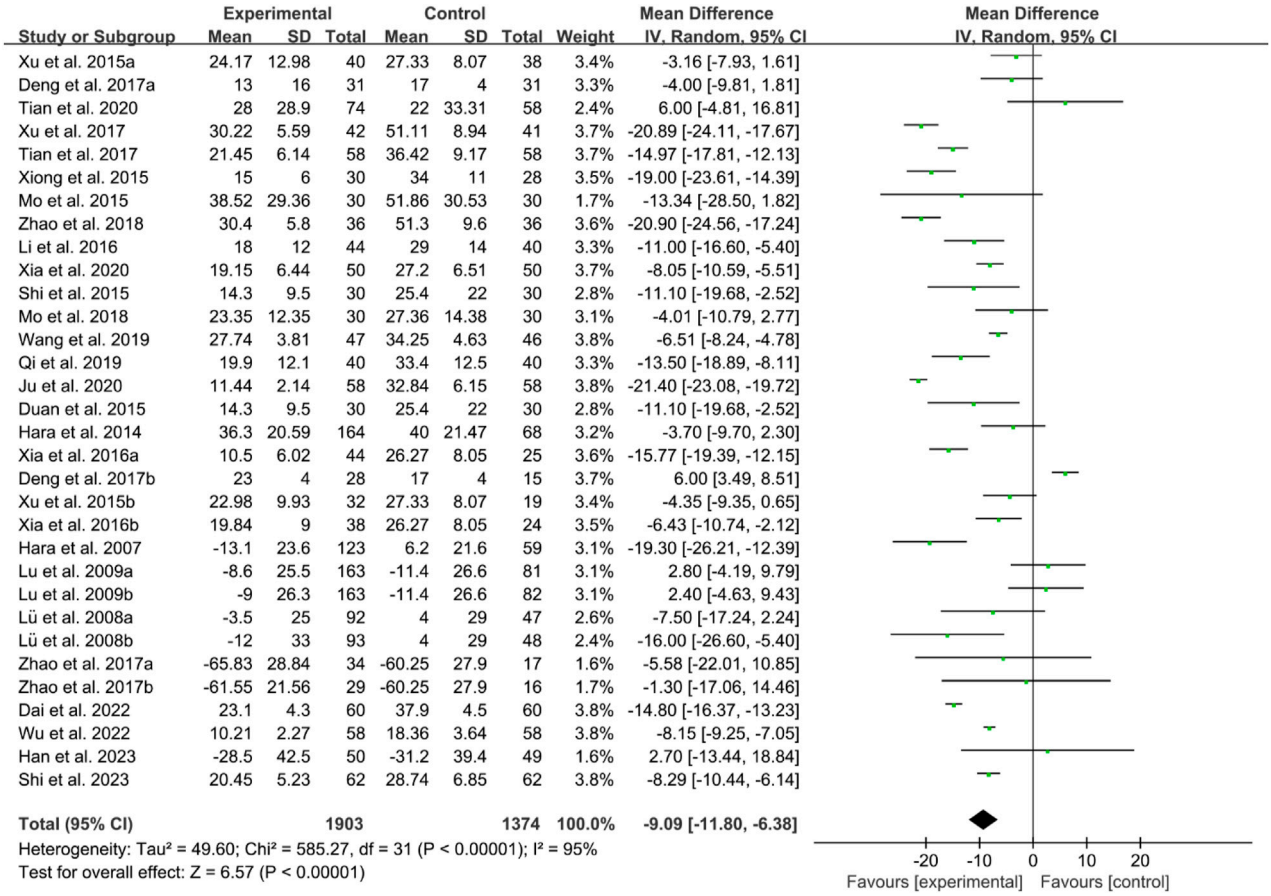

FIGURE 19
ESR.

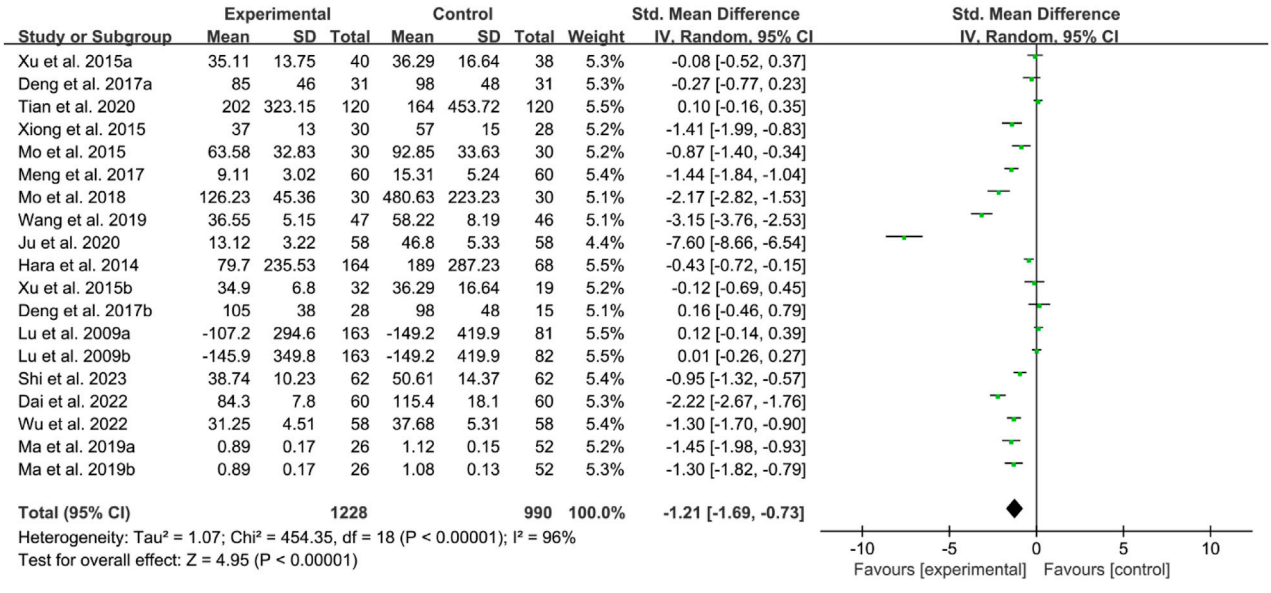

FIGURE 20
RF.

