Respiration

Thematic Review Series

Respiration 2020;99:819–829
DOI: 10.1159/000511200

Received: April 13, 2020
Accepted: August 28, 2020
Published online: December 3, 2020

Immunomodulation in Autoimmune Interstitial Lung Disease

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Keywords
Immunomodulation · Interstitial lung disease · Immunosuppression

Abstract
Interstitial lung diseases (ILDs) associated with autoimmune or systemic disease are increasingly recognized and our pathophysiological understanding rapidly expanding. Treatment modalities, however, are still mainly driven by established disease-modifying antirheumatic drugs (DMARDs) where, despite decades of experience of their use in the underlying diseases such as rheumatoid arthritis, mostly retrospective data exist informing their effect on the course of interstitial lung disease (ILD). In recent years, randomized trials investigating the effects of biological DMARDs (bDMARDs) have been completed or are currently running, generating new treatment options for often relentlessly progressive diseases. Herein, we summarize the evidence and current use of both synthetic DMARDs and bDMARDs in the context of ILDs associated with autoimmune/systemic disease.

From the Thematic Review Series: "Immunomodulation in Lung Diseases" Series Editors: Marek Lommatzsch and Stephan F. van Eeden.

Introduction

Interstitial lung diseases (ILDs) comprise a spectrum of disorders driven by either inflammatory or fibrosing processes or a combination of both. Patients with idiopathic pulmonary fibrosis (IPF) [1] have been shown to respond adversely to immunosuppression in the landmark PANTHER trial [2], rendering immunosuppression contraindicated for IPF in the absence of acute exacerbations or inflammatory comorbidity [3]. A large proportion of ILDs, on the other hand, present in the setting of either established autoimmune or connective tissue diseases (CTDs), such as systemic sclerosis (SSc), rheumatoid arthritis (RA), or idiopathic inflammatory myositis (IIM), in which therapy is primarily driven based on evidence of the respective underlying disease. Moreover, some patients with fibrotic lung diseases show evidence of autoimmunity (such as the presence of autoantibodies or clinical features) without fulfilling the diagnostic criteria for a given rheumatological disorder. The latter group has been summarized under the umbrella term "interstitial pneumonia with autoimmune features" (IPAF) to propel the research agenda for these undifferentiated forms of ILD and inform diagnostic and therapeutic implications [4]. Other fibrotic lung diseases in which immunosuppressive treatment is widely used are hypersen-

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sitivity pneumonitis and sarcoidosis. The level of inflammatory processes may differ between the various diseases and also the level of immunocompetency to combat infectious disease. Balanced and individualized treatment concepts are needed. Although large-scale studies informed treatment guidelines for various systemic diseases associated with ILD, little evidence exists regarding the impact of these therapies in the context of established ILDs other than SSc-ILD.

In 2014, a new classification of disease-modifying antirheumatic drugs (DMARDs) was introduced [5]: synthetic DMARDS (sDMARDs) were divided into those developed and applied without knowledge of the specific target (conventional sDMARDs, e.g., azathioprine or methotrexate (MTX)) and those which were developed using an a priori targeted approach (e.g., tofacitinib), termed targeted sDMARDS (tsDMARDs). Biological DMARDs on the other hand subsume agents directed at particular, well-defined molecules, making distinctions between the original substances (e.g., infliximab), termed biological originator DMARDS, and those that essentially copy the structure of a parent originator compound, termed biosimilar DMARDs. In this review, we summarize the evidence for sDMARDs or biological DMARDs currently in use (Table 1) or under investigation (Table 2) for CTD-ILDs, sarcoidosis, IPAF, and fibrosing chronic hypersensitivity pneumonitis.

