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Biological therapy in systemic lupus erythematosus, antiphospholipid syndrome, and Sjögren's syndrome: evidence- and practice-based guidance

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Systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), and Sjögren's syndrome (SS) are heterogeneous autoimmune diseases. Severe manifestations and refractory/intolerance to conventional immunosuppressants demand other options, namely biological drugs, and small molecules. We aimed to define evidence and practice-based guidance for the off-label use of biologics in SLE, APS, and SS. Recommendations were made by an independent expert panel, following a comprehensive literature review and two consensus rounds. The panel included 17 internal medicine experts with recognized practice in autoimmune disease management. The literature review was systematic from 2014 until 2019 and later updated by cross-reference checking and experts' input until 2021. Preliminary recommendations were drafted by working groups for each disease. A revision meeting with all experts anticipated the consensus meeting held in June 2021. All experts voted (agree, disagree, neither agree nor disagree) during two rounds, and recommendations with at least 75% agreement were approved. A total of 32 final recommendations (20 for SLE treatment, 5 for APS, and 7 for SS) were approved by the experts. These recommendations consider organ involvement, manifestations, severity, and response to previous treatments. In these three autoimmune diseases, most recommendations refer to rituximab, which aligns with the higher number of studies and clinical experience with this biological

agent. Belimumab sequential treatment after rituximab may also be used in severe cases of SLE and SS. Second-line therapy with baricitinib, borteomib, eculizumab, secukinumab, or tocilizumab can be considered in SLE-specific manifestations. These evidence and practice-based recommendations may support treatment decision and, ultimately, improve the outcome of patients living with SLE, APS, or SS.

KEYWORDS

systemic lupus erythematosus, antiphospholipid syndrome, biological therapies, small molecules, systemic autoimmune diseases, recommendations, Sjögren's syndrome

1 Introduction

Systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), and Sjögren's syndrome (SS) are systemic autoimmune diseases (SAIDs) characterized by changes in immunity and inflammation pathways (1). As a result, several body tissues may be affected by the patient's immune system. SAIDs often present relapse-remission courses, and critical flares or severe manifestations can occur, sometimes life-threatening (2).

The Standard of care (SoC) in SAIDs consists of treatment with corticosteroids and conventional immunosuppressive drugs (3). These agents are effective in most patients, but side effects and refractory cases can occur (3, 4). For that reason, drugs with a better benefit/risk profile are needed, especially after inadequate control by SoC (5). Biologic agents, immunoglobulins, and biotechnology small molecules have become a hallmark in the treatment of severe manifestations of SAIDs, alone or as adjunctive therapy to conventional immunosuppressive drugs (3, 6). However, many of these drugs have been used off-label due to a lack of randomized trials in such heterogenous and often rare conditions. Furthermore, despite its efficacy and often safe profile, biological therapy has frequently higher costs and access constraints (3, 4).

Within this context, the Study Group of Autoimmune Diseases of the Portuguese Society of Internal Medicine (NEDAI) aimed to review the evidence (from clinical trials and real-world settings) and to define recommendations for the off-label use of biologics in SAIDs, namely, SLE, APS, and SS.

2 Methods

Recommendations were made by an independent expert panel, following a comprehensive literature review and two consensus rounds (Figure 1). This is a useful methodology when RCT evidence is limited and when the clinical questions to be addressed are clearly defined (2, 7).

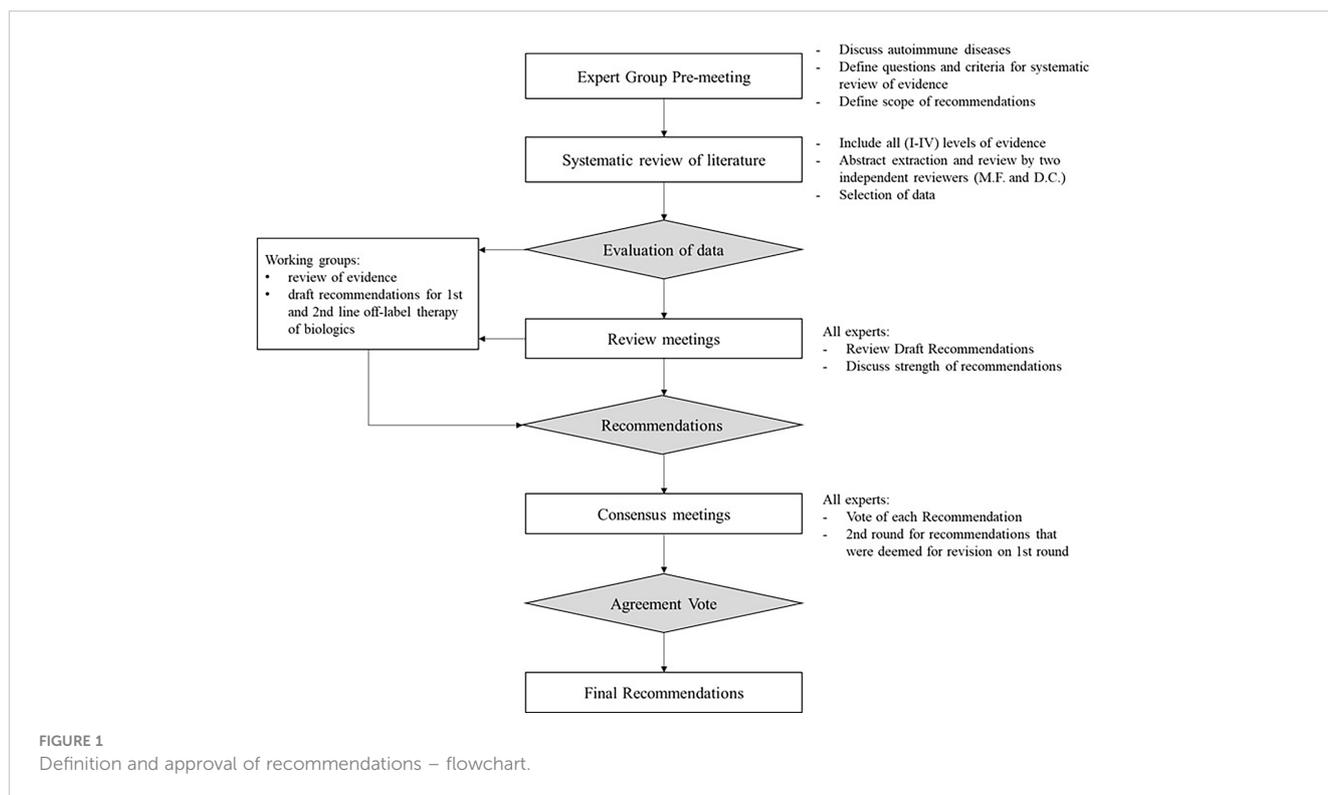
All NEDAI members in 2019 (n=19) were invited and 17 experts participated. All experts have a long-standing experience in the care of SAIDs patients at university and tertiary hospitals in Portugal.