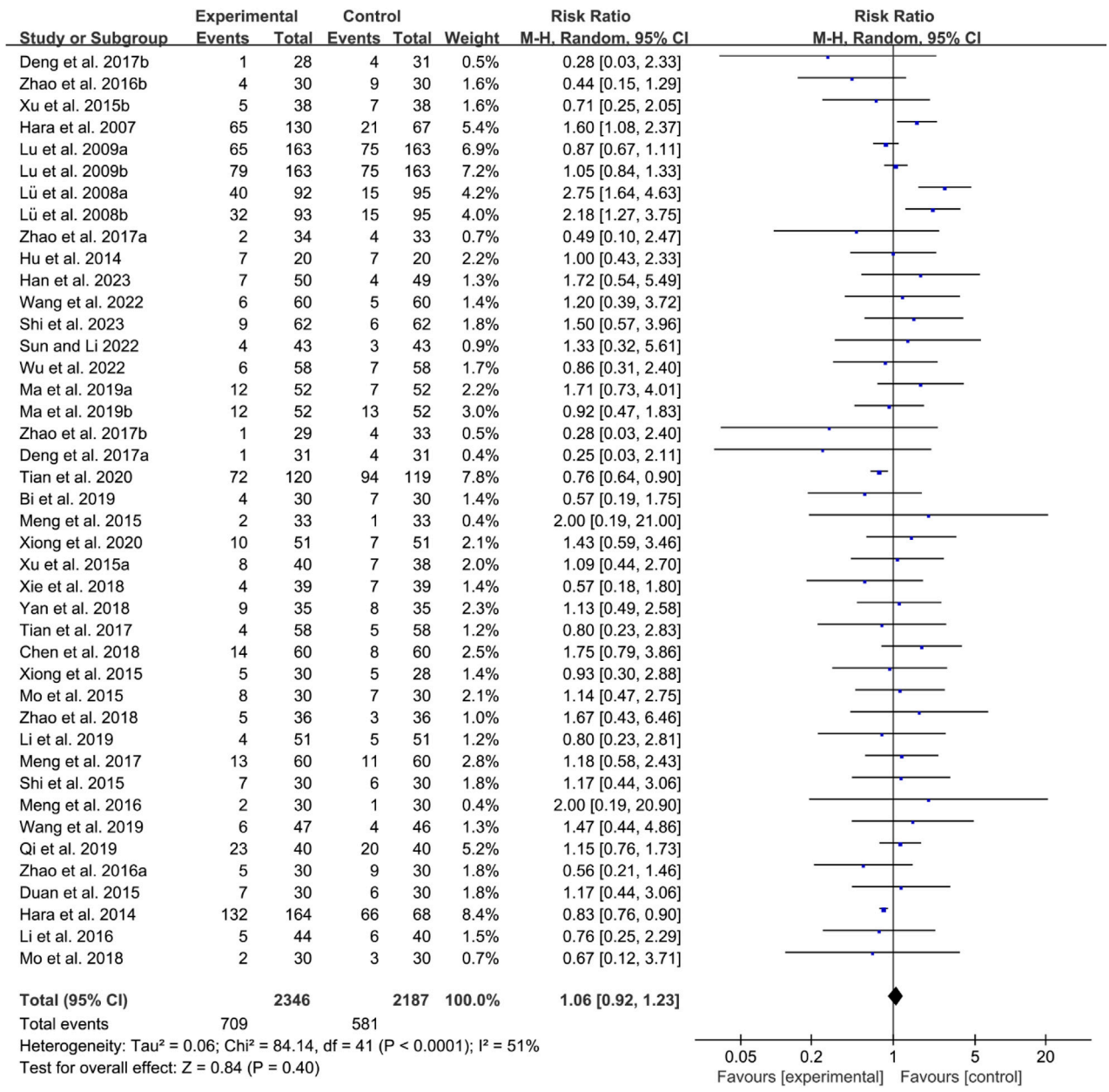

FIGURE 21
Adverse events for RA.

inflammatory cytokines while increasing the expression of anti-inflammatory cytokines. This dual modulation reduces the infiltration of inflammatory cells in the bloodstream and affected tissues, enhancing its anti-inflammatory effect. In addition, IGU protects against inflammatory arthritis by activating the nuclear factor-κB (NF-κB) signaling pathway and downregulating sodium bicarbonate cotransporter e2 (NBCe2) in RA patients to inhibit protein citrullination and inflammation. In both acute and chronic inflammation models, such as carrageenan-induced paw edema and adjuvant-induced arthritis in rats, IGU demonstrated anti-inflammatory and analgesic effects. Unlike traditional NSAIDs, IGU does not cause gastrointestinal ulcer-like side effects in fasting rats and can inhibit kininogen in kaolin-induced inflammatory responses (Peng et al., 2024). IGU significantly reduces IgM production in mouse B cell cultures and promotes the switch to IgG1 under lipopolysaccharide and/or IL-4 induction (Chen et al., 2023; Nozaki, 2021). In human multiple myeloma cell cultures (ARH-77 cell line), IGU inhibits spontaneous IgG antibody production without affecting cell proliferation, and in human peripheral blood B cells induced by autologous T cells and anti-CD3 antibodies, IGU suppresses the production of both IgM and IgG, effectively inhibiting immunoglobulin production in B cells without causing blockage (Zeng et al., 2022a).

A study found that in chronic rheumatoid arthritis models, such as adjuvant-induced arthritis (AIA) rats and Murphy Roths large lymphoproliferation (MRL/lpr) mice, IGU not only improved

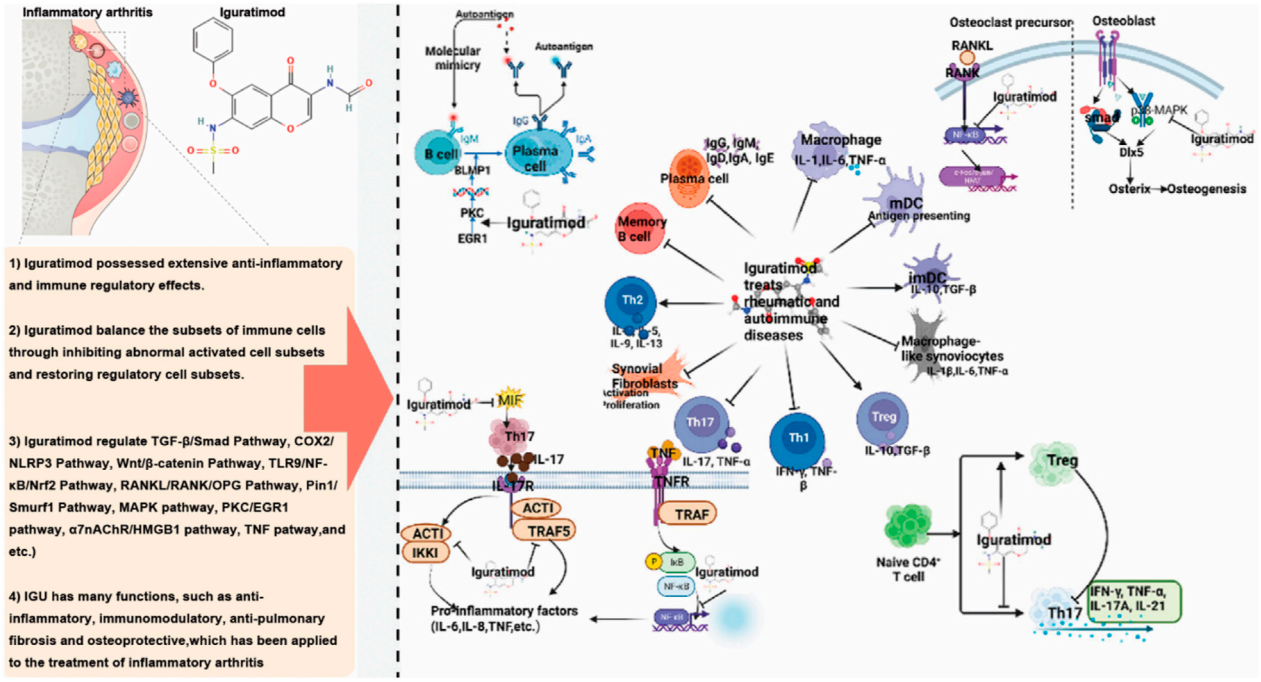

FIGURE 22
The molecular mechanism of IGU in treating inflammatory arthritis.

