THERAPIES IN THE PIPELINE FOR SYSTEMIC AUTOIMMUNE DISEASES

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ABSTRACT

The current goals in the development of novel therapeutics of systemic autoimmune diseases are to develop agents more effective than conventional therapies as well as to reduce the risk of organ damage. To achieve this goal, large multicentre randomised controlled trials are needed to confirm the efficacy and safety of novel agents. Whether these novel modalities are synergistic to conventional drugs, the optimal dosages, and duration of treatment, need to be explored.

As expected, the development of new molecules for the treatment of autoimmune diseases is constant, and there are different ongoing clinical trials. We review the different molecules in the pipeline, summarised in Tables 1, 2, and 3. We also show the successes, failures, and molecules that require more evidence.

Keywords: Systemic lupus erytematosus (SLE), Sjögren's syndrome (SS), anti-phospholipid syndrome (APS), new therapies.

SYSTEMIC LUPUS ERYTHEMATOSUS

Systemic lupus erythematosus (SLE) is a chronic multisystemic autoimmune disease of unknown aetiology, with unpredictable disease course intermingled with periods of remission and exacerbation.[1,2] For decades, therapy for SLE has been based on glucocorticosteroids, hydroxychloroquine, and immunosuppressive agents leading to an improvement in the prognosis of the disease. However, the occurrence of refractory disease and adverse events related to conventional therapies still represents a challenge.[3] The immunopathogenesis of SLE is complex with dysregulation of T helper Type 1, 2, and 17 pathways that results in the elevation of the levels of a number of pro-inflammatory cytokines such as tumour necrosis factor alpha, interleukin (IL)-6, 10, 15, 18 and interferon (IFN)-α in patients with active SLE.[3]

B Cell Therapies

B cells can be selectively targeted for depletion either via direct B cell molecules such as CD19, CD20 (rituximab and ocrelizumab), and CD22 (epratuzumab) or by inhibition of B cell survival factors: B lymphocyte stimulator (BLyS) (belimumab, tabalumab, blisibimod) and a proliferation-inducing ligand (APRIL) (atacicept).[3]

The use of rituximab in patients with SLE has been investigated in two randomised controlled trials (RCT): the EXPLORER study (Exploratory Phase II/III SLE Evaluation of Rituximab)[4] in patients with moderate-to-severe extra-renal SLE receiving immunosuppressants and corticosteroids, and the LUNAR study[5] in patients with proliferative lupus nephritis (LN) treated concomitantly with mycophenolate mofetil (MMF) and corticosteroids. These studies failed to demonstrate additional benefit and superiority of rituximab, respectively. Despite these results, rituximab is still extensively

used 'off-label', especially in refractory cases to standard treatment, in light of 'experience-based' medicine and their use is included in the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) recommendations for refractory LN.[3,6,7]

Belimumab

The efficacy and safety of belimumab was tested by two pivotal RCT, BLISS-52[8] and BLISS-76,[9] that included 1,684 SLE patients with mild-to-moderate disease activity (excluding severe renal or central nervous system involvement). In both studies a dose of 10 mg/kg plus standard treatment met the primary efficacy endpoint: a greater SLE responder index (SRI) index atb Week 52. *Post hoc* analyses of the two BLISS trials found that patients that had a SELENA-SLEDAI score ≥10, with low complement, were anti-dsDNA positive, or had baseline corticosteroid use, demonstrated greater response.[10]

Table 1: New therapies in the pipeline for systemic lupus erythematosus.

