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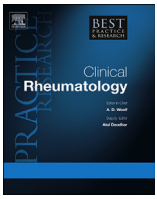

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Targeted therapies in systemic sclerosis, myositis, antiphospholipid syndrome, and Sjögren's syndrome

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A B S T R A C T

Targeted therapies using biological disease-modifying antirheumatic drugs (bDMARDs) and small molecule synthetic drugs have revolutionized rheumatological practice. Initially developed for the treatment of immune arthritis (rheumatoid arthritis, psoriatic arthritis, and spondylarthritis), both bDMARDs and small molecule synthetic drugs are now increasingly entering the space of connective tissue disease (CTD) treatment. Recent clinical trial data in systemic sclerosis (SSc) have been particularly encouraging with positive effects on outcomes having been observed with nintedanib preventing the decline of lung function in patients with SSc-related interstitial lung disease. Randomized trials targeting B-cells by rituximab in primary Sjogren's syndrome have led to mixed results. Novel strategies to target B-cells in primary Sjögren's syndrome including ianalumab and belimumab are underway and will hopefully result in clear treatment effects. Inflammatory idiopathic myositis (polymyositis (PM) and dermatomyositis (DM)) and antiphospholid syndrome are proving to be more difficult to tackle but are nonetheless the subject of ongoing studies. To what extent new compounds can replace more traditional immunosuppressive drugs remains to be determined, but if the experience in immune arthritis has taught us anything it is that combination therapy may be the way to go.

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Systemic sclerosis

SSc is a systemic autoimmune disease characterized by clinical features of vasculopathy (Raynaud's, erectile dysfunction, pulmonary arterial hypertension (PAH), and renal crisis), fibrosis of skin and visceral organs (notably the gut, heart, and lungs), and musculoskeletal inflammation (joints, muscles, and tendons) [1]. SSc encompasses the limited cutaneous subset (lcSSc) and the diffuse cutaneous subset (dcSSc), which are associated with different autoantibody profiles, different clinical presentations, and different prognosis. Some patients have an intermediate form. In general, dcSSc is the more aggressive variant where rapidly progressive and severe skin-thickening heralds organ dysfunction, which can be fatal. Long-term outcomes of patients with both lcSSc and dcSSc have improved over the years because of early identification of SSc and the recognition that intensive therapy of vascular manifestations with calcium channel antagonists, endothelin-1 receptor antagonists, phosphodiesterase inhibitors and prostaglandins, and supportive care has a positive impact on patients' well-being and outlook. Just as in most other systemic autoimmune diseases, immunosuppressive therapy remains the cornerstone of SSc therapy with mycophenolate mofetil (MMF), methotrexate, and cyclophosphamide being commonly used for skin disease and MMF and cyclophosphamide also being used for lung disease [1]. In addition, there is now ample evidence that the disease course of dcSSc patients with poor prognosis disease can be altered with potent immunoablative therapy and autologous stem cell transplantation resulting in better long-term survival when compared to patients treated with i.v. cyclophosphamide [2]. The notion that SSc is amenable to treatment has spurred the search for safer and equally effective and more targeted therapies directed at its vascular, fibrotic, or immunosuppressive components. Early attempts to target TNF and TGF beta, key cytokines in inflammation and fibrosis respectively, in SSc were not successful, however [1], more recent clinical studies with other targeted therapies discussed below have been more encouraging, raising the specter that the addition of targeted therapies to background immunosuppression with MMF may become an effective therapeutic strategy in selected patients.

Rituximab

Based on the success of B-cell depleting therapies in rheumatoid arthritis and preclinical data supportive of a role of B cells in SSc [3], a large number of clinical studies, most open-label uncontrolled studies including large registry analyses, were conducted to investigate the effect of B-cell depletion with rituximab, targeting CD20-expressing B cells, in SSc. While consistent effects were seen on biomarkers such as lesional and circulating B cell numbers, the clinical results are, however, conflicting with some of the early studies showing a beneficial effect on skin thickening and/or lung function, but other studies reporting no clinical benefit (reviewed in Ref. [4]). These discrepancies may be related to differences in patient and disease characteristics. Interpretation is further compounded by the fact that almost all studies were unblinded, precluding definitive conclusions. In the latest analysis of the European Scleroderma Trials and Research (EUSTAR) database, those SSc patients treated with rituximab ($n = 254$) had a greater likelihood of improvement of skin thickening when compared to 9575 propensity score-matched patients but not of lung function [5]. Better outcomes were observed in patients treated with concomitant MMF, but the results were less positive than an earlier analysis of the same EUSTAR database in 63 SSc patients and 23 controls, which also suggested a benefit of rituximab on lung function [6]. This underscores the importance of adequate sample size and the selection of appropriate controls and highlights the fact that the interpretation of aggregated data is hampered by the observational nature and potential sources of bias inherent in analyses of international registries. Nevertheless, such real-world data provide useful insights into routine clinical practice across a wide variety of centers and countries. Rigorously designed prospective, randomized, controlled trials remain indispensable though to generate more robust scientific data. In this context, a recent open label, randomized, controlled trial in 60 dcSSc patients with interstitial lung disease (ILD), a single course of rituximab (1000 mg at days 0 and 15) is of interest being the first head-to-head trial with rituximab in SSc-ILD [7]. The results demonstrated that rituximab was significantly more effective in preventing progressive ILD, as measured by FVC and skin score when compared to six monthly pulses of i.v. cyclophosphamide 500 mg/m2 and associated with fewer serious adverse events. Similar favorable

results of rituximab treatment versus cyclophosphamide were seen in a small retrospective analysis in Japanese patients with Scl70-positive SSc-associated interstitial lung disease [8]. Whilst these results are encouraging, long-term data from sufficiently powered prospective randomized (and ideally blinded) controlled clinical trial(s) with rituximab are needed to change clinical practice. Thus, despite its appeal and widespread use in RA, rituximab in SSc has yet to convincingly prove its pivotal role as an effective bDMARD in SSc.