Conventional sDMARDs

Azathioprine

Azathioprine is a nonselective agent which inhibits B-cell and T-cell proliferation via blockage of purine synthesis and DNA replication in lymphocytes [6]. Azathioprine is generally well tolerated with dose-dependent mainly transient adverse events occurring as nausea, diarrhea, or elevated liver enzymes. In combination with uric acid-lowering medication such as allopurinol or febuxostat however, increased concentrations of the active metabolite 6-mercaptopurine can cause severe bone marrow suppression. Likewise, a low TPMT activity may result in similar adverse events, and some centers perform regular testing before initiation of azathioprine treatment [7, 8]. Usual doses implemented in studies range between 2 and 2.5 mg/kg of body weight and are usually given at a dose of 150–200 mg/day. The PANTHER trial of 2012 demonstrated increased mortality with its use in IPF [2], but in ILD associated with autoimmune diseases, it is one of the most commonly used steroid-sparing DMARDs. Although widely used, only limited data exist with regard to the therapy of ILD. Prospective trials were only performed for the treatment of SSc. In a multicentric randomized controlled trial (RCT) (FAST), 45 patients were assigned to receive induction therapy with cyclophosphamide (CYC) for 6 months followed by either azathioprine (2.5 mg/kg BW) or placebo [9]. The study showed a trend toward better maintenance of forced vital capacity (FVC) improvement following CYC, though not statistically significant ($p = 0.08$) with overall good tolerability of azathioprine. Another prospective (but open label) trial compared oral CYC versus azathioprine for early diffuse SSc in 60 patients but showed a significant decrease of FVC with azathioprine [10]. Since then, azathioprine has usually been evaluated as a maintenance therapy following induction therapy with more potent immunosuppressants. Using such a protocol, a multicentric analysis showed improvement or stabilization of FVC in 52% of the patients [11]. Apart from SSc, azathioprine was retrospectively compared to mycophenolate mofetil (MMF) in a mixed CTD-ILD cohort including 97 patients [12] and IIM-associated ILD [13], demonstrating similar efficacy with regard to FVC stabilization, but an overall higher rate of adverse events with azathioprine. Another IIM-associated ILD cohort found similar results compared to CYC and MMF but with the lowest toxicity for azathioprine [14]. For steroid-dependent sarcoidosis, azathioprine was compared to MTX in a large multicenter retrospective study including 200 patients (55 with azathioprine) and found similar steroid-sparing effects and improvement in FVC and forced expiratory volume in 1 s (FEV_1) [15]. Based on the prospective data available for SSc, azathioprine is considered as a steroid-sparing agent for SSc if MMF is not tolerated. Based on the evidence from various retrospective studies, azathioprine can be used as a steroid-sparing agent in sarcoidosis, hypersensitivity pneumonitis, and fibrotic CTD-ILD including systemic lupus erythematosus, mixed CTDs, Sjögren's syndrome (SjS), IIM, and RA.

Methotrexate

MTX is an antifolate metabolite that exerts its anti-inflammatory effects via a combination of suppression of transmethylation reactions, inhibition of purine and pyrimidine synthesis, promotion of adenosine release with adenosine-mediated suppression of inflammation, and reduction of antigen-dependent T-cell proliferation [16]. MTX is associated with acute onset of ILD, and its historic association with development of ILD in RA has certainly precluded it from prospective evaluation in many