arthritis lesions but also reduced hypergammaglobulinemia (Jiang et al., 2020). Regarding cytokine inhibition, IGU suppressed the production of IL-1β, TNF-α, IL-6, IL-8, and monocyte chemoattractant protein (MCP)-1. In synovial cell cultures derived from patients with rheumatic diseases, IGU significantly reduced the production of IL-6, IL-8, and colony-stimulating factors. Additionally, IGU inhibited the upregulation of costimulatory molecules, including CD54, CD58, and CD106, in synovial cells stimulated by IFN-γ. In a mouse model of subcutaneous air pouch inflammation, oral administration of IGU at doses of 30–100 mg/kg significantly suppressed TNFα-induced MCP-1 production (Jiang et al., 2020; Li et al., 2019). Pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α play a crucial role in bone resorption and are key pathological factors in RA, closely associated with disease activity (Xie et al., 2020). These cytokines activate osteoclasts, increasing bone resorption and subsequent loss. Inhibiting IL-1, IL-6, and TNF-α can effectively control RA and prevent related bone degradation. MRI results in the collagen-induced arthritis (CIA) rat model showed that IGU nearly completely suppressed inflammation and bone marrow edema associated with CIA. X-ray and CT scans revealed significant inhibition of bone resorption and joint destruction in rats treated with IGU (Zeng et al., 2022b).

IGU also plays a significant role in promoting bone formation and regulating bone metabolism. *In vitro* studies have shown that IGU enhances osteoblast differentiation. At the same time, *in vivo* experiments demonstrate its ability to augment bone morphogenetic protein (BMP)-2-mediated bone formation, which is believed to be associated with increased Osterix (Osx) expression. Osx is crucial for bone differentiation and formation (Sun et al., 2023). Recent research has revealed that IGU improves disuse osteoporosis in mice by inhibiting sclerostin and the receptor activator of NF-κB ligand (RANKL) through the extracellular signal-regulated kinase/early growth response protein 1/TNF-α pathway in osteocytes (Miura et al., 2024). In the ST2 bone marrow stromal cell line, Osx expression is minimal in the absence of recombinant human BMP (rhBMP)-2, but IGU can stimulate Osx expression by more than threefold when rhBMP-2 is present. In the pre-osteoblast cell line MC3T3-E1, IGU directly stimulates Osx expression, independent of rhBMP-2, thereby promoting osteoblast differentiation. Further studies have shown that IGU dose-dependently stimulates the secretion of osteocalcin in both ST2 and MC3T3-E1 cells; in the presence of rhBMP-2, IGU increases calcium content in ST2 cells by 14-fold, leading to the formation of mineralized nodules. In mouse models, IGU increased calcium content in the ossicles by 1.7-fold (Hou et al., 2021).

4.2 IGU in the treatment of AS

AS is a chronic inflammatory disease that affects the spine and joints, and its pathogenesis is still not entirely understood. Current understanding suggests that AS results from interactions among genes, microbes, and other factors, leading to an imbalance where osteogenesis by osteoblasts surpasses bone resorption by osteoclasts, ultimately culminating in joint ankylosis (Rodolfi et al., 2024). Throughout the inflammatory process of AS, cellular factors like TNF-α and IL-1 play pivotal roles (Liu et al., 2023). Current guidelines for AS treatment still recommend the use of NSAIDs and TNF antagonists, while drugs like sulfasalazine (SSZ) and methotrexate (MTX) are recommended for those with peripheral joint involvement (Mysler et al., 2024; van de Sande and Elewaut,

2023). Studies have shown that IGU can inhibit the production of inflammatory cytokines such as interleukin-1 (IL-1), IL-6, IL-17, and TNF-α. Here, TNF-α is a crucial inflammatory factor in the pathogenesis of AS, and the IL-23/IL-17 pathway has been proven to be important in the mechanism underlying AS (Li et al., 2020; Ishikawa and Ishikawa, 2019; Macleod et al., 2023). Consequently, in recent years, multiple studies have been progressively examining the efficacy of IGU in treating AS.

This systematic review and meta-analysis showed that IGU can reduce disease activity (reduce BASDAI and BASFI) and improve patients' inflammatory response (reduce ESR, CRP and TNF-α) in patients with AS. In terms of safety, compared with the control group, the incidence of adverse events with the addition of IGU was lower. However, given the high risk of bias in blinding and the unknown risks associated with allocation concealment and random sequence generation in most RCTs, the stability of the conclusions may be compromised. Therefore, the findings should be interpreted with caution.

4.3 IGU in the treatment of OA

OA is a disease that affects all joints. The increasing prevalence of OA is attributed to the accelerated aging of the population, escalating rates of obesity, and subsequent joint injuries (Knights et al., 2023; Kim, 2022). Furthermore, recent studies indicate a trend towards a younger age of onset for OA. In the early stages of OA, the primary manifestation is joint pain during activity, with relief experienced at rest. As the disease progresses, continuous pain may develop, potentially leading to joint deformity, impairing joint function, and, in severe cases, resulting in disability (Zhou et al., 2024). Research has confirmed that IGU can inhibit the production of inflammatory factors such as IL-17, TNF-α, and IL-6, exhibiting anti-inflammatory effects, while simultaneously acting as an NSAID. The mechanism of action of this drug aligns closely with the therapeutic goals of treating OA (Horváth et al., 2023). It has been found that IGU has clear chondroprotective effects in rheumatoid arthritis currently (Cong et al., 2021), and new research similarly suggests that IGU assists in protecting cartilage in OA (Xu B. et al., 2019; Xu et al., 2023). Studies have shown that in rats with IGU administered orally, there is an increase in the expression of transient receptor potential cation channel subfamily V member 4 (TRPV4) in cartilage, resulting in significant pain reduction and notable inhibition of cartilage destruction. Following *in vitro* experiments involving the cultivation of cartilage cells post-IGU intervention, it is observed that in rats receiving IGU treatment, the differentiation, activity, and migratory capabilities of rat cartilage cells are significantly enhanced. Hence, based on preliminary results, IGU appears to delay cartilage degradation and promote differentiation and migration, possibly acting through the TRPV4 ion channel (Xu et al., 2023).

This systematic review and meta-analysis showed that IGU can reduce pain caused by OA (reduce VAS and WOMAC) and improve patients' inflammatory response (reduce IL-6). Regarding safety, adding IGU does not increase the incidence of adverse events. However, as the number of RCTs was only two and there was a high risk of bias in blinding and an unknown risk of bias in allocation concealment, the conclusions need to be interpreted with caution.