Abatacept

Costimulation blockade of T cells and antigen-presenting cells with abatacept (CTLA4-Ig) has proven to be an effective strategy in RA. In SSc, a small study in 10 dcSSc patients of whom seven were treated with abatacept and three with placebo raised expectations as more pronounced improvements of skin scores were observed in those patients treated with abatacept having inflammatory gene signatures in the skin [9]. These clinical observations were supported by preclinical data in an experimental fibrosis model [10]. Unfortunately, a 12-month, randomized, double-blind, placebo-controlled trial in 88 dcSSc patients did not demonstrate a significant impact on change in the skin score of abatacept versus placebo, although abatacept did have a significant positive effect on HAQ-DI, a composite measure (the CRISS score) and the need for escape therapy (36 vs 16%) [11]. Interestingly, a robust differential effect was found in a subset of patients who demonstrated an inflammatory skin gene expression profile. Similar results were observed in an earlier analysis of the EUSTAR database, which suggested an improvement of joint symptoms with abatacept (consistent with findings in RA) but not of skin- or lung disease [12]. These data suggest that abatacept might be considered in SSc patients with predominantly musculoskeletal manifestations including those with SSc/RA overlap syndrome.

Belimumab

Belimumab is a human monoclonal antibody directed against B-cell activating factor (BAFF), also known as B lymphocyte stimulator, which is licensed for use in SLE. Belimumab has not yet been extensively studied in SSc, but a 52-week small investigator-initiated, single-center, double blind, placebo-controlled pilot study in 20 patients with early dcSSc and background MMF-treatment was reported [13]. Belimumab was safe but not statistically significantly superior to placebo in terms of efficacy as assessed by the modified Rodnan skin score (mRSS) [13]. Of note, belimumab treatment resulted in a significant decreased expression of B cell signaling and profibrotic genes and pathways in the skin of patients from the belimumab group whose mRSS improved. Further studies are needed to corroborate these findings in a larger patient sample.

Tocilizumab

Interleukin-6 (IL-6) is a pleiotropic cytokine, which was first identified as a B-cell growth factor but later recognized to be a pivotal cytokine in many biological processes including systemic inflammation and fibrosis. Preclinical data pointed to a possible critical role of IL-6 in SSc pathogenesis. Positive clinical trials with tocilizumab (TCZ), an anti-IL-6 receptor monoclonal antibody, used in treating rheumatoid arthritis, paved the way for clinical studies in SSc. Early publications of case reports and case series suggested the potential benefit of TCZ in SSc [14]. Two placebo-controlled clinical trials with TCZ in early dcSSc have been completed: the phase 2 faSScinate trial including open label extension and the (as yet unpublished) phase 3 FOCUSSCED trial [15]. Both trials failed to reach the primary endpoint on the mRSS, but interestingly both showed a statistically significant benefit on pulmonary function (FVC), a key secondary outcome parameter. Also, in placebo-treated patients from the faSScinate-trial who transitioned to TCZ skin scores improved and FVC stabilized, at the expense of an (expected) increased rate of serious infections [16]. Of note, patients had not been selected on the basis of clinical lung involvement. It is therefore tempting to speculate that the inhibition of IL-6 with TCZ can slow down the progression of subclinical alveolitis to overt lung fibrosis. Further trials designed to assess lung disease at various stages are needed to confirm this

speculation. A recent case series in 9 SSc patients with refractory ILD suggested TCZ may also be effective in more established ILD [17]. Interestingly, ex vivo culture of fibroblasts cultured from skin biopsies of a subset of SSc patients participating in the faSScinate-trial showed significant shifts in gene expression related to TCZ treatment when compared to placebo-treated patients, suggesting TCZ treatment did in fact shut down IL-6 driven fibrogenesis. This finding suggests that measures of biological processes are important outcome measures and raises doubts about the mRSS as the optimal instrument to assess disease modification [18].

Riociguat

Riociguat, an oral selective soluble guanylate cyclase stimulator with beneficial effects in isolated PAH, was recently tested as a potential drug for SSc-associated digital ulcers. In a 16-week multicenter, double-blind, randomized, placebo-controlled proof-of-concept trial followed by a 16-week open label extension in 17 patients, riociguat did not reduce the net burden of digital ulcers compared with placebo [19]. Based on the antifibrotic effects in animal models, riociguat has also been investigated as a potential disease-modifying therapy in early dcSSc with a disease duration of 18 months or less in the phase 2b, multicenter, randomized (1:1), double-blind, placebo-controlled RISE-SSc study. In total, 121 patients were randomized, but the primary endpoint (mRSS at week 52) was not met, although the mRSS progression rate and the prevention of lung function decline favored riociguat [20].

Nintedanib

Nintedanib is an intracellular inhibitor of tyrosine kinases, which was shown to have antifibrotic, anti-inflammatory, and vascular remodeling effects in animal models of SSc. Nintedanib at 150 mg bd was shown to be effective in slowing down the decline of FVC in patients with idiopathic pulmonary fibrosis (IPF), for which it is now a licensed drug. A recent randomized, double-blind, placebo-controlled trial in 576 SSc patients, the SENSCIS trial, demonstrated the efficacy of nintedanib in SSc-associated interstitial lung disease (on HRCT) as well, as assessed by the annual decline in FVC (primary endpoint), which was almost halved in the active drug group [21]. Nintedanib was effective irrespective of background MMF-use but greater declines in FVC were seen in those not on MMF. No differences were found in pulmonary symptoms as measured by the St Georges Respiratory Questionnaire, or in the skin thickening using the mRSS. Response to active treatment was seen across all subgroups. Gastrointestinal adverse events were more common with nintedanib than with placebo, but this had a limited effect on treatment discontinuation. In general, the adverse-event profile of nintedanib in the SENSCIS trial population was similar to that of the IPF trial. The results of the SENSCIS trial indicate that nintedanib could be a valuable addition to MMF in the management of SSc-ILD. Further studies are needed to determine at what stage of lung disease nintedanib is best used.

Selexipag

Selexipag is an oral, selective IP prostacyclin receptor agonist approved for the long-term treatment of PAH in adults with World Health Organization functional class II/III symptoms. Selexipag was developed to avoid off-target prostanoid effects in the treatment of PAH, especially of the gastrointestinal system. In a post-hoc analysis of the GRIPHON study in PAH, 334 patients were identified with PAH related to underlying CTD, the majority of whom were patients with SSc ($n = 170$). Selexipag reduced the risk of composite morbidity/mortality events in patients with PAH-CTD by 41% (HR 0.59; 95% CI, 0.41–0.85) and the treatment effect was consistent irrespective of baseline PAH therapy or CTD subtype [22]. Selexipag was well-tolerated among PAH-CTD patients, including those with PAH-SSc. To determine the effects of an 8-week course of selexipag on the frequency of attacks of Raynaud's phenomenon in SSc, a multicenter, double-blind, randomized, placebo-controlled, parallel-group, phase II study was conducted in 74 SSc patients [23]. No significant difference was observed between placebo and selexipag on the number of Raynaud's attacks, neither on their duration nor on the Raynaud Condition Score with similar improvements seen in both groups. Placebo-treated patients reported fewer adverse events, but the safety profile of selexipag in SSc patients did not differ from

those with PAH in previous studies. Several explanations were mooted by the authors for the lack of benefit, including the selection of SSc patients with frequent attacks at enrollment, the oral route of administration (as opposed to the use of intravenous prostaglandins in routine practice), and a short titration period, which might have contributed to more patients experiencing side effects. As such the study provided valuable lessons for the design of future trials in this area.