Therapy	Target	Clinical stage for SLE treatment	Primary result
B cell depletion			
Rituximab	CD20	Off-label label use, LUNAR (N=144) and EXPLORER (N=257) Phase II/III	LUNAR: renal response rates 56.9% for RTX and 45.8% for placebo (p=0.18) EXPLORER: no difference in major/partial clinical responses, overall response rate 28.4% versus 29.6% for placebo and RTX, respectively
Ocrelizumab	CD20	Phase III BEGIN and BELONG (N=381) trials	BEGIN: interrupted early, no benefit to patients with active SLE BELONG: stopped due to increased serious infections, mainly ocrelizumab+MMF
Epratuzumab	CD22	Phase II trials ALLEVIATE 1 (N=14) and 2 (N=90) and EMBLEM (N=227), Phase III EMBODY 1 and 2 trials	ALLEVIATE 1 and 2: improved rates of BILAG, terminated due to disruption in drug supply EMBLEM: improved rates of BICLA, higher proportion of responders in all groups than placebo
Blockade of B cell cytokine activation			
Belimumab	BAFF	Approved pivotal trials BLISS 52, BLISS 76	Greater SRI index at Week 52
Belimumab	BAFF	Phase III for LN	
Atacicept	BAFF/ APRIL	Phase II/III APRIL-SLE (N=461), APRIL-LN (N=6)	APRIL-SLE: 150 mg dose beneficial effects versus placebo in flare rates and time to first flare, reduced total Ig levels, anti-dsDNA, increased complement APRIL-LN: terminated prematurely, unexpected reduced IgG and serious infections
Blisibimod	Anti-B-Lys	Phase II PEARL-SC (Phase III: CHABLIS-SC1 on course)	Improved SR-5, reduced proteinuria, reduced anti-dsDNA and B cells, increased complement
Tabalumab	Anti-B-Lys	Phase III ILLUMINATE 1 (N=1,164) and 2 trials (discontinued due to lack of efficacy)	ILLUMINATE I: no significant improvement SRI-5 Week 52, secondary endpoints did not meet. ILLUMINATE 2: higher dose only met primary endpoint
Blockade of T cell co-stimulation			
Rigerimod		Phase IIB (N=136)	Higher SRI than placebo Week 12 (62 versus 39)
Abatacept	CTLA4	Phase IIB (N=118)	Failed to meet the primary/secondary end-point (new flare/BILAG)
Edratide		Phase II (N=340)	Failed to achieve co-primary endpoints: SLEDAI-2K and adjusted mean SLEDAI
CDP7657	CD40L	Phase I (N=17)	100% patients with mild AE, moderate intensity, two serious AE
AMG 557	ICOS: B7RP1	Phase I NCT00774943	
MEDI-570	ICOS	Phase I NCT01127321	Terminated (business reasons)
JAK116439	JAK	Phase II	

Table 1 continued.

Therapy	Target	Clinical stage for SLE treatment	Primary result
Cytokine-directed therapy			
Tocilizumab	IL-6	Phase I (N=16) (RCT are awaited)	Improvement in SLEDAI score >4 in 53% patients, reduction in anti-dsDNA
Sirukumab	IL-6	Phase I (N=46) II	Phase II: fails improve proteinuria. Interrupted due high infection rates
Laquinimod	IL-6, 12, 17 and 23, TNF-α	Phase IIa (N=46)	Additive effect with MMF and CS, improve renal function and proteinuria
Rontalizumab	IFN-α	Phase II ROSE study (N=159)	Reduced IFN signature, BILAG and SRI were similar between rontalizumab and placebo groups. *Post hoc*: improvement signs and symptoms, flare rates, steroid burden Week 24
Sifalimumab	IFN-α	Phase IIb (N=431)	Reduced SRI-4 at Day 365, clinical improvements skin, joint, and patient-reported outcomes
Anifrolumab	IFN-R	Phase II (N=305)	Reduced SRI-4 at Day 365, steroid sparing, lower rates of BILAG
AMG-811	IFN-γ	Phase I (N=21)	Reduction levels CXCL10 (IP-10) levels and IFN-γ, improvement proteinuria
IFN-α kinoïd	IFN-α	Phase I/II (N=28)	Higher anti-IFN-α titres in signature-positive patients, and C3 levels
AGS-009	IFN-α	Phase Ia (N=28)	Safe and well tolerated, no signficant neutraliztion of IFN signture at doses >0.6 mg/kg
Fcy receptor modulation			
SM101	FcyRIIB	Phase IIa (N=51)	SRI-4 response rate was twice as high in the SM101-treated patients versus placebo, response in patients with LN was greater, improvement skin and arthritis
Toleragen molecule			
Abetimus sodium	Anti-dsDNA	Phase II/III ASPEN trial (N=890)	Reduced anti-dsDNA. Not meet the expected endpoint. Study stopped
Proteasomes			
Bortezomib	Proteasome inhibitor	Phase II (N=12) (7 patients discontinued)	Disease activity decline and remained stable for 6 months. AE: 17