4.4 IGU in the treatment of RA

RA is an autoimmune disease primarily characterized by symmetrical damage to small joints. Research indicates that IGU can selectively inhibit cyclooxygenase-2 (COX-2) and NF-κB to alleviate inflammatory responses, particularly in cases of primary or secondary drug resistance in RA (Deng et al., 2022). IGU primarily functions by suppressing inflammatory cytokines to inhibit the occurrence and progression of synovitis. Recent studies demonstrate that IGU can effectively restrain the proliferation of RA-FLS. Wang et al. substantiated that IGU can selectively repress the expression of COX-2 mRNA and c-fos mRNA, subsequently inhibiting RA-FLS proliferation, with the inhibitory effects conforming to a dose-response relationship (WANG and SHEN, 2015). Du et al. revealed that IGU decreases the expression of matrix metalloproteinase (MMP)-1 and MMP-3, thereby suppressing excessive proliferation of FLS (Du et al., 2012). Additionally, Meng et al. demonstrated that IGU reduces vascular endothelial growth factor release, enhances endothelin production, and reduces synovial vascular neogenesis consequently (Meng D. Z. et al., 2016).

Lin J. et al. (2019) showed that through cell migration experiments, IGU significantly inhibits the invasive behavior of RA-FLS via the mitogen-activated protein kinase (MAPK) signaling pathway and promotes apoptosis. Pathological changes in bone loss in RA joints are closely associated with the activation of pro-inflammatory factors leading to osteoclast activation and bone resorption. Osteoprotegerin (OPG) competes with the receptor activator of NF-κB ligand (RANKL) for binding to the activator of NF-κB receptor (RANK). Clinical studies illustrate that IGU can lower serum IL-17 levels to attenuate the expression of inflammatory factors like IL-9 and IL-8, reduce RANKL levels, and directly modulate the OPG/RANKL/RANK axis system, consequently delaying bone destruction. Combining with MTX can significantly increase OPG levels, yielding better therapeutic outcomes (Luo et al., 2013). Feng et al. indicated that IGU plays a pivotal role in inhibiting the expression of genes essential for osteoclast differentiation and activation, such as RANK, acidic phosphatase, tissue protease K, and MMP-1, thereby inhibiting osteoclast proliferation and differentiation, and showing a dose-dependent relationship with efficacy (Feng et al., 2019). Positive anti-citrullinated protein antibody status is closely associated with bone loss in RA, and IGU can dose-dependently downregulate peptidyl arginine deiminase (PADI) 2 and PADI4 in neutrophils, thereby suppressing protein citrullination and alleviating bone loss (Li et al., 2020).

MTX serves as an anchor drug for treating RA and is commonly used in combination with IGU. A meta-analysis by Shrestha et al. suggested that at 24 weeks, the therapeutic effects, disease status, and adverse reactions exhibited by IGU and MTX are similar, indicating the potential of IGU as a substitute for MTX (Shrestha et al., 2020). Additionally, another meta-analysis by Wu et al. revealed that the combination of IGU and MTX in the treatment of RA leads to superior efficacy in increasing ACR20/50/70 response rates, reducing ESR, CRP, assessing the activity of 28 joint diseases, and VAS scores compared to individual use, without a significant increase in adverse reactions (Wu et al., 2018). A study by Ren et al. (2017) suggested that combination therapy can significantly reduce abnormally elevated platelet counts and decrease serum

immunoglobulins (IgA, IgG, IgM) and T lymphocyte subsets (CD3+, CD4+ and CD8+ T cells).

The lungs are one of the most frequently affected extra-articular organs in RA, primarily manifesting as interstitial lung disease. Prolonged, low-dose use of MTX can lead to adverse reactions, causing interstitial lung disease. Han et al. found in animal experiments that IGU improves bleomycin-induced spontaneous pulmonary fibrosis by suppressing inflammation (Han et al., 2018). Short-term clinical observations by Hao et al. indicate that IGU effectively treats RA combined with chronic interstitial pneumonia, with a lower incidence of adverse reactions and no concomitant infections (L and i, 2014). Zhao et al. demonstrated that IGU can ameliorate lung tissue fibrosis by inhibiting the expression of factors like MMP-9, IL-1, and IL-6 (Zhao et al., 2019). Therefore, in patients with lung complications, consider prioritizing IGU. RA specifically impacts the cardiovascular system, including the cardiac conduction system. An essential factor contributing to heart function impairment in RA patients is the imbalance between oxidation and the antioxidant system. A clinical study on refractory RA revealed that the combination of IGU and MTX can increase superoxide dismutase, reduce total antioxidant capacity, and, in controlling oxidative stress, suppress cardiovascular diseases associated with RA (Lai, 2018).

This systematic review and meta-analysis showed that IGU can reduce disease activity (increase RA remission rate and reduce DAS28) and improve patients' inflammatory response (reduce ESR, CRP and RF) in patients with RA. Regarding safety, adding IGU does not increase the incidence of adverse events. However, considering that most RCTs have a high risk of bias in blind implementation and an unknown risk of bias in allocation concealment and random sequence generation, especially Mo et al. (2018), which has a high risk of bias in selective reporting, the stability of the conclusions has been affected to a certain extent, and the conclusions need to be interpreted with caution.

4.5 Possible sources of heterogeneity

The heterogeneity of BASDAI, WOMAC, ACR and some inflammatory factors was high. We consider that this may be related to the following reasons: 1) basic characteristics of patients (such as age, gender, severity of disease, etc.); 2) different IGU preparations, or different combination therapies or basic treatments for each patient and RCT; 3) The heterogeneity of subjective outcome indicators (BASDAI, WOMAC and ACR) may be related to the high risk of bias of the blinding method.

4.6 Limitations and future prospects

This systematic review and meta-analysis has several limitations. First, most of the included RCTs were conducted in China and Japan, which may limit the applicability of the findings to the East Asian populations. As a result, the conclusions drawn from this analysis may primarily reflect the effectiveness of IGU in treating RA, AS, and OA in East Asian individuals. Additionally, the limited number of RCTs focusing on IGU for OA patients underscores the need for more studies to strengthen the evidence base. Furthermore, since IGU has only been recently introduced, its mechanisms of action and interactions with other medications, such as MTX and leflunomide, require further exploration. In summary, IGU demonstrates superior efficacy in treating RA, OA, and AS compared to control groups without increasing the incidence of adverse reactions. This suggests that IGU offers a promising new treatment option for these conditions. However, further multicenter, large-sample, high-quality randomized controlled trials are needed to provide more robust evidence.

5 Conclusion

Given the existing data, IGU might emerge as a promising and secure therapeutic modality for addressing AS, OA, and RA. Nevertheless, additional RCTs are imperative to assess its effectiveness across other inflammatory joint disorders.

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 authors.

Author contributions

ZL: Data curation, Formal Analysis, Writing–original draft, Writing–review and editing. LZ: Conceptualization, Data curation, Formal Analysis, Writing–original draft, Writing–review and editing. KY: Data curation, Formal Analysis, Writing–original draft, Writing–review and editing. JC: Data curation, Formal Analysis, Writing–original draft, Writing–review and editing. YL: Data curation, Formal Analysis, Writing–original draft, Writing–review and editing. CD: Data curation, Formal Analysis, Writing–original draft. QH: Conceptualization, Data curation, Formal Analysis, Writing–original draft, Writing–review and editing. YD: Data curation, Formal Analysis, Writing–original draft, Writing–review and editing. AG: Data curation, Formal Analysis, Writing–original draft, Writing–review and editing. XZ: Data curation, Formal Analysis, Writing–original draft, Writing–review and editing. WH: Data curation, Formal Analysis, Writing–original draft, Writing–review and editing. LS: Data curation, Formal Analysis, Writing–original draft, Writing–review and editing.