Two preliminary expert meetings were conducted in June 2018 and June 2019, to define the scope of recommendations. The following clinical questions and definitions were considered:

- Can “biologic therapy” be considered as 1st/2nd line treatment? In which clinical circumstances? Which “biologic drug” can be used in 1st/2nd line, considering the affected organ/clinical setting?
- “Biologic therapy” included all biological agents, small molecules, and immunoglobulins.
- Off-label use: the use of biological therapy in unapproved SAIDs (in Europe), regardless of being approved for the treatment of other diseases.
- 1st line therapy: biologic therapy used concomitantly to or after glucocorticoid use.
- 2nd line therapy: biologic therapy used after SoC immunosuppressive drugs or 1st line biological agents.

A systematic review was conducted on PubMed. The inclusion criteria were defined before the literature search. Publications that met all the following criteria were included: 1) evaluation of treatment with biologic agent/small molecule; 2) in one of the defined SAIDs, 3) among adult patients, 4) irrespective of the type of study (case reports and reviews were included), and 5) written in English. Publications reporting diseases other than the defined ones or secondary SAIDs, diagnosis or identification of risk factors, molecular or biomarker evaluation, or *in vitro* or *ex vivo* studies, were excluded. Screening of publications was conducted by two independent reviewers. Cases of non-agreement were debated and, when required, a third reviewer was consulted. The process and results from the systematic review are presented in [Supplementary Material](#).

Working groups, with experts allocated to only one disease, were provided with an overview of the resulting evidence to produce a set of preliminary recommendations for biologic as 1st and 2nd therapy line. The writing of recommendations was overviewed by all experts during a meeting in February 2020. After the revisions of the working groups, recommendations were classified according to the level of evidence, and the strength of recommendation, according to the 2016 standards of the Oxford Centre for Evidence-Based Medicine ([Supplementary Material](#)) (8). Experts



also defined six categories for clinical use, based on the available evidence and their clinical experience (Table 1).

Draft recommendations were then voted during a remote consensus meeting in June 2021 (Supplementary Material). If the degree of agreement (i.e., the number of experts who agreed with the recommendation over the total number of experts) was lower than 75%, the recommendation was revised by the working group and, if applicable, submitted to a second consensus round (online survey) in September 2021. Tables 2–4 present only the approved recommendations (i.e., ≥75% agreement).

3 Recommendations

3.1 Off-label biologic therapy in systemic lupus erythematosus

3.1.1 Disease background

SLE can affect several organs, including the skin, kidney, heart, lungs, and the hematological, musculoskeletal, and nervous systems

(2, 9). The incidence of flares is about 0.65 per patient-year and even though the 10-year survival is higher than 90% (10), about one-third of SLE deaths seem to result from disease activity (11). Hence, treatment should aim at preventing damage and maintaining disease control whilst using the lowest possible dose of corticosteroids, ultimately aiming at reducing morbidity and mortality (2, 9, 12). However, up to 20% of SLE patients do not adequately respond to conventional treatments with corticosteroids and immunosuppressive drugs (10). In addition, drug-induced toxicity is frequent, particularly in patients receiving longer treatments and those with refractory disease and/or lupus nephritis (LN) (13).

Data about most biological therapies in SLE treatment is scattered, although several RCTs were conducted and RTX has been extensively used (14). Belimumab is approved for SLE treatment, as add-on therapy in adult patients with high disease activity despite SoC therapy and in combination with background immunosuppressive therapies for the treatment of adult patients with active LN. A pooled analysis of belimumab RCTs confirmed its efficacy irrespective of concomitant medication (15), with an

TABLE 1 Guidance for off-label use of biological therapy.