SLE: systemic lupus erythmatosus; RCT: randomised controlled trials; IL: interleukin; TNF: tumour necrosis factor; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; SRI: SLE Responder Index; AE: adverse effects; BICLA: BILAG-based Combined Lupus Assessment; BILAG: British Isles Lupus Assessment Group; CS: corticosteroids; IFN: interferon; Ig: immunoglobulin; IP-10: interferon gamma-induced protein 10; LN: lupus nephritis; MMF: mycophenolate mofetil; RTX: rituximab; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

Ocrelizumab

Two Phase III RCT, the BEGIN and renal BELONG, investigated the efficacy of ocrelizumab in non-renal and renal SLE, respectively.[11] The BEGIN study was interrupted early because ocrelizumab was not likely to benefit patients with SLE. The BELONG trial recruited patients with proliferative LN (Class II/IV), treated them with high dose steroids, and either MMF or cyclophosphamide.[12] A total of 381 patients were recruited before the trial was terminated due to an imbalance of the rate of adverse effects; 233 patients passed the 32-week point and the difference was nonsignificantly higher than placebo (67% versus 55%).

Epratuzumab

Early studies with epratuzumab in SLE included two small trials (ALLEVIATE-1 and ALLEVIATE-2)[13] which compared two treatment arms with epratuzumab (360 mg/m^2 or 720 mg/m^2) and

a placebo arm. Although after 12 weeks of treatment, patients who had received treatment with epratuzumab improved in British Isles Lupus Assessment Group (BILAG) indices, these trials were interrupted prematurely due to a lack of drug supply. Recently, the EMBLEM[14] Phase IIb trial was published. This study included 227 patients with SLE who were assigned to six different arms: one placebo arm and five arms with varied doses of epratuzumab. The results of this study (BILAG responses after 12 weeks of treatment) suggested that epratuzumab could be effective in the treatment of SLE, for this reason two Phase III trials (EMBODY 1 and 2) are ongoing.[15,16]

Tabalumab

The ILLUMINATE trials include two Phase III trials evaluating the efficacy and safety of tabalumab. In ILLUMINATE-1 the primary endpoint, the SRI-5 response, was not met for either dose group (120 mg once every 2 weeks [Q2W] and 120 mg once every 4 weeks) at Week 52. Statistical significance was not achieved on secondary measures of clinical efficacy, despite the observed biological response.[17] In ILLUMINATE-2 the primary endpoint was met in the 120 mg Q2W group but the secondary endpoint was again not met.[18] Collectively, these data did not meet expectations for efficacy in the context of existing treatments, leading to discontinuation of the development of tabalumab for SLE.

Blisibimod

Blisibimod is a fusion protein between the fragment crystallisable region domain of one immunoglobulin (Ig)G and four B cell activating factor (BAFF) binding domain peptides, that selectively binds to BLyS. The efficacy and safety of subcutaneous blisibimod was evaluated in the Phase IIb trial PEARL-SC in 547 patients with SLE.[19] The SRI-5 was higher in the patients randomised to the highest dose of blisibimod 200 mg once weekly compared to placebo, reaching statistical significance at Week 20 (p=0.02). This response was higher in patients with SLEDAI improvements ≥8, and in the subgroup of patients with SLEDAI ≥10 at baseline. A significant reduction in proteinuria was observed in subjects with a protein to creatinine ratio of 1:6 at baseline. Their biological effect was evidenced by the normalisation of biomarkers of SLE activity: decrease in anti-dsDNA (p<0.01) and increase in complement C3 (p<0.01) and C4 (p<0.001). These encouraging results have led to the evaluation of the effects of blisibimod through ongoing Phase III trials (CHABLIS-SC1-NCT01395745).[20]