Table 1. Overview of immunomodulating agents used for ILD

Agent	Regimens	Important reports [refs.]	Current treatment option in ILD	Routine monitoring/comment
Conventional sDMARDs				
Azathioprine	2–2.5 mg/kg BW (max 150–200 mg)	Multicentric RCT: [9] (FAST) Prospective open-label: [10, 110] Retrospective studies: [11–15, 111]	SSc-ILD CTD-ILD (RA; IIM) Sarcoidosis	CBC, Cr (BL), LFTs TPMT genotyping at BL
MTX	10 mg once weekly p.o. or s.c. (max 15–20 mg)	Multicentric RCT [21] Retrospective studies [15]	Sarcoidosis RA-ILD	CBC, Cr, LFTs
Leflunomide	20 mg once daily p.o. (consider loading dose 100 mg on 3 consecutive days)	Retrospective studies [25–27]	Sarcoidosis RA-ILD	Exclude latent TB CBC, LFTs
Mycophenolate	Twice daily with target dose 2,000–3,000 mg/day	Multicentric RCTs: [30, 32, 112] (SENSCIS; SLS II) Retrospective studies: [12, 13, 33–36, 113]	SSc-ILD CTD-ILD (IIM) Fibrotic chronic hypersensitivity pneumonitis	CBC, LFTs, Cr
CYC	≤2 mg/kg BW p.o. daily 0.6 g/m^2 BS i.v. every 4 weeks (6 cycles)	Multicentric RCTs: [30, 49, 114, 9] (SLS I, FAST, SLS II) Prospective open label [69] Retrospective studies [51–53]	SSc-ILD Rapid-progressive IIM-ILD AFOP LIP in SjS-ILD Rapid-progressive RA-ILD	CBC, urinalysis, Cr, electrolytes, leukocyte nadir, signs of cardiac toxicity, signs of hemorrhagic cystitis Pneumocystis pneumonia prophylaxis
FK506	Twice daily p.o.; target trough levels initially 5–20 μg/L, reduce to 5–8 μg/L	Retrospective studies [40–42]	Rapid-progressive IIM-ILD	CBC, LFTs, Cr, fasting glucose, lipids, electrolytes, trough levels Pneumocystis prophylaxis recommended when used with second DMARD
CSA	Twice daily p.o.; target trough level 100–200 μg/L	Prospective open label [46] Retrospective studies [41–45]	Rapid-progressive IIM-ILD	CBC, LFTs, Cr, fasting glucose, lipids, electrolytes, trough levels Pneumocystis prophylaxis recommended when used with second DMARD
Targeted sDMARDs				
Tofacitinib	5 mg twice daily per o.s.	Prospective open label [61] Retrospective studies [60, 63]	Anti-MDA5-DM-ILD (Cutaneous) sarcoidosis	CBC, lipids, LFTs
bDMARDs				
Tocilizumab	162 mg weekly s.c.	Multicentric RCTs: faSScinate [89, 90]; Focused [91] Retrospective studies [94]	SSc-ILD RA-ILD	Exclude latent TB CBC, LFTs, lipids CRP not usable
Infliximab	3 or 5 mg/kg BW i.v. at weeks 0, 2, and 6; then every 6–8 weeks	Multicentric RCTs: [95, 115] Retrospective studies [97]	Sarcoidosis	Exclude latent TB and HBV CBC, LFTs
Abatacept	10 mg/kg BW s.c. every 4 weeks 125 mg s.c. weekly	Retrospective studies [104, 105]	RA-ILD Sarcoidosis Inflammatory myositis-associated ILD	Exclude latent TB and HBV CBC, LFTs, Cr
RTX	1,000 mg i.v. at day 0 and day 14 and at 6 months	Single-center RCT [66] Prospective open label [67, 73, 77] Retrospective studies [71, 72, 78–81, 83, 85]	CTD-ILD (SjS, RA-ILD, inflammatory myositis-associated ILD, SSc) CVID-ILD [65] Chronic hypersensitivity pneumonitis	Exclude HBV CBC, Cr Immunoglobulin levels (IgM, IgG, IgA) Pneumocystis prophylaxis recommended

BW, body weight; BS, body surface; CBC, complete blood count; CRP, C-reactive protein; CTD, connective tissue disease; FK506, tacrolimus; ILD, interstitial lung disease; IIM, idiopathic inflammatory myositis; LIP, lymphocytic interstitial pneumonia; LFTs, liver function tests; HBC, hepatitis B virus; TB, tuberculosis; MDA, melanoma differentiation-associated gene; p.o., per os; RA, rheumatoid arthritis; RCT, randomized controlled trial; s.c., subcutaneously; SLS, Scleroderma Lung Study; SjS, Sjögren's syndrome; SSc, systemic sclerosis; TPMT, thiopurine S-methyl transferase; sDMARDs, synthetic disease-modifying antirheumatic drugs; bDMARDs, biological disease-modifying antirheumatic drugs; CYC, cyclophosphamide; CSA, cyclosporine A; RTX, rituximab; MTX, methotrexate.