	Categories	Availability
I	Recommended use	Often used in clinical practice for other autoimmune diseases
II	Suggested use	Used in patients with specific characteristics or underlying clinical conditions
III	Possible use	Not contraindicated and successful case reports/series available
IV	Use not recommended	No additional benefits
V	Use not recommended	Contraindicated use

TABLE 2 Recommendations for off-label biologic therapy of systemic lupus erythematosus.

Recommendation (clinical circumstance and drug)	LoE ^{a)}	GoR ^{a)}	Off-label guidance ^{b)}
First-line therapy			
1. In pts with very active disease (i.e., SLEDAI>20 or BILAG 3A's)			
RTX is recommended	2a	B	I
RTX-BEL may be used	2b	B	II
2. In pts with severe hemolytic anemia or severe thrombocytopenia (i.e., risk of death or organ damage)			
RTX is recommended	4	C	I
3. In pts with severe kidney disease (stage IV, presence of glomerular crescents and/or renal failure [GFR < 60 ml/min/1.73 m ²])			
RTX is recommended	2a	C	I
RTX-BEL may be used	2b	C	II
4. In pts with severe CNS disease			
RTX is recommended	4	C	I
RTX-BEL may be used in recurrent cases	4	C	II
Second-line therapy			
5. In pts with persistently active disease for at least one year, with flares			
RTX is recommended in RTX-naïve cases	2a	C	I
baricitinib may be used in pts with predominant arthritis flares	1b	B	II
tocilizumab can be considered in pts with predominant arthritis flares	4	C	III
6. In pts with severe kidney disease,			
RTX is recommended in RTX-naïve cases	2a	C	I
RTX-BEL may be used in multi-refractory cases	4	C	II
secukinumab can be considered in multi-refractory cases	4	D	III
7. In pts with very active disease,			
RTX is recommended in RTX-naïve cases	2a	B	I
RTX-BEL may be used in RTX-naïve cases	2b	B	I
bortezomib can be considered in multi-refractory patients	4	D	III
8. In pts with hemolytic anemia or thrombocytopenia,			
RTX is recommended in RTX-naïve cases	4	C	I
bortezomib can be considered in multi-refractory cases	4	D	III
9. In pts with moderate or severe CNS disease,			
RTX is recommended in RTX-naïve cases	4	C	I
RTX-BEL may be used in multi-refractory cases	4	D	II

LoE, Level of Evidence; GoR, Grade of Recommendation; BILAG, British Isles Lupus Assessment Group index; CNS, Central Nervous System; GFR, Glomerular Filtration Rate; pts, patients; RTX, rituximab; RTX-BEL, rituximab, and belimumab (sequential therapy); SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

^{a)}LoE and GoR according to the Oxford CEMBE 2009 guidelines (see Table S1).

^{b)}Guidance of off-label use of biologic therapy, as defined by experts (see Table 1).

improvement in disease activity, particularly in the musculoskeletal and mucocutaneous organ domains (16), a better quality of life (17), reduction of long-term organ damage (18) and effectiveness maintained for up to 7 and 12 years (19). A two-year phase III RCT showed an improvement in renal response among active LN patients that received belimumab plus standard therapy while reducing the risk of renal-related events or death (20). The efficacy

of belimumab was also observed in several open-label and real-world studies (21).

Anifrolumab is a type I interferon receptor antagonist that reduces disease activity in patients with moderate-to-severe SLE (22, 23). A phase III RCT (TULIP 2 study) demonstrated anifrolumab efficacy through a composite endpoint at week 52 – reduction in any moderate-to-severe baseline disease activity and

TABLE 3 Recommendations for off-label biologic therapy of antiphospholipid syndrome.

Recommendation (clinical circumstance and drug)	LoE ^{a)}	GoR ^{a)}	Off-label guidance ^{b)}
First-line therapy			
1. RTX is recommended as first-line therapy for APS patients with severe thrombocytopenia	2b	B	I
2. The SoC in CAPS consists of combined therapy with anticoagulants, corticosteroids, plasmapheresis or IVIG, and systemic antibiotics if adequate	2b	D	I
3. In patients with CAPS, RTX may be added to the combined therapy	2b	D	II
4. In patients with CAPS and other SAIDs (e.g., SLE), RTX may be added to combined therapy	4	D	II
Second-line therapy			
5. As second-line therapy, the evidence available is insufficient to support any recommendations	–	–	–

LoE, Level of Evidence; GoR, Grade of Recommendation; APS, antiphospholipid syndrome; CAPS, catastrophic antiphospholipid syndrome; IVIG, intravenous immunoglobulin; RTX, rituximab; SAIDs, systemic autoimmune diseases; SLE, systemic lupus erythematosus; SoC, standard of care.

^{a)}LoE and GoR according to the Oxford CEMBE 2009 guidelines (see Table S1).

^{b)}Guidance of off-label use of biologic therapy, as defined by experts (see Table 1).

no worsening in any of nine BILAG organ systems, no SLEDAI worsening, no increase of ≥ 0.3 points in the Physician Global Assessment of disease activity (24). Anifrolumab was authorized by EMA in 2022, as an add-on therapy for the treatment of adult patients with moderate to severe, active autoantibody-positive SLE, despite standard therapy.