Atacicept

Atacicept is a recombinant fusion protein consisting of the TACI receptor that binds both BLyS and APRIL fused with the fragment crystallisable region portion of IgG; neutralising both BLyS and APRIL might be more effective than BLyS alone. In Phase Ib studies with different dose regimens the biological activity of atacicept was observed, with dose response reduction of B lymphocytes and immunoglobulin levels, particularly IgM, followed by the IgA and IgG.[21] A later Phase II/III RCT of two doses of atacicept (75 mg or 150 mg) was designed to assess whether it could prevent flares in patients treated with corticosteroids. Two fatal infections occurred in the atacicept arm of 150 mg leading to premature termination of this group, but in this group a significant reduction in the flare rate (43% versus 60%; odds ratio [OR]: 0.49 [0.26–0.92], p=0.027) and a delayed time to first flare compared to placebo (hazard ratio [HR]: 0.56 [0.36–0.87], p=0.009) were observed.[22] Based on the fact that APRIL could be a potential biomarker for predicting hard-to-treat cases of LN, a Phase II/III RCT was initiated to evaluate their efficacy and safety in patients with active LN who recently started corticosteroids and MMF. An unexpected decline in serum IgG and serious infections occurring in six patients led to early termination of the trial.[23] These results suggest that the dose of concurrent immunosuppressive medications should be reduced.

Targeting the Interferon

The key role of IFN-α in lupus has been substantiated by transcriptome analysis in which the upregulation of numerous IFN-α dependent genes in peripheral blood mononuclear cells from lupus patients was reported, constituting an overall 'IFN signature' in SLE. This signature is present in 50–80% of SLE patients.[24] There is promising preclinical evidence that the inhibition of the secretion and downstream effectors of both IFN-α and IFN-γ may be effective for the treatment of SLE. The primary agents that are currently in development are monoclonal neutralising antibodies that bind to and neutralise IFN-γ (AMG 811), IFN-α (sifalimumab, rontalizumab, and

AGS 009) or its receptor (anifrolumab [ANIFR]), and IFN-α-kinoid.[24]

Anifrolumab

The efficacy and safety of ANIFR were assessed in a Phase II RCT in SLE patients (N=305) stratified by SLEDAI score, corticosteroid dose, and IFN gene signature (IFN high versus IFN low). Patients were randomised to receive ANIFR (300 mg, 1,000 mg) or placebo.[25] The primary endpoint, SRI-4 response at Day 169, was met by a greater proportion of ANIFR-treated patients (placebo: 17.3%; 300 mg: 34.3%, p=0.014; 1,000 mg: 28.8%, p=0.063). Corticosteroid reduction to ≤7.5 mg/day at Day 365 was achieved by 26.6% of placebo, 56% of 300 mg (p=0.001), and 31.7% of 1,000 mg (p=0.595) patients. At Day 365, the secondary SRI endpoint was met by 51.5% of the patients taking a 300 mg dose of ANIFR (p>0.001), 38.5% of those taking a 1,000 mg dose (p=0.048), and 25.5% of those taking a placebo. A persistent benefit across multiple global and organ-specific measures was also demonstrated, as well as lower rates of BILAG moderate/severe flares.

Table 2: New therapies in the pipeline for primary Sjögren's syndrome.

Drug	Target	Clinical stage for pSS treatment	Primary result
Hydroxychloroquine	IFN inhibition	JOQUER trial Phase III RCT (N=120)	No score improvement by at least 30% on two of the three VAS (dryness, pain, and fatigue) at Week 24. No significant difference between the two groups in any of the secondary clinical endpoints: ESSPRI, ESSAI, Schirmer's test, salivary flow, Ig levels, SF-36, PROFAD, SSI, HAD
B cell depletion			
Rituximab	CD20	TEARS (N=120)	No sustained score improvement by at least 30% on two of the four VAS (dryness, pain, fatigue, and global)
		TRACTISS (N=133)	No improvement by at least 30% on oral dryness and fatigue, no improvement on overall dryness, ESSAI, lacrimal flow, QoL; improved unstimulated salivary flow
Epratuzumab	CD22	Open label (N=16)	Improved Schirmer's test, unstimulated salivary flow, and VAS fatigue score
Belimumab	BLISS	Open label (N=30)	60% of patients responded, with a decrease in the ESSDAI without change in salivary flow or Schirmer's test; a significant decrease in Ig levels and RF was also observed
Abatacept		Open label (N=11) ASAP trial (N=15)	Reduced glandular inflammation, reduced number of lymphocytic foci and numbers of local FoxP3 T cells Increased saliva production Reduced ESSDAI and ESSPRI, reduced RF IgG levels, reduced fatigue, increased QoL
Tocilizumab	IL-6	ETAP trial RCT Phase II/III (N=110 estimated enrolment) NCT01782235	To evaluate: improvement ≥3 points of the ESSDAI score
Baminercept	Lymphotoxin-β	Phase II RCT (N=72 estimated enrolment) NCT01552681	To evaluate: change in stimulated whole salivary flow