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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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1440584/full#supplementary-material

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Effectiveness of biologic therapies in achieving treatment targets in inflammatory bowel disease; real-world data from the Middle East (ENROLL study)

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Background: Real-world data assessing the effectiveness of biologics in patients with inflammatory bowel disease (IBD) in the Middle East are not well-established. In our study, we evaluated the effectiveness of biologic therapies in achieving clinical and endoscopic outcomes in biologic-naïve patients with IBD.

Design: A retrospective chart review was conducted at two tertiary care gastroenterology centers using electronic medical records of patients with moderate-to-severe IBD. The study period was from October 2017 to October 2023. Patients who were on infliximab, adalimumab, ustekinumab, or vedolizumab for 12 months were included in the analysis. The primary outcomes were the percentage of IBD-related hospitalizations or surgeries, achieving steroid-free remission, and endoscopic remission.

Results: A total of 422 patients were included in the study, of whom 264 (62.5%) patients had Crohn's disease (CD) and 158 (39%) had ulcerative colitis (UC). In patients with CD, endoscopic remission was attained in 51 (52%) of the patients on adalimumab, 38 (53%) of the patients on infliximab, 34 (56%) of the patients on ustekinumab, and 16 (51%) of the patients on vedolizumab. In patients with UC, endoscopic remission was attained in 40 (56%) of the patients on infliximab, 26 (61%) of the patients on adalimumab, 8 (55%) of the patients on ustekinumab, and 11 (53%) of the patients on vedolizumab.

Conclusion: adalimumab, infliximab, ustekinumab, and vedolizumab were all effective in achieving clinical and endoscopic clinical outcomes in IBD in both UC and CD. The findings of this study suggest that the efficacy of biologics in a Middle Eastern population is similar to that in a Western population.

KEYWORDS

surgery, hospitalization, steroids, endoscopic, remission, biologics, inflammatory bowel disease

Introduction

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are immune-mediated disorders characterized by chronic inflammation of the gastrointestinal (GI) tract. Over recent decades, the treatment of IBD has changed considerably, culminating in the use of biologic therapies in the late 1990s (Alatab et al., 2020). With the increasing availability of biosimilars and the resulting reduction in cost, it is estimated that the use of biologic therapy in IBD is likely to increase (Anisdahl et al., 2021).

The goals of treatment of IBD are inducing and maintaining remission. Treatment of CD and UC, the two types of IBDs, is different; however, it can include many therapy classes such as aminosalicylates, immunosuppressants (corticosteroids and cyclosporine), antimetabolites (i.e., azathioprine (AZA), 6-mercaptopurine (6 MP)), and biologic therapy (Eltantawy et al., 2023).

However, the evidence is changing rapidly; national and international guidelines are being updated continuously, and the pattern of biologic therapy use varies among different countries. Currently, the use of biologic therapies is recommended if conventional agents such as 5-aminosalisylic acids, corticosteroids, and immunomodulators fail (Gordon et al., 2024). Nonetheless, the initiation of biologic therapies in patients with IBD is mainly affected by disease severity, as well as other clinical factors. The increasing availability of biologic therapies makes it essential to understand the prevalence of their use, duration of therapy, and sequence of initiation to better optimize the treatment of IBD (Alulis et al., 2020).

The superiority of one biologic over another is unclear; there are few head-to-head clinical trials comparing the effectiveness of different biologic agents with each other, and given cost consideration and sample size, it is unlikely that many clinical trials will be performed in the near future (Laredo et al., 2022). The choice of biologic agents in biologic-naïve patients is primarily driven by patient preference, relative cost based on insurance coverage, and experience of the treating physician.

Real-world data assessing the effectiveness of biologics in biologic-naïve patients with IBD in the Middle East region are not well-established. Therefore, this study aims to assess the effectiveness of biologics (adalimumab, infliximab, ustekinumab, golimumab, and vedolizumab) for treating biologic-naïve patients with moderately to severely active IBD.

Methods

Patient or public involvement

No patient or public involvement.

Study design and patient population

This study was a retrospective, observational study that involved chart reviews of patients with inflammatory bowel disease (IBD) at two tertiary care centers in Kuwait, Haya Alhabib Gastroenterology Center and Farwaniya Hospital. The enrollment period was between October 2017 and October 2023.

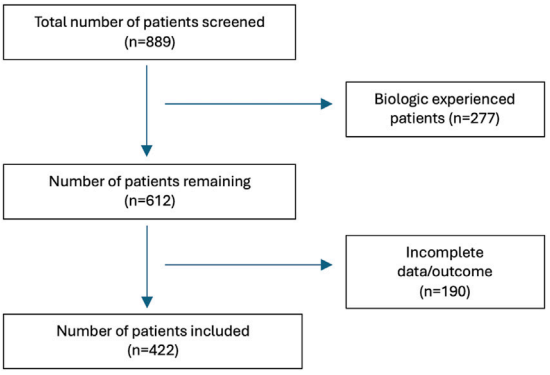

FIGURE 1
Flow diagram showing the enrollment process.

The study inclusion criteria were as follows: 1] age ≥ 18 years; 2] patients with moderate-to-severe ulcerative colitis defined as a clinical Mayo score of >6, with an endoscopic score of 2–3 (Feuerstein et al., 2020); 3] patients with moderate-to-severe Crohn's disease defined as a Crohn's disease activity index [CDAI] >220); with a simple endoscopic score for Crohn's disease (SES-CD) ≥ 7 (Lichtenstein et al., 2018); 4] patients receiving adalimumab, infliximab, ustekinumab, or vedolizumab; 5] patient had been on the current biologic therapy between 6 weeks and 12 months of treatment, and 6] patient should not have received prior biologic therapy (biologic naïve).

Patients who did not continue their treatment for 12 months due to primary or secondary treatment failure were considered not to achieve endoscopic remission. In addition, if they were hospitalized, received corticosteroids, or had surgery due to medication failure before 12 months of therapy, they were considered not to have achieved the outcome and thus were counted as a failure.

Exclusion criteria included: 1] Patients who had been treated with biologic therapy previously (biologic experience); 2] patients with incomplete outcome or therapy data; 3] patients who received other concomitant biologic or small-molecule therapy for other conditions, for example, rheumatological disease, 4] pregnant patients, 5] patients who had intermittent suspension of therapy during the 12 month period.

Outcomes and definitions

The primary endpoints were the percentage of hospitalization, surgery, corticosteroids-free remission, and endoscopic remission in patients with IBD receiving biologic therapies at week 52. Patients were considered to be on steroids if they received a course of prednisolone, budesonide, or any steroidal medication 6 weeks after starting the current biologic, that is, excluding the induction corticosteroid course. Patients who did not receive any steroid courses after 6 weeks from starting the biologic were considered to be in corticosteroid-free remission. Endoscopic remission is regarded as the total number of patients who

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TABLE 1 Demographic characteristics of patients with Crohn's disease.