3.1.2 Definitions

- SLE with inadequate response to SoC: residual disease activity not allowing tapering of glucocorticoids to less than 5 mg/day and/or frequent relapses (2).
- very active SLE: patients scoring SLEDAI >20 or BILAG 3A's (25).
- persistent active SLE: patients presenting some disease activity for 1 or more years (26).

- flare: measurable increase in disease activity usually leading to a change of treatment (2).
- severe kidney disease: defined as stage IV nephritis, presence of glomerular crescents, and/or renal failure (GFR < 60 ml/min/1.73 m²).
- severe CNS disease: defined as neuropsychiatric or ophthalmological involvement.

3.1.3 Recommendations and summary of evidence

Recommendations for the off-label biological therapy of SLE are presented in Table 2.

3.1.3.1 Rituximab

RTX is recommended as 1st line therapy in patients with very active disease, severe hemolytic anemia, or thrombocytopenia with

TABLE 4 Recommendations for the off-label biological therapy in Sjögren's syndrome.

Recommendation (clinical circumstance and drug)	LoE ^{a)}	GoR ^{a)}	Off-label guidance ^{b)}
First-line therapy			
1. In pts with SS and with sicca symptoms only, biological therapy is not recommended.	1a	A	IV
2. In pts with SS and severe systemic manifestation, with risk of lymphoma (at least 3 risk factors for lymphoma) and recent onset (<12 months of evolution), RTX can be used as first-line therapy.	4	C	II
3. RTX may be used as first-line therapy in pts with SS (<12 months of evolution) and peripheral neuropathy, severe thrombocytopenia, severe CNS disease, severe parotid swelling, and/or cryoglobulinemic vasculitis.	1b	B	II
4. RTX may be used as first-line therapy in pts with SS (>12 months of evolution) and peripheral neuropathy, severe thrombocytopenia, severe CNS disease, severe parotid swelling, and/or cryoglobulinemic vasculitis.	2b	C	II
5. Fatigue in SS patients is not a recommendation for biological therapy.	1a	A	IV
Second-line therapy			
6. RTX is recommended in pts with refractory SS who present the systemic manifestations indicated for the first-line therapy.	1b	B	I
7. In RTX-experienced pts, sequential therapy of BEL-RTX may be used.	2b	C	II

LoE, Level of Evidence; GoR, Grade of Recommendation; BEL, belimumab; CNS, central nervous system; SS, Sjögren's syndrome; pts, patients; RTX, rituximab.

^{a)}LoE and GoR according to the Oxford CEMBE 2009 guidelines (see Table S1).

^{b)}Guidance of off-label use of biologic therapy, as defined by experts (see Table 1).

risk of death or organ damage, severe kidney disease (Stage 4, presence of glomerular crescents and/or renal failure), or with severe CNS disease. RTX is recommended as 2nd line therapy in patients with persistently active disease for at least one year with flares and particularly in patients with very active disease, hemolytic anemia or thrombocytopenia, severe kidney disease, or moderate or severe CNS disease.

Even though RCTs had not shown the efficacy of RTX in the treatment of SLE (27) and LN (28), several observational studies – including registries (29–32) and large retrospective studies (33–35) – showed RTX effectiveness and a low incidence of adverse events in the treatment of refractory SLE, including in patients more treatment-experienced (36). These differences between observational studies and RCTs may be due to the heterogeneity of the SLE population in the real-world setting and some methodological problems of RCTs (such as lack of power and selection of endpoints) (37, 38). Some meta-analyses that included observational results demonstrated the RTX effectiveness in SLE and LN, with complete response estimates of 46%–57% and 36% 51%, respectively (38–40).

The successful use of RTX as induction therapy in refractory LN was also reported in several studies (41), including for patients with poorer prognostic factors in terms of renal disease (42) and patients with membranous LN (type V) (43). A pooled analysis of data from European cohorts showed that add-on treatment with RTX was successful in patients with type IV and type V LN – although less than in patients with type III (44). A recent network meta-analysis placed add-on therapy with RTX in line with combination treatment with leflunomide and tacrolimus but, since the population treated with RTX seems to have more severe disease, conclusions may have been biased (45).

RTX was used successfully in the treatment of SLE-associated refractory cytopenia (46, 47), including thrombocytopenia (48) and autoimmune hemolytic anemia (AIHA) (49). Additionally, a meta-analysis demonstrates the effectiveness of RTX in the treatment of AIHA and microangiopathic hemolytic anemia (50). A case report indicated the effectiveness of RTX treatment in corticosteroid-resistant immune thrombocytopenia purpura associated with SLE (51).

The effectiveness of RTX treatment was also reported in refractory cases with neuropsychiatric involvement, in patients with delirium or psychosis (52–54), and in the presence of ophthalmologic manifestations (55). Furthermore, some case reports suggest that RTX may be useful as 1st line therapy in severe neuropsychiatric SLE (56), including demyelinating syndrome secondary to SLE, severe cognitive dysfunction, brainstem disease, cranial nerve palsies, and weakness and numbness in limbs (57) or with concurrent neuropsychiatric and renal involvement (58).