pSS: primary Sjögren's syndrome; ESSDAI: Sjögren's syndrome Disease Activity Index; ESSPRI: EULAR Sjögen's syndrome Patient Reported Index; HAD: hospital anxiety and depression; IFN: interferon; Ig: immunoglobulin; PROFAD: profile of fatigue and discomfort; QoL: quality of life; SF-36: 36-item Medical Outcomes Study Short Form Health Survey; SSI: Sicca Symptoms Inventory; VAS: Visual Analogue Scale; RCT: randomised controlled trial.

The lack of dose response was likely due to the fact that even the lower dose suppressed ~90% of activity in 21 IFN-regulated genes. At present, ANIFR's Phase II results outpace sifalimumab, which had smaller effect sizes. If the results hold, ANIFR could become the second new drug to treat SLE in more than 50 years.

SJÖGREN'S SYNDROME

Sjögren's syndrome (SS) is a systemic autoimmune disease that mainly affects the exocrine glands and usually presents as persistent dryness of the mouth and eyes due to functional impairment of the salivary and lacrimal glands.[26] B lymphocytes are some of the key therapeutic targets, either directly or indirectly by inhibiting IFN, BAFF, IL-6, or IL-21.[27] Symptomatic and topical treatments are essential in most patients with limited glandular disease; systemic immunomodulatory treatments must be used in patients with extra-glandular manifestations, occurring in one-third of the patients.[28]

Interferon Inhibition

According to the new insights into its pathogenesis, SS is considered an innate immune-triggered epithelitis resulting from the activation of toll-like receptors, IFN pathways, and B and T lymphocytes.[29] Hydroxychloroquine is the only IFN inhibitor evaluated in SS[30] and is usually prescribed for patients with fatigue, arthralgia, and myalgia, rather than severe systemic manifestation. Evidence regarding its efficacy is limited, with data derived from open retrospective studies and one crossover trial.[31-34]

To clear this issue, the JOQUER trial, a multicentre RCT was conducted in 120 SS patients.[35] Patients were randomised (1:1) to receive hydroxychloroquine (400 mg/day) or placebo until Week 24. The primary endpoint was the improvement at 24 weeks by ≤30% of two of the three patient visual analogue scales (VAS) of the most frequent symptoms: dryness, pain, and fatigue. No efficacy was observed for this endpoint. In addition, there was no significant difference between the two groups in any of the secondary clinical endpoints, or in systemic disease activity assessed by the EULAR SS disease activity index (ESSDAI). There was no efficacy in patients with anti-Ro autoantibodies, high IgG levels, or systemic involvement.[35]

B Cell Targeted Therapies

Several B cell molecules can be targeted. CD20, CD22, and the BAFF are potential targets for strategies designed to modify B cell function in SS, both directly and indirectly.[36,37] The most widely studied target for achieving B cell depletion is the CD20 antigen. Observational studies as well as open-label studies and registries have shown that rituximab is effective in SS patients with active disease and extra-glandular disease, improving both subjective and objective complaints including salivary function, with an observed overall efficacy in up to 60% of the patients.[38]

In two small RCT, rituximab showed a significant improvement from baseline on fatigue, the stimulated whole saliva flow-rate, and several other variables (e.g. B cell and rheumatoid factor [RF] levels, unstimulated whole saliva flow rate, lacrimal gland function, multi-dimensional fatigue inventory scores, Short Form 36 health survey scores, and VAS scores for sicca symptoms).[39,40]

To assess if rituximab can be used in large populations of patients and if it changes the course of the disease, two large double blind studies were undertaken. The TEARS study (Tolerance and Efficacy of Rituximab in primary Sjögren's syndrome) which included 120 patients having either recent and active disease and/or at least one extra-glandular severe involvement, was recently published.[41] The primary endpoint was the improvement in 6 months of at least 30 mm of two of the four patient VAS: pain, fatigue, dryness, and disease activity. At Week 6, the proportion of patients with improvement in the primary endpoint was significantly higher in the rituximab group, without sustained significant improvement at 24 weeks. Showing that rituximab does not appear to relieve symptoms of SS, at least in the short-term.[41]