Crohn's disease (n = 264)	Baseline	Follow-up
Age (years), mean (SD)		
At the time of study	33.9 (10.2)	—
At diagnosis	32.1 (7.7)	—
Sex, n (%)		
Male	136 (51.5%)	—
Female	128 (48.5%)	—
Ethnicity, n (%)		
Mediterranean	248 (94.0%)	—
Others	16 (6.0%)	—
BMI m^2/kg, mean (SD)	24.9 (7.3)	—
CDAI, mean (SD)	318 (6.1)	181 (3.4)
SES-CD, mean (SD)	11 (3)	1.7 (1)
L1: ileal	137 (52%)	—
L2: colonic	26 (10%)	—
L3: ileocolonic	96 (36%)	—
L4: upper gastrointestinal	5 (2%)	—
P: perianal	44 (16.8%)	—
B1: inflammatory	124 (47%)	—
B2: stricturing	55 (21%)	—
B3: penetrating	85 (32%)	—
Co-morbidities		
Diabetes	17 (6.3%)	—
Osteoarthritis	13 (4.8%)	—
Hypertension	11 (4.3%)	—
Cardiovascular disease	16 (6.0%)	—
Asthma	19 (7.2%)	—
Laboratory tests, mean (SD)		
CRP, mg/L	15.5 (6.3)	9 (4.3)
Stool fecal calprotectin, mcg/g	274 (14.5)	16 (15.7)
Albumin, g/L	40 (5.6)	40 (5.3)
Current biologics n (%)		
Adalimumab	99 (37.5%)	—
Infliximab	72 (27.2%)	—
Ustekinumab	61 (32.1%)	—
Vedolizumab	32 (12.1%)	—
Concomitant immunomodulator use	57 (21.5%)	—
Previous medications n (%)		
Immunomodulators	89 (33.9%)	—
Azathioprine	47 (52.4%)	—
Methotrexate	22 (25.5%)	—
6-Mercaptopurines	20 (22.1%)	—

Crohn's disease activity index [CDAI] with a simple endoscopic score for Crohn's disease (SES-CD).

achieved endoscopic remission, defined as an endoscopic Mayo score of 0–1 for patients with ulcerative colitis (Feuerstein et al., 2020) and a simple endoscopic score for Crohn's disease (SES-CD) of 0–2 for Crohn's disease (Lichtenstein et al., 2018). The number of patients with surgeries is the number of patients who underwent inflammatory bowel-related surgeries 6 weeks or more after starting the current biologic. Location and type of surgery were reported if patients had IBD-related surgery. Hospitalization, on the other hand, is the number of patients hospitalized 6 weeks or more after starting the current biologic for an IBD-related issue or complication. Examples of reasons for IBD-related issues include but are not limited to exacerbation of IBD, IBD-related infection, or any hospitalization, either due to IBD-related symptoms or complications.

This study was performed and reported in accordance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (von Elm et al., 2007). The international classification of diseases (ICD-10 version:2016) was used to make the diagnosis of IBD. Patients were considered to have IBD when they had ICD-10 K50, K50.1, K50.8, or K50.9 corresponding to Crohn's disease (CD) and ICD-10 K51, K51.0, K51.2, K51.3, K51.5, K51.8, or K51.9 corresponding to ulcerative colitis (UC) (World Health Organization, 2022). The following baseline patient data were extracted from the clinical records and entered into a common database: sex, age, ethnicity, IBD type, body weight, duration of disease, smoking status, location, co-morbidities, and previous IBD medications.

TABLE 2 Demographic characteristics of patients with ulcerative colitis.

Ulcerative colitis (n = 158)	Baseline	Follow-up
Age (years), mean (SD)		
At the time of study	34.5 (11.4)	—
At diagnosis	33.1 (8.7)	—
Sex, n (%)		
Male	86 (54.3%)	—
Female	72 (45.7%)	—
Ethnicity, n (%)		
Mediterranean	145 (91.5%)	—
Others	13 (8.5%)	—
BMI m^2/kg, mean (SD)	25.4 (6.9)	—
Mayo score, mean (SD)	8.8 (2.1)	3 (1.3)
Mayo endoscopic score (MES), mean (SD)	2.5 (0.2)	1.3 (0.3)
E1: ulcerative proctitis	30 (19%)	—
E2: left-sided colitis	52 (34%)	—
E3: extensive colitis	76 (49%)	—
Co-morbidities		
Diabetes	12 (7.7%)	—
Osteoarthritis	10 (6.3%)	—
Hypertension	9 (5.9%)	—
Cardiovascular disease	4 (2.6%)	—
Asthma	13 (8.0%)	—
Laboratory tests, mean (SD)		
CRP, mg/L	16.3 (5.2)	9.5 (4.1)
Stool fecal calprotectin, mcg/g	277 (11.6)	16 (12.5)
Albumin, g/L	42 (4.8)	40 (4.1)
Current biologics n (%)		
Adalimumab	51 (32.2%)	—
Infliximab	72 (45.5%)	—
Ustekinumab	14 (8.8%)	—
Vedolizumab	21 (13.2%)	—
Concomitant immunomodulator use	58 (36%)	—
Previous medications n (%)		
5-Aminosalicylates	103 (65%)	—
Immunomodulators	46 (29%)	—

Ethical considerations

All methods were carried out in accordance with relevant guidelines and regulations. This study was reviewed and approved by the Ethical Review Board of the Ministry of Health of Kuwait (reference:3616, protocol number 3678/2021). All methods were carried out according to the guidelines and regulations of the Declaration of Helsinki and of the US Federal Policy for the Protection of Human Subjects. Patient consent was waived by the Ethical Review Board of the Ministry of Health of Kuwait.

Statistical analysis

Statistical analyses were executed with the IBM SPSS Statistics package (Version 25.0. Armonk, NY: IBM Corp). Descriptive statistics were used to calculate frequencies and central tendency, expressed as means with standard deviation (SD), median with interquartile range (IQR), and percentages. Covariates included in the study were CRP, fecal calprotectin, and albumin because of their effect on disease activity (Turner et al., 2021).

Results

Initially, 889 patients on biologic therapies of interest were screened. Of this group, 277 were excluded because they were biologic experienced. Of the remaining 612 patients, 190 patients were excluded due to incomplete data. Of those 190 patients, 103 (54.2%) patients were excluded because they had not yet reached the week 52 timepoint (Figure 1). Therefore, a total of 422 patients were included in the study, of which 264 (62.5%) patients had Crohn's disease (CD), and 158 (39%) had ulcerative colitis (UC). The median timepoint for endoscopic remission was 52 weeks ± 2.

In patients with CD, the mean age (SD) was 33.9 (10.2) years, and approximately half were male patients 136 (51.5%). Of the CD patients, 99 patients were on adalimumab, 72 were on infliximab, 61 were on ustekinumab, and 32 were on vedolizumab. The mean (SD) CRP (mg/L) and albumin (g/L) were 15.5 (6.3) and 40 (5.6), respectively. The mean stool fecal calprotectin (mcg/g) in patients with CD was 274 (14.5). Previous medications included azathioprine 47 (52.4%), methotrexate 22 (25.5%), and 6-mercaptopurines 20 (22.1). Co-morbidities in the CD cohort included diabetes (6.3%), hypertension (4.3%), and cardiovascular disease (6.0%). The demographic characteristics of patients with CD are described in Table 1.