3.1.3.2 Sequential therapy with Rituximab followed by Belimumab

The sequential therapy of RTX followed by belimumab may be used as 1st line therapy in patients with very active disease or with severe kidney disease (Stage IV, presence of glomerular crescents and/

or renal failure [GFR < 60 ml/min/1.73 m²]) and can be considered in patients with severe CNS disease. RTX-belimumab is recommended as 2nd line therapy in RTX-experienced patients with very active disease, severe kidney disease, or moderate to severe CNS disease.

While the efficacy of belimumab has been demonstrated in SLE, some patients maintain disease activity. In line with several case reports (59), the phase II SynBioSe study showed significant clinical and immunological improvements from baseline in patients with severe refractory SLE who received RTX followed by belimumab, and that patients maintained response over two years (60, 61). Other studies described the successful treatment of LN refractory to RTX (62, 63), although the CALIBRATE study (an open-label phase II RCT) showed no clinical improvement of belimumab infusions after RTX plus cyclophosphamide, for treatment of refractory LN (64). One case was reported with a successful result of sequential treatment in neuropsychiatric SLE (65). The BEAT-LUPUS study (66) and the BLISS-BELIEVE study (67) evaluated this combination, and findings suggest that adding a single cycle of RTX to belimumab therapy does not improve disease control rates. However, patients with anti-double-stranded (ds)DNA antibodies showed a significantly greater decrease in median levels at 52 weeks among those in the belimumab-RTX group than those in the belimumab-placebo arm, with reductions of 69.2% versus 46.1% (68).

3.1.3.3 Baricitinib

Baricitinib may be used as 2nd line therapy in patients with persistently active disease and predominant arthritis flares. Baricitinib is an oral selective Janus kinase (JAK)1 and JAK2 inhibitor approved for the treatment of rheumatoid arthritis and atopic dermatitis (69). A double-blind phase II RCT, with 314 active SLE patients involving skin or joints showed that baricitinib 4mg significantly improved the signs and symptoms of active SLE – with a greater proportion (vs. placebo) of patients achieving resolution of arthritis/rash – in patients who failed adequate control with an SoC approach (70). A high rate of serious infections was observed, although similar to what was observed with belimumab (70–72). On January 2022, the phase 3 development program of baricitinib in SLE treatment was stopped due to poor efficacy results in the SLE-BRAVE-II trial (NCT03616964), even though the SLE-BRAVE-I (NCT03616912) showed a significant reduction in disease activity as evaluated by the SRI-4 standard measurement tool.

3.1.3.4 Bortezomib

In patients with very active disease and RTX-experienced, bortezomib can be considered as 2nd line therapy. Bortezomib reduced disease activity in refractory SLE (73) and LN (74, 75) and treated successfully one SLE patient with warm-type hemolytic anemia refractory to RTX (76). However, its safety profile requires the monitoring of adverse events, such as peripheral neuropathy and hypogammaglobulinemia (77). A double-blind RCT failed to demonstrate bortezomib efficacy after a high discontinuation rate occurred, due to adverse events (78). A case report showed that lower doses of bortezomib (i.e., with longer intervals for the

administration of the drug) could be useful for the treatment of patients with concomitant multiple myeloma, although the patient presented mildly active SLE (77). Sequential treatment with belimumab may reduce the regeneration of autoreactive B cells, according to a report of two cases (79).

3.1.3.5 Eculizumab

In patients with refractory lupus nephritis, eculizumab can be considered in multi-refractory cases. Eculizumab is a recombinant humanized monoclonal antibody (mAb) that binds to the complement component C5 and prevents its activation (80). A placebo-controlled, double-blind phase I RCT with 24 SLE patients failed to demonstrate the efficacy of eculizumab, according to laboratory and clinical parameters and SLEDAI scores (81). However, case reports described good results with eculizumab in the treatment of refractory LN (82, 83). In a review of SLE with renal involvement, irrespective of concomitant LN, all patients (n=6) showed a sustained improvement in renal function and normalization of complement parameters after treatment with eculizumab (median follow-up of 9 months) (80). This successful response was also observed in patients with refractory thrombotic microangiopathy associated with LN or SLE (84).

3.1.3.6 Secukinumab

In patients with active lupus nephritis, secukinumab can be considered as 2nd line therapy in multi-refractory cases. Secukinumab is a human IgG1κ mAb that binds to the interleukin (IL)-17A. It has been suggested for the treatment of lupus since T-helper 17 cells are involved in the SLE pathogenesis (85). A case report of a 62-year-old female who presented with psoriasis vulgaris and refractory LN – showing proliferation of activated T helper 17 cells in peripheral blood, and renal infiltration of IL-17-positive lymphocytes – was treated successfully with secukinumab, for both psoriasis and LN (86). An ongoing phase 3 RCT will evaluate subcutaneous secukinumab vs. placebo, in combination with SoC, in patients with active LN (NCT04181762).

3.1.3.7 Tocilizumab

Tocilizumab can be considered in persistent active SLE for at least one year with predominant arthritis flares. An open-label, phase I study with 16 patients with mildly to moderately active SLE showed clinical and serological response after tocilizumab treatment (87). Its use as add-on therapy in SLE has been described in case reports, with successful outcomes in patients with arthritis flares (88, 89) or with refractory serositis (90, 91). Tocilizumab was also used successfully in one SLE patient with AIHA refractory to RTX treatment (92). Neutropenia and the increased risk of infection limit tocilizumab use in SLE treatment (87).