The other trial, TRACTISS study (Anti-B-cell therapy in patients with primary Sjögren´s syndrome), the largest randomised trial of biologic therapy in SS, included 133 patients to receive rituximab or placebo.[42] The primary endpoint was the improvement in VAS scores of fatigue and oral dryness. Secondary outcomes were VAS scores for fatigue or oral dryness separately, global assessment of SS activity, pain, ocular and overall dryness, as well as salivary and lachrymal flow rates, quality of life, and ESSDAI. In this trial there was no improvement of symptoms in the rituximab

arm; the response rates were 39.8% and 36.8% in the placebo arm (adjusted OR: 1.13, 95% confidence interval [CI]: 0.50–2.55). In addition, there were no significant differences in any outcome measure, except unstimulated salivary flow.[43]

Epratuzumab

In an open-label study, 16 SS patients (14 women, 2 men) were scheduled to receive four epratuzumab infusions at 2-week intervals. The most commonly improved parameters were Schirmer's test, unstimulated whole salivary flow, and VAS fatigue scores. A clinical response was noted in 53% of patients at 6 weeks and 67% at 32 weeks. Epratuzumab is not currently approved for the treatment of any autoimmune diseases and no double blind studies are currently planned in SS to confirm these data.[44]

B Cell Activating Factors in Sjögren´s Syndrome

BAFF transgenic mice develop autoimmune-like manifestations reminiscent of SS as they age: enlarged salivary glands, severe sialadenitis, and decreased production of saliva.[45,46] Histological analysis of salivary glands reveals numerous features also present in human SS: the formation of germinal centres (GC) and ectopic GC.[46] In SS, BAFF provides anti-apoptotic signals and their expression may be increased in lymphoma.

Table 3: New therapies in the pipeline for antiphospholipid syndrome.

Treatment	Target	Clinical stage for APS treatment	Primary result
Direct oral anticoagulants			
Rivaroxaban	Factor-Xa inhibitor	Phase II/III RAPS (N=156) with/ without SLE, on warfarin target INR 2.5 for previous VTE (on course) Phase III RCT TRAPS (N=536) triple positive patients with APS (on course)	Non-inferior to warfarin, pending results
Hydroxychloroquine	Annexin A5 resistance	Observational 12 week (unknown) NCT01475149	Change in annexin V resistance assay
	Inhibition of toll like-receptors	Phase III APS ACTION trial (N=75) NCT02635126	Changes in the number of acute thrombosis (arterial or venous)
B cell inhibition			
Rituximab	CD-19	RITAPS trial (N=19)	Safe, does not change aPL profiles, effective in controlling some but not all non-criteria manifestations: skin ulcers, aPL, cognitive dysfunction, nephropathy, thrombocytopenia
Complement inhibition			
Eculizumab	Terminal complement protein C5	Phase II (N=10) renal transplanted patients with history of CAPS NCT01029587 Mouse models	Prevention of CAPS after kidney transplant attenuates thrombosis in mouse models of APS, prevents pregnancy loss
Sirolimus	mTORC (anti-phospholipid syndrome nephropathy)	Observational (N=10)	aPL IgG stimulated mTORC through PI3K-AKT pathway, patients treated with sirolimus showed no recurrence of vascular lesions and had decreased vascular proliferation, 70% functioning renal allograft 144 months after transplantation versus 11% untreated Activation of mTORC was found in vessels of autopsy specimens from patients with CAPS

APS: antiphospholipid syndrome; aPL: antiphospholipid antibodies; CAPS: catastrophic antiphospholipid syndrome; VTE: venous thromboembolism; mTORC: mammalian target of rapamycin; IgG: immunoglobulin G; SLE: systemic lupus erythematosus; INR: international normalised ratio.