Table 2. Currently recruiting RCTs in ILD investigating immunomodulating agents

Study acronym (NCT)/phase	Indication	Intervention	Estimated enrollment	Estimated completion
Scleroderma Lung Study III (NCT03221257)/phase 2	SSc-ILD (FVC ≤85%)	MMF (3,000 mg/d) + pirfenidone (3×801 mg/d) versus MMF + placebo	150	March 2022
RECITAL (NCT01862926)/phase 2 (RTX), phase 3 (CYC)	CTD-ILD (SSc, IIM, MCTD)	RTX (1 g d1 + d15) versus CYC (600 mg/m^2 6 doses 4 weekly)	116	November 2021
EVER-ILD (NCT02990286)/phase 3	IPAF, CTD-ILD, or NSIP	MMF (2 g/d) + RTX (1,000 mg d1 + d15) versus MMF + placebo	122	January 2021
ATtackMy-ILD (NCT03215927)/phase 2	IIM-associated ILD (antisynthetase syndrome)	Abatacept (125 mg weekly) versus placebo	20	May 2021

FVC, forced vital capacity; MCTD, mixed connective tissue disease; MMF, mycophenolate mofetil; RTX, rituximab; CYC, cyclophosphamide; SSc, systemic sclerosis; CTD, connective tissue disease; IIM, idiopathic inflammatory myositis; IPAF, interstitial pneumonia with autoimmune features; NSIP, nonspecific interstitial pneumonia.

forms of fibrotic ILD. Studies suggest that the risk for MTX pneumonitis is highest in the elderly, smokers, and individuals with pre-existing fibrotic lung lesions [17, 18]. Current evidence suggests a falling rate of MTX-associated pneumonitis and that this may even delay the development of RA-ILD [19, 20]. MTX is considered the first-choice steroid-sparing second-line agent for steroid-dependent sarcoidosis based on an RCT demonstrating the feasibility of faster steroid reduction with MTX than placebo with good tolerability [21]. It was compared to azathioprine in sarcoidosis retrospectively in the aforementioned study [15]. MTX is usually commenced at a dose of 10 mg p.o. or s.c. once weekly with a maximum dose of 15–20 mg. Overall, MTX is the first choice second-line agent for steroid-refractory or dependent sarcoidosis [22].

Leflunomide

Leflunomide is an antilymphocyte agent and inhibits de novo synthesis of deoxyuridine monophosphate (dUMP) via inhibition of dihydroorotate dehydrogenase. Note that leflunomide is not considered a tsDMARD because its precise target of action only became known after its development and clinical application [5]. Leflunomide selectively suppresses lymphocyte responses in active T lymphocytes, where p53-mediated apoptosis is triggered in the absence of intracellular dUMP (but not in resting lymphocytes) [23]. Similarly to MTX, leflunomide has long been associated with pulmonary complications with its use in RA, but again recent data suggest no additional risk for ILD with leflunomide, although cases of acute pneumonitis rarely do occur [24]. In ILD, leflunomide is mostly used as a steroid-sparing agent [25, 26] but also showed similar efficacy to MTX in RA-ILD in one retrospective analysis [27]. Leflunomide is used orally 20 mg once daily, with some centers using loading doses of 100 mg for the first 3 days [25]. The very limited available data suggest leflunomide can be used as second-line steroid-sparing therapy in sarcoidosis if MTX and azathioprine are not tolerated [22], in RA-ILD and SjS, where current recommendations include leflunomide despite lacking dedicated evidence regarding its efficacy for SjS complicated by ILD [28].

Mycophenolate Mofetil

MMF is an inhibitor of the de novo synthesis of guanine nucleotides via inhibition of inosine monophosphate dehydrogenase, on which, in contrast to many other cell types, lymphocytes solely depend for synthesis of guanine nucleotides [29]. Notably, MMF is shown in vitro and clinically to not only inhibit proliferation of lymphocytes but also fibroblasts in a dose-dependent fashion [29]. MMF has multiple side effects, but it most commonly causes gastrointestinal adverse events including diarrhea, nausea, and vomiting [29]. MMF efficacy in ILD, as with azathioprine and CYC, is best studied in SSc-ILD. In the Scleroderma Lung Study (SLS) II, 142 patients with SSc-ILD were randomized to receive MMF with a target dose of 1,500 mg twice daily or oral CYC (2 mg/kg BW per day) and demonstrated similar improvement in FVC, while fewer deaths and adverse events occurred in the MMF group [30]. Comparison of the pooled patients from the SLS I who received placebo and patients from the SLS II also showed FVC and diffusing capacity of the lungs for carbon monoxide (DLCO) improvement with MMF but not with placebo [31]. The recent multicenter