Pirfenidone

Pirfenidone is an orally active small molecule, which inhibits the production of profibrotic and inflammatory cytokines (TGFb, PDGF, IL-6, and TNF), blocks myofibroblast differentiation and fibroblast proliferation, and collagen production, although its precise mechanism of action is incompletely understood. It is licensed for use in idiopathic lung fibrosis. In the Phase II LOTUSS study, a 16-week open-label, of pirfenidone in 63 patients with SSc-ILD, the adverse event profile of pirfenidone was similar to that seen in patients with IPF, and not affected by the concomitant use of MMF, although a longer titration period may be associated with better tolerability [24]. Exploratory disease outcomes remained largely unchanged. The effects of pirfenidone versus placebo in patients with SSc-ILD who are receiving MMF are being investigated in SLS III (ClinicalTrials.gov identifier NCT03221257).

Several other targeted therapies are currently being investigated for safety and efficacy in SSc. These include bortezomib (an inhibitor of the ubiquitin-proteasome proteolytic pathway), dabigatran (a thrombin inhibitor), abituzumab (a humanized monoclonal antibody targeting integrins), and ajulemic acid (lenabasum, a synthetic, orally active, nonimmunosuppressive cannabinoid-derived drug that preferentially binds to the CB2 receptor and is nonpsychoactive). Enrollment in the placebo-controlled RESOLVE-1 phase 3 study of lenabasum for the treatment of dcSSc was recently completed.

Polymyositis and dermatomyositis

PM and DM are idiopathic inflammatory myopathies characterized by symmetrical proximal muscle weakness and muscle inflammation. In DM specific skin lesions are seen, sometimes in the absence of muscle disease (amyopathic DM). DM may affect children (juvenile DM, JDM) and adults, although only in adults DM is linked to the development of cancer. Myositis-specific or myositis-associated antibodies including so-called anti-synthetase antibodies have improved the diagnosis of PM and DM and are helpful in identifying subsets of patients. ILD is a feared complication of PM and DM, in particular in those with specific autoantibodies, such as those against melanoma-associated gene 5 (anti-MDA5). The initial treatment of PM and DM consists of high-dose glucocorticoids. Azathioprine and methotrexate may be used as steroid-sparing agents. If response is suboptimal, other immunosuppressive therapies may be used [25].

Rituximab

Case series of PM or DM patients treated with rituximab have suggested the benefit of RTX (reviewed in Ref. [25]). The largest study on RTX in PM and DM studied its effects in 200 patients of whom 48 patients were with JDM. Patients with refractory disease, despite the use of other immunosuppressive agents were randomized to receive two infusions of RTX either at weeks 0 and 1 or to receive RTX at weeks 8 and 9 in a double blind, placebo-controlled fashion. No additional prednisone infusions were given with RTX for the prevention of infusion reactions; although all patients were on stable doses of prednisone at randomization (mean dose 20 mg/day). In the final analysis, there was no difference in the time to reach a predefined improvement definition, which was reached on average by 20 weeks in both treatment arms, irrespective of receiving RTX at 0 or 8 weeks of inclusion. At week 8 (when the late treatment arm did not yet receive RTX), no statistically significant difference in the proportion of responders was noted between groups.

The unusual trial design makes it difficult to conclude if RTX is effective in PM or DM. At week 44, the end of the trial, 83% of patients had met the predefined response criterion. Given that only patients with disease refractory to (a mean of 3) standard immunosuppressive agents were included, the high response rate of 83% may suggest the benefit of RTX in PM and DM [26].

Anti-TNFα

Anti-TNFα agents have sporadically been used for the management of PM and DM since the early 2000s [27]. Initial hopes were diminished when one open-label pilot study reported an increased incidence of flares in patients treated with infliximab [28], whereas another was stopped prematurely because of a low inclusion rate [29]. A randomized placebo-controlled trial of etanercept reported a response in 5/11 patients treated with etanercept as compared with 0/5 patients treated with placebo [30]. A recent study on infliximab versus placebo in 12 patients with PM or DM revealed one responder at week 16 in the infliximab-treated group as compared with no responder placebo-treated group [31]. A substantial benefit of infliximab could therefore not be demonstrated. In addition, case reports have suggested the development of PM or DM in patients treated with TNF inhibitors for other indications. As a result, anti-TNFα agents are not routinely recommended for the treatment of PM or DM.

Tofacitinib

In a recent open-label study, 18 patients with anti-MDA5 antibody positive amyopathic DM associated with severe interstitial lung disease were treated with the janus kinase inhibitor tofacitinib (in addition to glucocorticoids). Patients were compared with 32 historical controls not treated with tofacitinib. At 6 months, no deaths occurred in patients treated with tofacitinib as compared with 7 (22%) deaths in historical controls, suggesting the benefit of tofacitinib in anti-MDA5 antibody-associated ILD in patients with DM [32]. Case reports suggest the benefit of tofacitinib also for cutaneous and extra-cutaneous manifestations in other subsets of patients with PM or DM [33–35].

Abatacept, apremilast, and tocilizumab

In a randomized controlled trial of abatacept, 20 patients with either PM or DM were randomized to receive abatacept either at inclusion or after a delay of 3 months, in a similar trial design as the aforementioned rituximab trial. After 3 months, 5/10 patients in the early treatment arm as compared with 1/9 patients in the late treatment arm (which at this point had not yet received abatacept) showed a response. After 6 months of active treatment, 8/19 patients in either arm had a favorable response, and the late-start treatment group also started to show improvement [36]. Other agents that have been tested in case reports or small case series include tocilizumab [37] and apremilast (a phosphodiesterase 4 inhibitor used for the treatment of psoriatic arthritis) [38]. Although promising results were obtained, it is impossible to draw firm conclusions on such anecdotal reports.