Of the patients with UC, 72 patients were on infliximab, 51 were on adalimumab, 21 were on vedolizumab, and 14 were on ustekinumab. In patients with UC, the mean age (SD) was 34.5 (11.4) years, and approximately half were male patients 136 (51.5%). Mean (SD) CRP (mg/L) and albumin (g/L) were 16.3 (5.2) and 42 (4.8), respectively. The mean stool fecal calprotectin (mcg/g) in patients with UC was 277 (11.6). Previous medications included 5-aminosalicylates 103 (65%) and immunomodulators 46 (29%). Co-morbidities in the UC cohort included osteoarthritis (6.3%), diabetes (7.7%), hypertension (5.9%), and asthma (8.0%). The demographic characteristics of patients with UC are described in Table 2.

Crohn's disease outcomes

In patients with CD, steroid-free remission was achieved in 65 (66%) of the patients on adalimumab, 50 (69%) on infliximab, 41 (68%) on ustekinumab, and 21 (65%) on vedolizumab. Additionally, endoscopic remission was attained in 51 (52%) of the patients on adalimumab, 38 (53%) of the patients on infliximab, 34 (56%) of the patients on ustekinumab, and 16 (51%) patients on vedolizumab. Some patients experienced primary (15 patients) and secondary (33 patients) non-response while taking adalimumab. Ten patients experienced primary non-response while taking infliximab, and 24 patients experienced secondary non-response. Seven patients taking ustekinumab experienced primary non-response, and 20 patients experienced secondary non-response. Five patients taking vedolizumab experienced primary non-response, and 11 patients experienced secondary non-response.

IBD-related hospitalization occurred in 30 (30%) of the patients on adalimumab, 17 (23%) patients on infliximab, 13 (21%) patients on ustekinumab, and 9 (27%) patients on vedolizumab. IBD-related

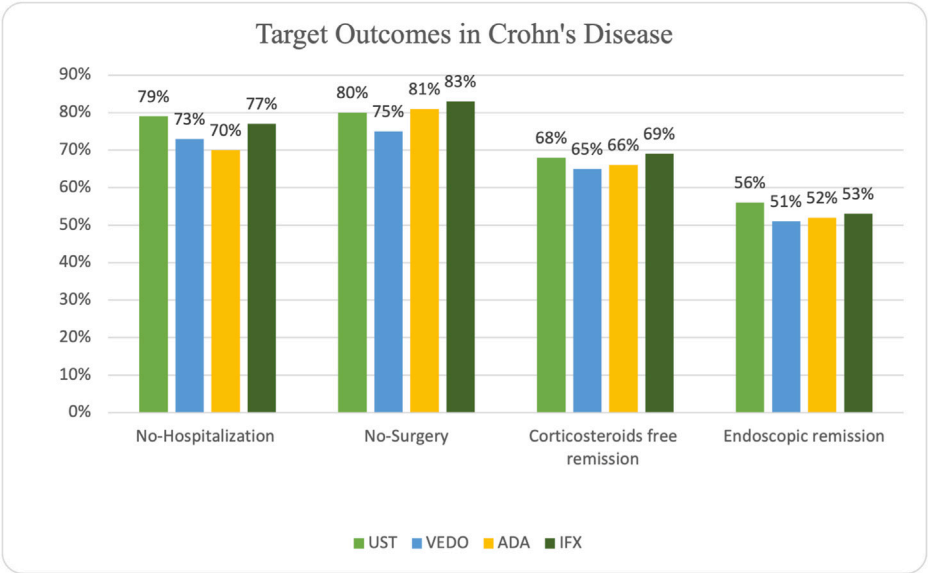

FIGURE 2
Graph depicting outcomes in biologic-naïve patients with Crohn's disease.

surgery occurred in 19 (19%) patients receiving adalimumab, 12 (17%) patients on infliximab, 12 (20%) patients on ustekinumab, and 8 (25%) patients receiving vedolizumab (Figure 2).

In total, 51 of the 264 patients (19.3%) underwent surgery (small bowel resection ± right hemicolectomy, see Table 3).

Ulcerative colitis outcomes

In patients with UC, steroid-free remission was achieved in 32 (62%) of the patients on adalimumab, 47 (65%) on infliximab, 9 (64%) on ustekinumab, and 13 (64%) on vedolizumab. Additionally, endoscopic remission was attained in 40 (56%) of the patients on infliximab, 26 (61%) of the patients on adalimumab, 8 (55%) of the patients on ustekinumab, and 11 (53%) patients on vedolizumab. Ten patients experienced primary non-response while taking infliximab, and 22 patients experienced secondary non-response. Six patients experienced primary non-response while taking adalimumab, and 19 patients experienced secondary non-response. One patient taking ustekinumab experienced primary non-response, and five patients experienced secondary non-response. Finally, four patients experienced primary non-response while taking vedolizumab, and six patients experienced secondary non-response.

IBD-related hospitalization occurred in 14 (28%) of the patients on adalimumab, 17 (24%) patients on infliximab, three patients on ustekinumab (23%), and 5 (26%) patients on vedolizumab. IBD-related surgery occurred in 8 (15%) patients receiving adalimumab, 5 (7%) patients on infliximab, 1 (9%) patient on ustekinumab, and 2 (11%) patients receiving vedolizumab (Figure 3).

In total, 17 of the 158 patients (10.8%) underwent surgery (colectomy followed by ileal pouch-anal anastomosis (IPAA) or proctocolectomy with end ileostomy, see Table 4).

Discussion

This study evaluated the effectiveness of biologic therapies in bio-naive patients with IBD. The primary outcomes were the percentage of hospitalization, surgery, steroid-free remission, and endoscopic remission, defined as a Mayo score of 1 or less in ulcerative colitis and an SES-CD score of less than 3 in Crohn's disease. All biologic therapies were effective in achieving clinical and endoscopic clinical outcomes in IBD.

Our finding is similar to a study performed in the United Kingdom (Kapizioni et al., 2024). The study presented data on the real-world use of biologic therapy in 13,222 patients. The authors found that the effectiveness of adalimumab, infliximab, ustekinumab, and vedolizumab were similar in IBD.

In our study, the rate of endoscopic remission in biologic-naïve patients with CD receiving infliximab was 53%, whereas the rate of endoscopic remission in patients with UC receiving infliximab was 56%. One real-world study investigated similar outcomes in patients with CD receiving infliximab for 12 months, and the authors found that the long-term response rate was approximately 60% (Kestens et al., 2013).

In our study, endoscopic remission in patients receiving adalimumab was 52% in CD and 51% in UC. One study included 263 patients with UC (87 naïve and 176 previously exposed to anti-TNF). Similar to our study, after 12 weeks, the authors found that endoscopic remission in the naïve group was 50% (Iborra et al., 2017). In a Spanish cohort study of patients with UC, adalimumab therapy was associated with a clinical response rate of 61% in anti-TNF-naïve and 47% in anti-TNF-experienced patients (Iborra et al., 2017).

The present study showed that in patients receiving vedolizumab, 51% of the CD cohort and 53% of the UC cohort achieved endoscopic remission. One multicenter study

TABLE 3 Patients with Crohn's disease who had IBD-related surgery.

	Small bowel resection	Small bowel resection + right hemicolectomy
Adalimumab (n = 19)	14	5
Infliximab (n = 12)	9	3
Ustekinumab (n = 12)	10	2
Vedolizumab (n = 8)	5	3

demonstrated the effectiveness of vedolizumab as a first-line biologic in IBD in a real-world setting (Kopylov et al., 2018). The study reported that at week 14, 82% of CD and 79.1% of UC anti-TNF-naïve patients responded to treatment with vedolizumab. At the last follow-up, 77.1% of CD and 76.7% of UC patients responded to vedolizumab.