3.1.3.8 Other biologics

RCTs have failed to demonstrate *abatacept* efficacy in the treatment of active LN (93, 94) or SLE (95), although some exploratory endpoints related to articular involvement showed good results.

A phase I RCT showed that 5 out of 12 patients treated with *dapirolizumab* achieved an SRI-4 response by week 12 (vs 1 out of 7 in the placebo group) (96). However, the phase IIb RCT in adults with moderately-to-severely active SLE failed to meet its primary endpoint at week 24, despite the improvement of other secondary endpoints and biomarkers (97). A phase III study is ongoing (NCT04294667).

Daratumumab, a monoclonal antibody targeting CD38, induced substantial clinical responses in cases with life-threatening lupus, sustained afterward by maintenance therapy with belimumab (98, 99).

According to some reviews, *IVIg* can be considered in acute severe flares or refractory SLE, as well as in LN treatment (100, 101). *IVIg* was also used successfully in the treatment of SLE-associated severe myelitis (102).

A prospective, open-label, single-arm, phase I/IIa trial evaluated the safety, tolerability, and response of Treg to low-dose *interleukin-2* (IL-2) in patients with active and refractory SLE (103). Even though the responsiveness to IL-2 in Treg from SLE patients showed no impairment, the clinical response was transient and declined almost to baseline levels in between the cycles, suggesting that the cyclic treatment modality may be suboptimal.

The use of anti-tumor necrosis factor (TNFα) in SLE is controversial, due to the risk of disease flare (14, 104). The short-term use of *infliximab* was successful in an open-label study with moderately active SLE patients (105). However, patients with lupus arthritis (n=5) maintained clinical response for less than 2 months after the last infusion. Long-term therapy was also associated with serious adverse events (SAEs) in two patients.

Obinutuzumab combined with mycophenolate and steroids was evaluated in active III/IV LN patients in a phase II, placebo-controlled RCT. At week 52, a higher proportion of obinutuzumab-treated patients achieved response (though not statistically significant), and a statistically significant improvement of 19% was observed at week 104 regarding complete renal response (106). In a small observational study with 4 non-responders to RTX who switched to *ocrelizumab*, three achieved and maintained clinical response during the following 5 years but six SAEs were observed (four serious infections) (107). Regarding *ofatumumab*, one case series with SLE patients intolerant to RTX showed that in 12 patients with LN, half achieved renal remission after 6 months of ofatumumab treatment (108).

Anti-CD19 *CAR T cell therapy* was evaluated in five patients with refractory SLE, who achieved SLE remission after 3 months following a well-tolerated treatment (109).

3.2 Off-label biologic therapy in antiphospholipid syndrome

3.2.1 Disease background

APS is characterized by the presence of persistent antiphospholipid antibodies (aPL) leading to thrombosis in veins, arteries, and microvasculature as well as obstetrical complications (110). About 1% of patients develop catastrophic APS (CAPS), a severe and frequently fatal manifestation (111, 112). CAPS is

defined as small vessel thrombosis in three or more organs, systems, and/or tissues either simultaneously or within 1 week, with histological confirmation of small vessel occlusion, in the presence of persistent aPL and absence of vasculitis (113). Patients with other SAIDs (most frequently SLE) can also present aPL, increasing the risk of thrombotic events (110).

Thrombosis prevention requires anticoagulation and anti-platelet aggregating agents (114). For patients with recurrent thrombosis, fluctuating INR, or for those who are at high risk of major bleeding, alternative therapies may be considered, including low-molecular-weight heparin, hydroxychloroquine, or statins (110). For patients with CAPS, acute management is based on a combined therapy using anticoagulation, corticosteroids, plasma exchange, and/or intravenous immunoglobulin administration and, in the case of CAPS initiated by an infectious event, systemic antibiotics (110, 113–115). Some recommendations suggest the use of rituximab for refractory APS patients (116), and rituximab or eculizumab for refractory CAPS (113, 114, 117).

3.2.2 Recommendations and summary of evidence

Recommendations for the off-label biological therapy of APS and CAPS are presented in Table 3.

3.2.2.1 Intravenous immunoglobulin

Acute treatment with anticoagulants, corticosteroids, and IVIG is the current SoC of CAPS. The CAPS registry has shown significantly lower mortality among CAPS patients receiving combination therapy, compared with those receiving other treatments (odds ratio [OR], 0.51; 95% confidence interval [CI], 0.27, 0.95) (117).

Even though the paucity and equivocal evidence retrieved from publications between 2014 and 2019, IVIG has been used in the treatment of APS patients with recurrent thrombosis (118), obstetric APS (119–122), and CAPS (123). Usually administered at doses of 0.4 g/kg/day for 5 days, IVIG may be more useful in patients with thrombocytopenia and has the advantage of being immunomodulatory rather than immunosuppressive (117, 118). However, IVIG was also associated with both increased thrombotic risk and worsening renal function, especially in elderly patients (117).