Sifalimumab

In a phase 1b placebo-controlled randomized trial, sifalimumab (an antibody against interferon α, IFNα) was evaluated in 51 patients with PM or DM [39]. In this early phase study, clinical efficacy was not formerly assessed although sifalimumab showed biological activity by inhibiting IFNα levels in PM and DM. Agents targeting IFNα are of interest in PM and DM, as IFNα levels are increased in blood and muscle in PM and DM [40]. Moreover, the occurrence of flares in infliximab-treated patients coincides with the activation of the IFNα axis [28].

The development of sifalimumab, however, was discontinued as a competitive agent manufactured by the same company named anifrolumab (an antibody against the receptor for IFNα) showed beneficial effects in SLE. Very recently the primary endpoint of a phase 3 study of anifrolumab in SLE was reported to be reached [41], suggesting that anifrolumab may soon be used for the treatment of SLE. Case series and hopefully randomized clinical trials of PM or DM patients treated with anifrolumab may shed light on whether targeting the IFNα axis is of benefit in PM and DM.

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by the presence of antiphospholipid antibodies (aPL) in patients with thrombosis or pregnancy complications.

Thrombosis affects both the arterial and venous vasculature. Pregnancy morbidity includes recurrent early miscarriages, fetal death, or premature birth due to (pre-) eclampsia or placental insufficiency. aPL are measured by either lupus anticoagulant or antibodies against cardiolipin (aCL) or β2 glycoprotein I. Patients who test positive for all three tests (triple positive) are at the highest risk of developing (re)thrombosis or pregnancy complications. Besides thrombosis and pregnancy morbidities, livedo reticularis, thrombocytopenia, cardiac valve disease, nephropathy, and cognitive dysfunction are seen in patients with APS [42]. A subset of APS patients develops life-threatening multiorgan thrombosis termed catastrophic APS (CAPS). APS may occur as a stand-alone disorder (primary APS) or may present in patients with other autoimmune diseases, most frequently SLE.

Direct anticoagulants in APS

Anticoagulants form the mainstay of treatment for both thrombotic and pregnancy complications in APS. Vitamin K antagonists (VKAs), with or without low-dose aspirin (LDA) are recommended for the secondary prevention of thrombosis and LDA and low-molecular weight heparin (LMWH) is used to prevent obstetric complications during pregnancy [43]. Episodes of CAPS are treated with glucocorticoids and plasma exchange or intravenous immunoglobulins in addition to anticoagulants [43].

Direct oral anticoagulants (DOACs) include inhibitors of factor Xa (such as rivaroxaban or apixaban) or IIa (dabigatran). DOACs have simplified the management of thrombosis in the past decade: DOACs anticoagulate faster, confer a lower bleeding risk, and do not require the monitoring of internationalized normalized ratios due to fewer food and drug interactions as compared with traditional VKA anticoagulants. As a result, DOACs are largely replacing VKAs for the treatment of thrombosis. However, randomized clinical trials and observational studies suggest DOACs may not be safe in APS [44] as outlined below.

A randomized controlled open label trial study of rivaroxaban versus warfarin in 116 patients with thrombotic APS found rivaroxaban to be inferior to warfarin when assessing the endogenous thrombin potential, a laboratory marker for the assessment of the intensity of anticoagulation. At 6 months, however, no thrombotic events occurred in any of the patients, suggesting the clinical efficacy of rivaroxaban in APS. Of note, patients with prior arterial thrombotic events were excluded and only 19 out of 116 patients were triple positive [45].

A second randomised controlled trial (RCT) compared rivaroxaban with warfarin in triple-positive APS patients with either arterial or venous thrombosis as a primary thrombotic event [46]. An interim analysis revealed more thrombotic events in the rivaroxaban arm and the trial was terminated prematurely. Seven out of 50 patients treated with rivaroxaban as compared with 0 out of 58 patients treated with warfarin developed an arterial thrombotic event (ischemic stroke or myocardial infarction) at a median follow-up of 1.5 years. Arterial thrombotic events occurred in patients with or without prior arterial thrombosis. No venous thrombosis was seen in either group of patients during follow-up.

A third RCT on rivaroxaban versus acenocoumarol in 190 thrombotic APS patients also reported an increased risk of arterial thrombotic events in patients treated with rivaroxaban (9 versus 0 events) [47]. In addition, the study protocol of an RCT on apixaban in APS was adjusted after an interim analysis revealed increased rates of ischemic stroke in APS patients treated with apixaban [48]. The full results of this trial are not yet available, but these studies confirm an increased risk on arterial thrombotic events in APS patients treated with DOACs. At present, EULAR guidelines recommend against the use of DOACs for thrombosis prophylaxis in high-risk APS patients or APS patients with prior arterial thrombosis [43].

Immunomodulatory targeted therapies in APS

Dysregulation of immune cells, increased levels of cytokines, and complement activation characterize patients with APS and contribute to its pathogenesis [49]. Immunomodulatory drugs have therefore been suggested as novel drug candidates in APS, which do not confer the bleeding risk associated with anticoagulants. Most evidence on the use of targeted immunomodulatory drugs is, however, based on case reports or case series as summarized below.

Rituximab and belimumab

Rituximab may decrease levels of aPL in patients with APS [50]. However, the largest prospective open-label study on rituximab reported no reduction in aPL levels in APS [51]. In this study the safety of rituximab was tested in 19 primary APS patients with thrombocytopenia, cardiac valve disease, skin ulcers, nephropathy, or cognitive dysfunction. Rituximab was well tolerated and a favorable effect was suggested for the treatment of skin ulcers and cognitive dysfunction, with variable responses for the other nonthrombotic APS manifestations [51]. Some case reports suggest the benefit of rituximab for the treatment of arterial or venous thrombosis or episodes of CAPS (reviewed in Ref. [52]). A 2013 evaluation of the CAPS registry revealed 20 cases of patients with CAPS treated with rituximab with an overall survival of 75%, slightly better than patients not treated with rituximab in the same period [53].

Belimumab (anti-BAFF) allowed the reduction of steroids in two primary APS patients with either diffuse alveolar hemorrhage or skin ulcers as APS manifestation [54]. No other reports of belimumab in primary APS exist. Among patients with SLE, belimumab treatment is associated with a reduction in aPL levels [55]. A post-hoc analysis of RCTs on belimumab in patients with SLE reported a greater reduction in IgG aCL levels in belimumab-treated SLE patients as compared with placebo-treated patients (−32.1% versus −22.7%), other aPL were not assessed [56]. In primary APS, increased BAFF levels correlate with higher adjusted global antiphosholipid syndrome scores [57] (defining patients at higher risk of thrombosis). These observations therefore warrant further study of belimumab in APS. The lack of controlled studies, however, hampers the interpretation of whether B-cell directed therapies are of benefit in the treatment of APS.