BAFF antagonists may be used in the treatment of SS. Patients with hypergammaglobulinaemia, autoantibody production, ectopic GC, and lymphomas would be candidates for this therapy.[46]

An open-label trial, the BELISS, included 30 patients who were treated with belimumab. The primary endpoint, assessed at Week 28, consisted of obtaining at least two of the following five response criteria: VAS reduction ≥30% of dryness, fatigue, pain, or systemic activity, and reduction >25% in serum levels of some markers of B cell activation. They found that 60% of the patients (18/30) responded to belimumab with a decrease in the ESSDAI, but had no change in salivary flow or Schirmer's test. A significant decrease in Ig levels and RF was also observed.[47] Therapy with belimumab also induced a significant reduction in transitional and naïve B cell subsets to levels similar to those observed in healthy donors, normalised BAFF-R expression in all subsets in the memory compartment, with a decrease in the levels of Ig, RF, and anti-nuclear antibodies, and an increase in the C4 complement fraction.[48]

Inhibition of T Cell Co-Stimulation

In SS, T lymphocytes represent the majority population of salivary infiltrate. Given the recognised role of T cells and B cells in SS, selective modulation of co-stimulation represents a rational therapeutic strategy. The first open trial of abatacept in 11 patients with SS significantly reduced glandular inflammation and induced several cellular changes: a decrease of the number of lymphocytic foci and numbers of local FoxP3 T cells, with an increase of saliva production. However, the clinical effects were not standardised by clinimetric measures (ESSDAI, EULAR SS patient-related outcomes [ESSPRI], and fatigue).[49]

Another open-label study, the ASAP trial, was performed in 15 SS patients. A significant reduction of disease activity (measured by ESSDAI and ESSPRI) was observed and laboratory parameters such as the RF and IgG levels were lowered during treatment with abatacept. Fatigue also improved and patients experienced better health-related quality of life. The function of the salivary and lacrimal gland did not change during treatment.[50]

ANTIPHOSPHOLIPID SYNDROME

Antiphospholipid syndrome (APS) is an autoimmune disorder characterised by venous and arterial thrombosis and recurrent fetal losses, frequently accompanied by a moderate thrombocytopenia, and the presence of persistent circulating antiphospholipid antibodies (aPL).[51] The main goal of clinical management in APS is to avoid thrombotic and/or obstetric complications. Long-term anticoagulation with an oral vitamin K antagonist (VKA) constitutes the cornerstone of the pharmacological approach to thrombotic APS. A recent report issued by the task force on aPL stated that VKAs remain the mainstay of anticoagulation in APS and that direct oral anticoagulants may be considered in APS patients with a first or recurrent venous thromboembolisation occurring off or on sub-therapeutic anticoagulation, only when there is known VKA allergy/intolerance or poor anticoagulant control.[52] There is a growing number of case series where direct oral anticoagulants have been used in APS with varying degrees of success and failure. Successes were achieved in one series in which rivaroxaban was used for secondary prevention in patients with previous deep vein thrombosis, labile international normalised ratio (INR), simplification of the anticoagulation regimen and no triple aPL positivity patients.[53-55] Failures had the common denominator of presence of either recurrent thrombosis, arterial thrombosis, autoimmune disease, triple antibody positivity, or non-thrombotic manifestations of the disease, constituting patients with the highest risk profile.[56-58] Two large-scale ongoing studies clarify this issue, the first: the Rivaroxaban in Antiphospholipid Syndrome (RAPS) trial,[59] involving patients with a similar profile to those who were successful with rivaroxaban treatment. If this study demonstrates that the anticoagulant effect of rivaroxaban is not inferior to that of warfarin in absence of/less adverse effects, this would provide sufficient supporting information to change the practice, making rivaroxaban the standard of care for the patients with APS with or without SLE who have venous thromboembolism requiring an INR target of 2.5 in first instance. The second: the Rivaroxaban in Thrombotic Antiphospholipid Syndrome (TRAPS)[60] trial will include patients with predictors of failure including triple aPL-positive patients with clinical manifestations of APS, arterial events, and/or pregnancy morbidity, and so is portending less promising results.

Despite the pathogenic role in thrombosis of aPL, therapy should not primarily be directed at effectively reducing the aPL levels. To date

this can be accomplished by several regimens, including high dose steroid administration, immunosuppression, or plasma exchange. This elimination is temporary as antibodies return on cessation of therapy and the use of immunotherapy is generally not indicated unless required for the treatment of the underlying condition, e.g. SLE, or in acute life-threatening situations such as the catastrophic APS.

The management of aPL-positive patients with or without APS is currently suboptimal due to the anticoagulation not being fully effective, the limited knowledge of the specificity, and biological activities of aPL, new drug development for aPL-positive patients is challenging. Perhaps in the future the antithrombotic approach in APS patients may be replaced by a potentially safer immunomodulatory approach.[52]

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