3.2.2.2 Rituximab

RTX may be used as 1st line therapy in CAPS patients, added to combination therapy (glucocorticoids, anticoagulation, plasmapheresis, and/or IVIG and systemic antibiotics if adequate). RTX has been reported to be successful in the acute treatment of CAPS first episodes, as part of combination treatment (124, 125), especially in the case of life-threatening complications (126). The CAPS registry showed that, among 20 patients treated with RTX at 375 mg/m² weekly for 4 weeks or 1g every 14 days for 2 sessions, 75% (n=15) recovered from whom 87% (n=13) had no recurrent thrombosis during follow-up (115, 127). Lack of response was reported in one patient with a subacute recurrence of CAPS

treated with combination therapy and rituximab (128), and in one patient with diffuse alveolar hemorrhage treated with RTX and glucocorticoids only (129).

Patients with CAPS and other SAIDs, namely SLE, may benefit from RTX added to combination therapy (glucocorticoids, anticoagulation, IVIG, systemic antibiotics if adequate). A single-center retrospective analysis showed consistent improvement in 5 out of 6 patients with SLE-associated APS after treatment with rituximab (130). Indications for RTX therapy were a failure in warfarin therapy despite the adequate target INR (4 cases), and life-threatening active disease refractory to conventional therapy (one case of transverse myelitis, and another of diffuse alveolar hemorrhage). All patients received prior conventional therapy. RTX also showed efficacy in case reports of SLE-associated APS (131) or CAPS (132, 133).

RTX can be used as 1st line therapy in APS patients with severe thrombocytopenia. An open-label pilot study with 19 patients aPL positive reported that RTX had some efficacy in controlling manifestations such as thrombocytopenia, hemolytic anemia, and skin ulcers (134).

3.2.2.3 Other biologic therapy

Eculizumab has been reported to successfully treat patients with refractory CAPS, and patients with renal transplants and APS or CAPS, and some authors suggest its use in refractory patients who are refractory to other therapeutics (135, 136).

3.3 Off-label biologic therapy in Sjögren's syndrome

3.3.1 Disease background

Sjögren's syndrome (SS) is among the most prevalent SAIDs and concurs frequently with other conditions, such as rheumatoid arthritis, SLE, scleroderma, or hypothyroidism, while SS (SS) shows a prevalence in Europe between 0.1% and 4.8% (137, 138). It is characterized by lymphocytic infiltration of the epithelium of exocrine glands, resulting in xerostomia and xerophthalmia (i.e., sicca symptoms) (139). Extra glandular involvement may occur in at least one-third of patients, with chronic fatigue, arthralgia, and organ involvement such as lungs, skin, kidneys, and nervous system (140).

Treatment of SS is mainly empirical and symptom-targeted (140, 141). Some recommendations suggest that the use of systemic immunosuppressive therapies, including glucocorticoids and immunoglobulins, should be restricted to patients with active systemic disease and only after evaluating the severity and organ damage (139, 142, 143).

3.3.2 Definitions

- Overall severity of SS should be evaluated based on the EULAR Sjögren's syndrome disease activity index (ESSDAI) (143).

- Severe systemic SS: patients with an ESSDAI score >14, or high activity in any of the ESSDAI domains (e.g., with organ damage) (143).
- Organ damage should consider blood (anemia, leukopenia, thrombocytopenia, lymphoma); kidney (diabetes insipidus, interstitial nephritis, glomerular disease); gastrointestinal (xerostomia, esophagitis, gastritis, primary biliary cholangitis), lung (interstitial pneumonitis); cardiovascular (vasculitis), serious swelling of the parotid gland, inflammatory arthritis, CNS involvement or peripheral neuropathy, and audition and visual disturbances.
- Refractory SS: patients for whom conventional therapies, including topical moisturizers, secretagogues, anti-inflammatories, and immunomodulators have proven to be insufficient.
- SS associated with other SAIDs should be treated according to these recommendations, in addition to the treatment of the associated SAID.

3.3.3 Recommendations and summary of evidence

Recommendations for the off-label biological therapy in SS are presented in Table 4.

3.3.3.1 Rituximab

In SS patients with sicca symptoms only, the use of biological therapy is not recommended. In the TEARS study (144), RTX did not show efficacy in reducing symptoms or disease activity in patients with SS at week 24 but did improve fatigue at weeks 6 and 16 of treatment, and the physician evaluation of disease activity at week 6. The TRACTISS study also failed to prove RTX efficacy in this population (145). Two meta-analyses reported the lack of RTX efficacy in SS, failing to improve lacrimal gland function, oral dryness, or fatigue at 6 months (146, 147).

RTX may be used as 1st line therapy in patients with SS and severe systemic manifestation, with risk of lymphoma (at least 3 risk factors for lymphoma) and recent onset (i.e., less than 12 months of evolution). The Spanish GEAS-SS Registry (148) of SS patients with lymphoma treated with RTX-based chemotherapy regimens showed that 41 out of 64 patients achieved a complete response. In a retrospective study with SS patients with mucosa-associated lymphoid tissue-type lymphoma of the parotid gland, a complete response was observed in 5 out of 13 patients treated with RTX only and in all 6 patients with RTX-based chemotherapy (149).