Inhibition of complement

Activation of the complement system is involved in fetal loss and thrombosis in patients with APS. Anecdotal reports suggest the benefit of complement inhibition of APS. Eculizumab is a humanized monoclonal antibody against complement component C5, which inhibits the formation of C5a and C5b thereby limiting further complement activation. It is currently used in paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, or generalized myasthenia gravis.

The use of eculizumab has been reported to manage episodes of CAPS [52] and to prevent CAPS after renal transplantation ([58] and NCT01029587) or cesarean section [59]. In addition, eculizumab has been used to prevent thrombosis during vascular surgery [60] and to prevent thrombotic microangiopathy in renal allografts in patients with prior APS nephropathy [61]. Although complement activation is clearly linked to adverse pregnancy outcomes in APS pregnancies [62], eculizumab has not been evaluated in APS pregnancies. A randomized clinical trial to assess the safety of olendalizumab (ALXN1007, a C5 inhibitor) to treat thrombocytopenia, APS nephropathy, or skin ulcers in APS was terminated after the inclusion of 9 patients due to slow enrollment. The results are currently limited to safety results published on clinicaltrials.gov (NCT02128269); the full results have not been published. Of note, more conventional treatments such as heparin [63] and rivaroxaban [64] result in decreased complement activation in APS as well.

Mammalian target of rapamycin

Increased activation of mTOR (mammalian target of rapamycin) has been identified in the vascular endothelium of patients with APS nephropathy [65]. A retrospective analysis of renal allograft survival revealed better graft survival in aPL-positive kidney transplant patients who were treated with sirolimus (an inhibitor of mTOR) as part of their transplantation rejection immunosuppressive regimen as compared with patients not treated with sirolimus [65]. Of note, this beneficial effect of sirolimus was not seen in aPL-negative patients. One case report suggests better efficacy of sirolimus drug-eluting stent to revascularize the myocardium as compared with a paclitaxel-eluting stent in an APS patient [66]. No other studies on mTOR inhibition in APS exist.

Anti-TNF

A case series of 18 aPL-positive women who failed to achieve live births despite the use of LMWH with LDA and hydroxychloroquine described the addition of anti-TNF (either adalimumab (n = 16) or certolizumab (n = 2) during an in vitro fertilization (IVF) attempt. Anti-TNF was continued until at least 8 weeks of gestation. There were 12 live births and 3 pregnancy losses before the 10th week of gestation. In 3 patients, the IVF procedure was unsuccessful. No maternal or fetal complications of the TNF inhibitors were reported [67]. A novel study in which 50 high-risk pregnant APS patients will be treated with certolizumab between 9 and 28 weeks of gestation in addition to standard of care is currently recruiting participants (NCT03152058). The enrolled patients will be compared to previous high-risk APS pregnancies. No studies have assessed the efficacy of anti-TNF in thrombotic APS.

Sjögren's syndrome

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by a lymphocytic infiltration of exocrine glands (predominantly lacrimal and salivary glands) leading to severe dryness of eyes and mouth. Fatigue and joint pain are a major cause of morbidity in pSS. The majority of patients are women (more than 90%) with a peak incidence between 30 and 50 years. pSS may present as a stand-alone ('primary') disorder or may affect patients with other rheumatic diseases, in particular rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), in which it is termed 'secondary' Sjogren's syndrome. The prevalence of pSS is estimated between 0.01 and 0.72% [68].

Focal lymphocytic sialadenitis of salivary glands is the pathological diagnostic hallmark of pSS. Other features include the detection of autoantibodies against nuclear antigens (ANA), Sjogren's syndrome-related antigen A (SS-A, also known as anti-Ro), antibodies against SS-B (also known as anti-La), or rheumatoid factor (RF). Patients with pSS have an increased risk of developing non-Hodgkin lymphoma and up to 40% of pSS patients develop systemic involvement (termed 'extra-glandular manifestations') such as interstitial nephritis, cryoglobulinemic vasculitis, or interstitial pneumonitis [68].

Ocular and oral dryness can be objectively assessed by the Schirmer tests or stimulated (after chewing gum or juice) or nonstimulated salivary flow rate as volume per time, respectively [68]. Disease activity is assessed by the ESSDAI (European Sjogren Syndrome Disease Activity Index), which was developed in 2010. A minimum or change in ESSDAI is nowadays frequently used as an inclusion criterion or outcome measure in clinical studies.

Topical agents are used for oral and ocular dryness. Conventional disease-modifying anti-rheumatic drugs have shown little efficacy in the general management of pSS. Severe extra-glandular organ manifestations are typically managed with immunosuppressants in accordance with the management of organ involvement in other CTDs [69], although their use is largely based on anecdotal reports.

Rituximab

The detection of autoantibodies, hypergammaglobulinemia, and the increased risk of the development of B-cell non-Hodgkin lymphomas highlight the central role for B-cells in the pathogenesis of pSS. Polymorphisms in genes involved in B-cell activation and migration increase the risk of developing pSS and B-cells are present in the site of inflammation in pSS, further confirming the role of B-cells in the disease. Targeting B-cells has therefore been a major strategy to improve treatment outcomes in patients with pSS [70].

Several open label studies and four placebo-controlled double-blinded placebo RCTs have been reported in patients with pSS. In all four RCTs [71–74], patients received two infusions of 1000 mg of rituximab (or placebo) at week 0 and 2. In one RCT, rituximab was repeated at weeks 24 and 26 [74]. Both rituximab- and placebo-treated patients received 100 mg methylprednisolone (with or without an oral course of prednisolone) to prevent infusion reactions.

The first RCT (from 2008) was intended as a pilot study [72]. In 17 patients a 30% reduction in fatigue was found in 7 out of 8 rituximab-treated patients as compared with 4 out of 9 patients treated with placebo ($p = 0.064$). This effect was seen from 6 weeks after the first infusion of rituximab. A reduction in RFs (but not serum immunoglobulins or autoantibodies) was noted and Schirmer-tests or unstimulated salivary flow rates were unaffected. For future studies, at least 37 patients per arm were suggested to be adequately powered to detect an effect on fatigue.