Several real-world studies (Kestens et al., 2013; Osterman et al., 2014; Cosnes et al., 2016; Bohm et al., 2020) concluded that infliximab and adalimumab appeared to have similar effectiveness in patients with CD, and the approval of vedolizumab and ustekinumab for CD expanded the options of biologics for moderate-to-severe disease. Two studies compare the safety and effectiveness of vedolizumab and TNF-antagonist therapy in adult patients with CD. Both studies indicated no significant difference in achieving disease remission (Bohm et al., 2020; Macaluso et al., 2021).

In our study, the proportion of biologic-naïve patients with UC who achieved corticosteroid-free remission after receiving infliximab or vedolizumab was 65% and 64%, respectively. A *post hoc* analysis of three UC clinical trial programs that included data on 795 biologic-naïve UC patients compared the efficacy of infliximab and vedolizumab for moderate-to-severe biologic-naïve UC (Narula et al., 2022). Differences in the proportions of patients achieving one-year corticosteroid-free clinical remission and endoscopic remission were reported. Rates of corticosteroid-free clinical remission were significantly higher in patients using infliximab (29.5%) than vedolizumab (15.0%, p= .004). Rates of 1-year endoscopic remission also were significantly higher in infliximab-treated patients (36.0% vs. 25.6% OR, 1.55; 95% CI, 1.08–2.22).

In terms of IBD-related surgery, our study showed that in patients with CD, 25% receiving vedolizumab and 20% receiving ustekinumab had undergone CD-related surgery. One study aimed to investigate the incidence of the first CD-related surgery following the initiation of treatment with vedolizumab or ustekinumab in biologic-naïve patients with CD (Onali et al., 2022). After 1 year of follow-up, the study reported that 7.7% of patients receiving vedolizumab and 11.6% of patients receiving ustekinumab had undergone a CD-related surgery. In patients with UC, the present study found that the proportion of patients who had surgery was 7% in patients receiving infliximab and 15% in patients receiving adalimumab. A nationwide study from Denmark compared the effectiveness of infliximab and adalimumab in biologic-naïve patients with UC. The study reported that the rate of abdominal surgery was 11 per 100 person-years in the infliximab cohort and 20 per 100 person-years in the adalimumab group (Singh et al., 2017).

One systematic review and network meta-analysis investigated the efficacy of different biologic therapies in patients with

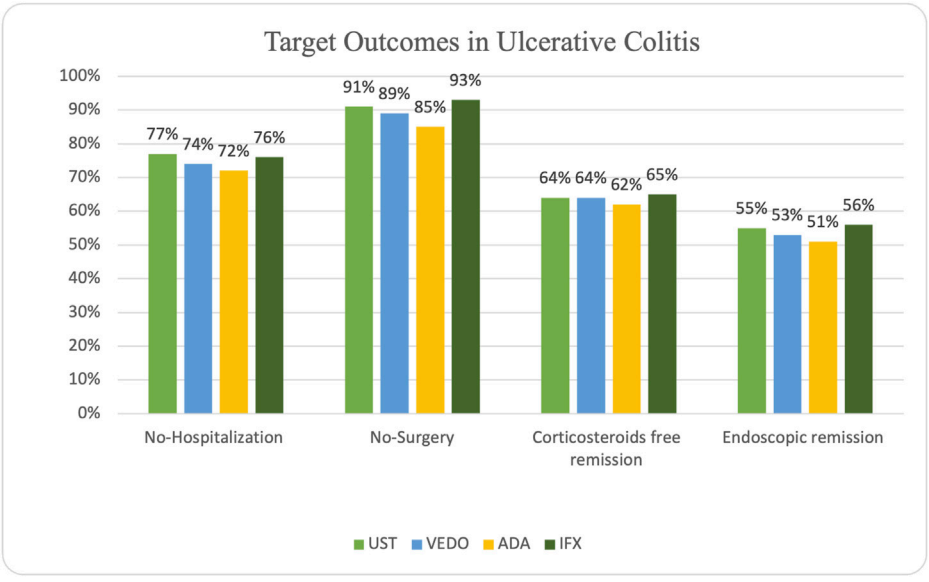

FIGURE 3
Graph depicting outcomes in biologic-naïve patients with ulcerative colitis.

TABLE 4 Patients with ulcerative colitis who had IBD-related surgery.

	Proctocolectomy with end ileostomy	Colectomy followed by IPAA
Adalimumab (n = 8)	1	7
Infliximab (n = 5)	0	5
Ustekinumab (n = 1)	0	1
Vedolizumab (n = 2)	1	1

IPAA, ileal pouch-anal anastomosis.

moderate-to-severe UC as a first-line choice. The meta-analysis included 12 RCTs, and they found that among biologic-naïve patients, infliximab and vedolizumab were ranked highest for induction of clinical remission and mucosal healing (Singh et al., 2018).

This study has several clinical implications. The widespread availability of different biologic therapies for patients with IBD adds challenges to the management of these patients. Currently, guidelines recommend either vedolizumab or anti-TNF therapy as first-line biologics in moderate-to-severe UC (Feuerstein et al., 2020; Rubin et al., 2019). Although the VARISTY trial (Sands et al., 2019) showed the superiority of vedolizumab compared to adalimumab in achieving clinical remission and endoscopic improvement in biologic-naïve patients with UC, it is still debated whether this superiority would hold against other anti-TNF therapies such as infliximab. Real-world data such as the present study help clinicians understand the effectiveness of biologics in achieving important clinical outcomes in patients with Arab ethnicity. Data from head-to-head trials would be ideal to understand and ascertain the effectiveness of biological therapies compared to each other and will aid in the generalization to different populations.

This study is not without limitations. First, it is a retrospective observational study; thus, generalization is not possible, and unmeasured confounding factors may be present. Second, we could not investigate the impact of dose escalation or therapeutic drug monitoring practices, which are common in practice. Third, a comparison between outcomes of different biologic agents was not assessed because the number of included patients was insufficient to perform such a comparison. Finally, a long-term evaluation of outcomes of more than 12 months was not assessed.

Conclusion

Adalimumab, infliximab, ustekinumab, and vedolizumab were all effective in achieving clinical and endoscopic clinical outcomes in IBD in both UC and CD. The findings of this study suggest that the efficacy of biologics in the Middle East is similar to that in the Western population. However, larger prospective comparative studies are warranted.

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 humans were approved by the Ethical Review Board of the Ministry of Health of Kuwait (reference: 3616, protocol number 3678/2021). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participant's legal guardians/next of kin in accordance with the national legislation and institutional requirements.

Author contributions

MS: conceptualization, data curation, methodology, supervision, writing–original draft, and writing–review and editing. AA: writing–original draft and writing–review and editing. IA: data curation, formal analysis, writing–original draft, and writing–review and editing. WA: data curation, writing–original draft, and writing–review and editing. AM: data curation, writing–original draft, and writing–review and editing. FA: project administration, supervision, visualization, writing–original draft, and writing–review and editing.

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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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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2024.1388043/full#supplementary-material

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