RTX may be used as 1st line therapy in patients with SS (<12 months of evolution) and peripheral neuropathy, severe thrombocytopenia, severe CNS disease, severe parotid swelling, and/or cryoglobulinemic vasculitis. One of the first RCTs with RTX (n=30 patients) described a significant reduction in reported extra-glandular manifestations and an improvement of the musculoskeletal features at weeks 12 and 36 (p=0.029) and vasculitis at week 24 (p=0.03) (150). Another RCT in patients with cryoglobulinemia (associated or not with SS) also had positive results (151). In a prospective cohort of 78 patients with high

disease activity, RTX showed a good safety profile and was effective for the treatment of SS with systemic manifestation, based on the reduction of the ESSDAI and of daily dose of corticosteroids (152). In a series of 16 patients (153), RTX was associated with an improvement of the systemic manifestations in ≥80% of cases. Most studies included patients with a recent onset of SS, hence the lower strength for the recommendation that *RTX may be used as 1st line therapy in patients with SS (>12 months of evolution) and multiple neuropathies, severe thrombocytopenia, severe CNS disease, severe parotid swelling and/or cryoglobulinemic vasculitis.*

RTX is recommended as 2nd line therapy in RTX-naïve patients with refractory SS and presenting lymphoma, multiple neuropathies, severe thrombocytopenia, severe CNS disease, severe parotid swelling, and/or cryoglobulinemic vasculitis. A multicenter registry showed that, among 15 refractory SS patients treated with RTX due to extra-glandular involvement, 10 (67%) had a complete response, 3 (20%) a partial response, and 2 (13%) were non-responders after 12 months (154). A retrospective study showed the effect of RTX in improving SS patients with thrombocytopenia refractory to conventional immunosuppressive drugs (46). More recently, a single-center retrospective study reported that, among 10 female patients with severe or refractory SS involvement, six became asymptomatic, two had symptomatic improvement and two had no benefit, suggesting that RTX can be considered in these cases (155).

3.3.3.2 Sequential therapy of Belimumab followed by Rituximab

In RTX-experienced patients, sequential therapy of belimumab-RTX may be used. The BELISS open-label trial showed a significant decrease in the mean ESSDAI score from 8.7 to 5.7 at week 28 (156). The primary composite endpoint was achieved in 18 (60%) patients – i.e., improvement in two of five items at week 28, comprising a 30% reduction in VAS scores of dryness, fatigue, pain, or physician-assessed systemic activity and/or >25% improvement in any B cell activation biomarker. Belimumab was effective in 3 out of 5 patients refractory to RTX. The BELISS extension showed that the improvement was significantly maintained in 19 patients that completed one year of treatment (157).

3.3.3.3 Other biologic therapy

Abatacept showed good results in open-label studies, with a significant reduction of ESSDAI and an improvement in fatigue and quality of life (158), but failed phase III trials in the treatment of active SS (159, 160).

4 Conclusions

To our knowledge, it is the first attempt to establish recommendations regarding the use of biologic therapies in SAIDs, namely in clinical settings with evidence gaps regarding the use of these therapies. After an extensive literature review and consensus methodology by a large expert panel, a total of 32 recommendations were defined for SLE, APS, and SS. The higher

number of recommendations for SLE treatment reflects the fact of being a less organ-specific syndrome, with pleomorphisms and multiple pathogenic mechanisms. APS and SS are also challenging to manage, especially when presenting with multisystemic and severe manifestations that can urge the prevention of extensive organ damage or even death, as happens in CAPS.

We acknowledge that supporting evidence is mostly derived from small trials and observational studies, except for some important RCTs on SLE. The scarcity of RCT is well recognized among SAIDs, thus limiting the evidence level of the recommendations, and increasing its susceptibility to experts' own experience. Nevertheless, bias was minimized by an extensive literature search and the number of experts who voted on the recommendations.

The management of patients living with SAIDs is demanding and goes beyond treatment recommendations (161). Future updates of this guidance should address dimensions such as vaccination strategies as less is known about the immunization of APS and SS patients and about SARS-CoV-2 vaccines in SAIDs receiving biologic therapy (162), although some studies have addressed the immunization of SLE patients (163, 164).

There are many innovative drugs available and being developed, but not all are effective across all SAIDs. The same clinical manifestation does not imply the same pathophysiology, and the active pathway at a given time may change within the same disease, thus making the demand for effective treatments even more challenging. In addition, the high costs of biologics and, consequently, the limitations in Europe on timely access to innovative drugs are barriers that need to be addressed. This evidence and practice-based guidance can help other clinicians in their therapeutic decisions and, ultimately, improve the outcome for patients living with these conditions.

Author contributions

Substantial contributions to study conception and design: AM, MF, CV. Drafting the article: JDA, JF, RF, MF, CV. Review of the article for important intellectual content: All authors. All authors contributed to the article and approved the submitted version.

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AM received consulting, speaker, and advisory board fees from AbbVie, Lilly, MSD, Novartis, Pfizer, and Roche, speaker fees from BMS and Janssen, consulting fees from Janssen and Takeda; and received support for attending meetings from AbbVie, Janssen, Novartis, and Pfizer. JDA received consulting, speaker, and advisory board fees from AbbVie, Lilly, and Novartis, and consulting fees from Pfizer. CV received advisory board fees from AstraZeneca, GSK, Janssen, Novartis, and Pfizer. MF is an employee of a contract research organization (CTI Clinical Trial & Consulting Services) that provides services to several pharmaceutical companies.

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

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Supplementary material

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