The second RCT (from 2010) included 30 patients randomized at a 2:1 ratio [71]. In this trial, the stimulated salivary flow rate was used as the primary outcome measure, and at twelve weeks a statistically significant difference in the change of stimulated salivary flow in favor of rituximab was found. Thereafter, the between group difference decreased and no statistically significant differences were found at 24 or 48 weeks. At 36 and 48 weeks, ocular dryness (as assessed by VAS) was ameliorated more in rituximab-treated patients as compared with placebo and RFs decreased. The positive results from both these RCTs paved the way for two large scale RCTs that were subsequently conducted [73,74].

In the TEARS trial, 120 patients with pSS were studied. A reduction of at least 30 mm (on a range from 0 to 100 mm) on 2 out of 4 visual analog scales (VAS) on pain, fatigue, dryness, or global disease activity was assessed at 26 weeks as the primary outcome. No difference was found between rituximab- and placebo-treated patients (23.0% versus 22.0%). Rituximab neither decreased ESSDAI scores (mean difference −0.5 (95% CI, −2.3 − 1.3) from a mean baseline ESSDAI of 10.1) nor decreased joint involvement or parotid swelling. At 6 weeks a greater response rate was found in patients treated with rituximab (22.4% versus 9.1%, treatment difference 13.3% (95% CI, 0.8%–25.8%)), which was driven by an effect on the VAS on fatigue (treatment difference 26.6% (95% CI, 15.7–37.5)). No effect was seen on the other VAS (on pain, global disease activity, or dryness) at week 6. This effect on fatigue, however, decreased over time (treatment difference of 26.6% at week 6, 18.3% (95% CI, 4.1%–32.6%) at week 16 and 9.3% (95% CI, −2.0%–20.5%) at week 24. In addition, rituximab decreased serum IgG levels (mean difference of −1.2 g/L (95% CI, −0.4 to −2.0) from a mean serum IgG of 16.4 g/L). Thus, rituximab treatment showed some beneficial effects, albeit quickly and short-lasting.

In the TRACTIS trial 133 patients were included, who received rituximab at weeks 0, 2, 24, and 26, after which the efficacy was assessed at week 48 [74]. A 30% reduction in a VAS on dryness or fatigue was used as primary outcome and was met by 36.8% and 39.8% of patients treated with placebo or rituximab, respectively. No statistically significant differences were found at any other time point on any of the 6 VAS measured (fatigue, overall dryness, oral dryness, ocular dryness, pain, and disease activity). The authors included a cost-effectiveness analysis and calculated that the use of rituximab was associated with an almost £8.000 increase in costs.

Some positive findings were noted in this trial: the unstimulated salivary flow rate remained constant in rituximab-treated patients, whereas it decreased in placebo-treated patients. ESSDAI scores showed a trend ($p = 0.07$) toward a statistically significant improvement in the rituximab-treated patients at week 48 (mean ESSDAI at baseline 5.7). In a subgroup analysis published separately, rituximab improved the ultrasonographic appearance of the salivary glands [75]. Thus, although the primary outcome was not met in both large RCTs, some beneficial effects were noted.

Despite the negative main results from these two RCTs, rituximab is still used in selected cases of pSS, as it has been debated whether the drug or the trials failed. A large placebo effect may have obscured results (36.8% placebo-treated patients met the primary outcome in one of the studies). Possibly, the use of methylprednisolone in placebo-treated patients, the subjective nature of the outcome measures, or the use of concomitant immunosuppressive drugs explain the high placebo response rates. pSS may show a variable course over time, which may obscure the additive effect of rituximab over the natural course of the disease.

The potentially more objective stimulated salivary flow rate was used as the primary outcome measure in one of the RCTs, showing a favorable result at early time points [71]. In this study, however, patients (randomly) assigned to rituximab already had higher stimulated (and unstimulated) salivary flow rates at baseline, which may relate to the positive effects on the salivary flow rate in these patients. Moreover, in this trial the patients were on average 10 years younger compared with the patients included in the other trials, suggesting a more recent onset of disease, a

stage at which the decreased salivary output may still be reversible. The other trials also attempted to include patients with "early" disease onset, although variable definitions were used, including disease duration less than 10 years [73], possibly passing this reversible stage and hence no effects were seen.

Overall, rituximab was well tolerated. In the TEARS trial, 5 out of 60 patients treated with rituximab (as compared with 1 out of 60 patients treated with placebo) did not receive the second infusion of rituximab due to adverse events [73]. Treatment guidelines for pSS endorse the use of rituximab in the management of selected cases of pSS [69]. Therefore, a situation analogous to SLE is unfolding, in which RCTs on rituximab did not reach their primary outcome but nonetheless, rituximab is frequently used to treat SLE. It is currently unknown as to how many patients with pSS are receiving rituximab in clinical practice.

Epratuzumab

The failure of the large rituximab RCTs may suggest that other B-cell targeting therapies are needed in pSS. Epratuzumab is a monoclonal antibody against CD22, a coreceptor for the b-cell receptor, which does not fully deplete B-cells but has a rather immunomodulatory effect. In an open-label study, epratuzumab was evaluated in 16 pSS patients in which it showed a clinically meaningful response in 8 patients [76]. Epratuzumab has been more extensively studied in SLE (in which it did not reach its primary outcome in phase III RCTs); however, in a post-hoc analysis the subset of SLE patients with associated Sjögren's syndrome had a significant response in terms of SLE disease activity as compared with placebo [77], although it remains unknown if this translates to pSS symptoms.

Belimumab

Belimumab, a monoclonal antibody against BAFF is licensed for use in SLE as reported above. In a label study, 30 patients with pSS were treated with belimumab at weeks 0, 2, and 4 followed by once every 4 weeks. The VAS on dryness, ESSDAI scores, and hypergammaglobulinemia and RFs decreased after 28 weeks, although no change was found in the stimulated salivary flow rate or Schirmer tests [78]. A 6-month extension of this study found persisting results and reported no change in the amount of lymphocytic foci in salivary gland biopsies in patients who had a repeat biopsy after treatment [79]. The open-label nature of this study hampers its interpretation and placebo-controlled studies on belimumab in pSS are underway (see below).

Ianalumab

Ianalumab (previously known as VAY736) is a novel BAFF-targeting antibody, which was recently evaluated in patients with pSS [80]. Ianalumab prevents BAFF signaling through its receptor BAFF-R and in addition depletes BAFF-R expressing B-cells through antibody-dependent cellular cytotoxicity. In this pilot trial, 18 patients with pSS were treated with a single infusion of lanalumab (either 3 mg/kg or 10 mg/kg) as compared with 9 patients treated with placebo. After 12 weeks, no differences in the reduction of ESSDAI scores, fatigue, or salivary flow rates were found between patients treated with lanalumab or placebo, although trends in favor of lanalumab were found. The results of a larger phase II clinical trial studying 190 patients were recently reported at the 2019 annual meeting of the American college of Rheumatology. Ianalumab given at 300 mg subcutaneously once a month led to a significant decrease in ESSDAI scores as compared with placebo-treated patients [81].

The other BAFF-targeting treatments that were (unsuccessfully) tested in SLE such as tabalumab, blisibimod, or atacicept have not been assessed in pSS. A pharmacokinetic study on tibulizumab, a bispecific antibody against BAFF, and interleukin-17 is currently underway in patients with PSS (NCT02614716).

Combining rituximab with belimumab

After rituximab treatment, serum levels of BAFF increase threefold as noted in one RCT on rituximab [82]. In a subgroup analysis of the TEARS trial, higher serum levels of BAFF at baseline were associated with ineffectivity of rituximab [83] (although no increase in BAFF levels after rituximab were reported after 26 weeks in the TEARS trial [73]). These findings suggest a rationale for the combination of belimumab with rituximab and such a trial is currently under way in patients with pSS (NCT02631538). In this study, placebo treatment is compared with belimumab monotherapy, rituximab monotherapy, and coadministration of rituximab with belimumab and should clarify if belimumab and/or its coadministration with rituximab is effective in pSS.

Anti-TNF

TNFα blockade was assessed in two large RCTs in pSS. In the TRIPSS study, 103 pSS patients were treated with placebo or infliximab (5 mg/kg) at weeks 0, 2, and 6 and followed for 22 weeks. At the end of study, the proportion of patients having a 30% reduction in 2 out of 3 VAS on pain, fatigue, or dryness did not differ between infliximab and placebo (16.7% versus 20.4%, respectively) and no effect on Schirmer tests, salivary flow rates, or histological scores on salivary glands was seen [84]. This RCT was preceded by an open-label study on infliximab in pSS, which showed 'impressive' [84] results, although these results were later retracted on the basis of methodological flaws [85]. After a reanalysis, no effect was seen in this open label study. An RCT on etanercept (a TNF-receptor fusion protein) did not show a favorable response over placebo in 28 patients with pSS [86] and no further trials on anti-TNF agents have been conducted in pSS.

Anakinra, tocilizumab, interleukin-7Rα antagonists and interleukin-2

Anakinra, a monoclonal antibody against IL-1β showed some reduction in fatigue after 4 weeks in patients with pSS as compared with placebo [87]. The results from a placebo-controlled RCT on tocilizumab (an antibody against the receptor for IL-6) in pSS are expected in the near future (NCT01782235). A monoclonal antibody that binds IL-7R (GSK2618960) is in development for pSS [88]. The administration of IL-2 at immunoregulatory doses is currently being evaluated in pSS, which may increase regulatory T-cell numbers and decrease T-helper 17 cells [89].

Type I interferon antagonists

A type I interferon (IFN) signature is present in pSS. This signature is caused by elevated levels of type I IFN (α and β predominantly) and is also seen in SLE, APS, PM, DM, and SSc [40,90]. In pSS, antibodies targeting IFNα or its receptor have not been evaluated yet. MEDI7734, a monoclonal antibody against ILT7 (causing the depletion of plasmacytoid dendritic cells, the main producers of type I IFN) is currently being evaluated in patients with pSS (NCT02780674). Other options include targeting the up- or downstream intracellular pathways of type I IFN signaling with drugs such as filgotinib (a JAK1 inhibitor), which reduces the IFN signature (NCT03100942). In the same trial, the effectivity of lanraplenib (a spleen tyrosine kinase inhibitor) and tirabrutinib (a Bruton's tyrosine kinase inhibitor), both involved in B-cell activation, are being evaluated.

Increasing RNase activity by RSLV-132 is a more upstream way of combating the IFN signature. This results in the increased digestion of RNA present in immune complexes of patients with pSS. RNA containing immune complexes is a trigger for IFNα production by plasmacytoid dendritic cells. In a small, placebo-controlled RCT of 30 patients, RSLV-132 was superior to placebo in reducing fatigue at 12 weeks; this study was presented at the EULAR annual meeting in 2019 [91].

Abatacept

Abatacept, a CTLA4-Ig, was evaluated in three open-label studies in patients with pSS. In the first study, 11 patients were treated with abatacept for 26 weeks, which resulted in improved

histological features of labial salivary gland biopsies, improved hypergammaglobulinemia, and improved salivary gland function [92]. In the second study, abatacept treatment in 15 patients with pSS resulted in a decrease in ESSDAI scores after 24 weeks of treatment (mean ESSDAI at baseline of 11 to a mean ESSDAI of 3 at week 24). After discontinuation of abatacept, ESSDAI scores rose again. ESSPRI and fatigue scores as well as serum IgG levels, RF, and anti-SSA/SSB ameliorated as well [93], although no effect on Schirmer tests or salivary flow rates were observed. Histologically no change in lymphocytic focus scores was found, although some improvement in the amount of germinal centers was reported [94]. The third open-label study treated patients with abatacept for 2 years, after which abatacept treatment resulted in a decrease in ESSDAI scores (a median decrease of 3 points, from a median ESSDAI of 7) and ameliorated salivary flow. No improvement on lacrimal gland function was reported [95]. In RA patients with secondary Sjögren's syndrome, abatacept treatment may improve salivary and lacrimal gland function [96], further suggesting clinical effectivity of abatacept in pSS.

Although the results from these open label studies are promising, placebo-controlled RCTs are eagerly awaited. The results from one of such large placebo-controlled trials were recently reported at the EULAR annual meeting. In 187 patients randomized to placebo or abatacept, the preliminary results showed no improvement on ESSDAI scores or salivary of lacrimal gland function, despite improvements in IgG and RF levels in favor of abatacept [97]. The results from a second placebo-controlled RCT on abatacept are expected soon (NCT02067910).

Iscalimab, lulizumab, and prezalumab

Iscalimab (also known as CFZ533) is a monoclonal antibody against CD40, which is involved in the interaction between T- and B-cells as well as the formation of germinal centers. In two cohorts of pSS patients treated with iscalimab or placebo, a reduction in ESSDAI scores was found in the active treatment arm in the larger of the two cohorts, the results of which were presented at the EULAR annual meeting in 2019 [98]. A study on lulizumab (anti-CD28) in pSS was terminated before completion of the study (NCT02843659). Prezalumab (also known as AMG 557) binds ICOSL (ICOS ligand) and prevents its interaction with ICOS, which is a costimulatory molecule expressed in T-cells. Prezalumab was evaluated in an RCT in patients with pSS (NCT02334306). Although its results have not yet been published, a press release revealed that the trial was negative and the development of prezalumab is discontinued.

Baminercept, seletalisib, leniolisib, iguratimod and petesicatib

Baminercept is a lymphotoxin b receptor (LTβR) fusion protein. LTβR is expressed in immune cells including T- and B-cells and is involved in the formation of ectopic lymphocytic structures that are found in the salivary glands of patients with pSS. In an RCT, 52 patients with pSS randomized in a 2:1 ratio to baminercept or placebo, no change in salivary flow rate or ESSDAI scores between the treatment groups was found. The included patients had a low mean ESSDAI score at baseline (mean ESSDAI of 3.2) which may explain the lack of effect on ESSDAI scores [99]. However, also no decrease in serum IgG or autoantibodies was reported.

Seletalisib and leniolisib are PI3Kδ inhibitors that are in development for pSS. PI3Kδ is involved in B-cell activation and germinal center formation. The results of placebo-controlled studies (leniolisib $n = 30$, seletalisib $n = 27$) on these two agents have only been communicated at conference meetings and no statistically significant improvements on outcome measures were reported [100,101]. Iguratimod is a small molecule that inhibits the activation of NFκB and is used in Japan and China to treat RA. In a randomized open-label study of 50 patients with pSS, iguratimod showed a greater improvement in ESSDAI scores than treatment with conventional immunosuppressive drugs, as was presented at the annual meeting of the ACR in 2016 [102].

Petesicatib (also known as RO 5459072) is a cathepsin S inhibitor, which may affect autoantigen presentation. A placebo-controlled RCT on 75 patients with pSS did not reach its primary outcome defined as an ESSDAI reduction of ≥ 3 (NCT02701985, results available on clinicaltrials.gov).

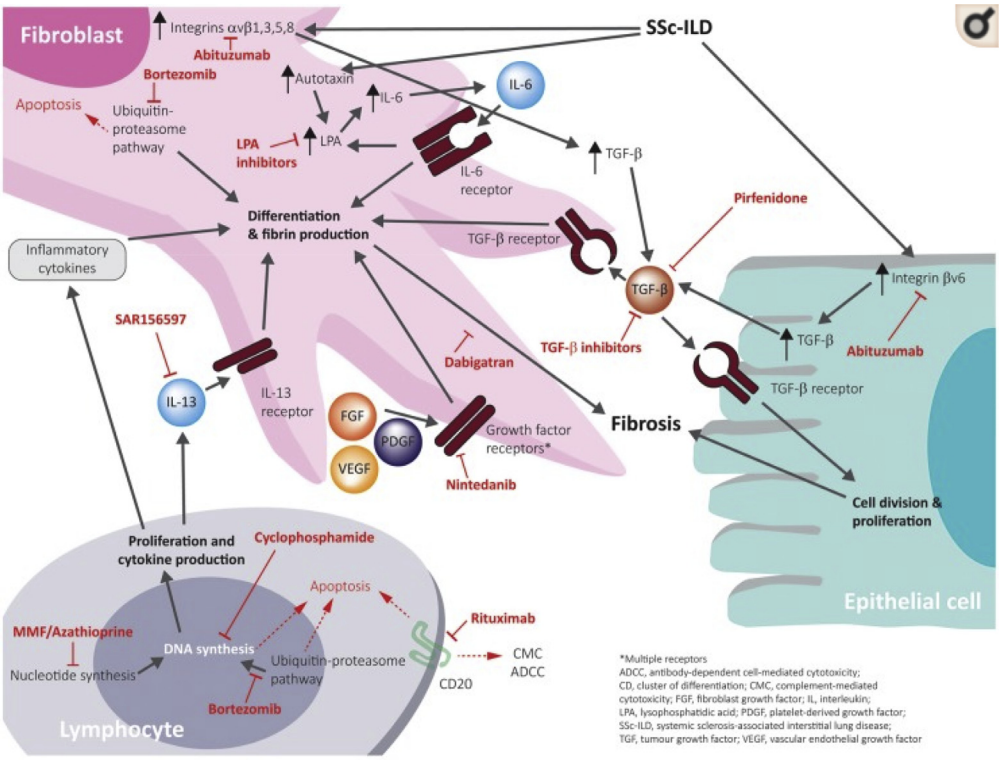

Fig. 1. Modes of action of existing and future candidate agents for the treatment of SSc-ILD.

Summary

The shortcomings of traditional immunosuppressive medication in CTDs and the success of bDMARDs and small molecule synthetic drugs in immune arthritis have spurred a concerted action to test their clinical utility in SSc, primary Sjogren's syndrome (pSS), and to a lesser extent in rarer diseases such as inflammatory idiopathic myositis, and APS. Clinical trial data are encouraging for nintedanib and IL-6 inhibitors in SSc, especially with respect to their inhibitory effect on declining lung function, raising hope that SSc lung disease is amenable to treatment with a range of targeted therapies (Fig. 1) [103]. Large randomized clinical trials on rituximab in primary Sjogren's syndrome have led to mixed results. Novel trials using B-cell-targeting strategies are underway, hopefully resulting in clearer treatment effects. The evidence in the other CTDs is more anecdotal or based on small studies with insufficient statistical power to support clinical decision-making. In those patients, treatment decisions still depend on sound clinical judgment, patient preference, and reimbursement. Important lessons have been drawn regarding trial design, which may inform future trials.

Practice points

- Targeted therapies hold promise for the treatment of CTDs based on their defined mechanism of action and better understanding of disease pathways.
- Nintedanib is the first targeted therapy with proven benefit in SSc-associated lung disease.
- DOACs are currently not recommended for APS.

Research agenda

- To identify patient and disease determinants of clinical responsiveness to new bDMARDs or small molecule drugs.
- To assess the role of background immunosuppressive therapy in clinical trials with new agents.
- To compare the safety and efficacy of new bDMARDs or small molecule drugs with active comparator (e.g., MMF in SSc-ILD).

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