RCT which evaluated nintedanib as an antifibrotic agent in SSc-ILD (SENSCIS) found that in both the nintedanib and placebo groups, FVC decline was significantly lower when patients additionally received MMF [32]. To evaluate the true impact on SSc-ILD progression, the currently recruiting SLS III study compares the addition of pirfenidone or placebo to MMF therapy (NCT03221257). Outside SSc-ILD, MMF showed a stabilizing effect in mixed CTD-ILD cohorts [12, 33] and pulmonary function test (PFT) improvement in IIM-ILD [13] and chronic hypersensitivity pneumonitis [34, 35]. In patients with IPAF, MMF treatment showed a trend toward slower DLCO and FVC decline than controls who did not receive MMF, but the effect was not statistically significant [36]. Extrapolating from the high-quality evidence from the SENSCIS and SLS II trials and its overall good safety profile, MMF has become widely used in fibrotic CTD-ILD, except for RA-ILD due to its lack of efficacy for arthritis [37], and may also be considered for fibrotic sarcoidosis and chronic hypersensitivity pneumonitis [38].

Calcineurin Inhibitors (Tacrolimus and Cyclosporine A)

Both tacrolimus (FK506) and cyclosporine A (CSA) inhibit T cells via inhibition of calcineurin which downregulates IL-2-dependent T-cell differentiation [29]. Their use is best characterized and widely adopted for prevention of allograft rejection following solid organ transplantation, foremost heart and lung transplantation. Side effects occur in virtually all patients including those with renal toxicity, anemia, leukocytopenia, and infection, mandating close and rigorous dose adjustment by trough-level measurements. In ILD, both agents have been most rigorously studied in patients with inflammatory myopathy-associated ILD and antisynthetase syndrome, especially in the setting of rapidly progressive ILD as salvage therapy with high short-term mortality [39]. Addition of calcineurin inhibitors (CNI) had a positive effect on PFTs [40–44] and survival [39, 45], all of which were retrospective and very heterogeneous concerning pace of ILD progression, reporting and type of antisynthetase antibodies, and co-administration of other DMARDs. One prospective pilot study with 10 patients who had acute or subacute ILD associated with inflammatory myopathies used CSA along with high-dose prednisolone and intravenous CYC, where the 3-month mortality was 50% [46]. Its use is recommended for rapid progressive ILD with inflammatory myopathies refractory to CYC or rituximab (RTX) in recent ERS-issued recommendations [47]. Target trough levels for FK506 in studies were 5–20 μg/L but should be reduced with response to 5–8 μg/L. Similarly, CSA target levels in studies were 100–200 μg/L. Evidence restricts the use of calcineurin inhibitors to rapid progressive IIM-associated ILD usually as an add-on therapy to another DMARD such as MMF. In this context, tacrolimus is preferred, given its overall better safety profile, but should be discontinued with lack of evidence or stabilized disease. Some experts consider it primarily a rescue therapy in refractory disease following CYC or RTX [47].

Cyclophosphamide

Apart from steroids, CYC was the first cytotoxic agent used in the treatment of progressive ILDs. It is an alkylating agent which depletes lymphocytic activity in both peripheral and central lymphoid tissue, suppressing macrophage influx and activation because of limited formation of monocyte precursors. Both humoral and cell-mediated immune response are inhibited by CYC [48]. Of all conventional agents discussed herein, CYC is one of the most potent but is also certainly associated with the most unfavorable safety profile, commonly causing leukocytopenia and infections and also less commonly secondary solid and hematological malignancy as well as gonadal failure [48]. In earlier studies, oral administration was the preferred route, but since it is associated with a higher cumulative dose and rate of adverse events, in ILD treatment in Europe it is only rarely used orally today and instead pulse-wise intravenously. CYC (orally 2 mg/kg BW) was first shown in the multicenter RCT (Scleroderma Lung Study I) to moderately improve pulmonary function in SSc-ILD compared to placebo over a study period of 6 months [49]. Following 6 months after discontinuation of CYC, the positive effect on FVC was, however, lost [49]. In the same year, the FAST trial which compared prednisolone with intravenous CYC (0.6 g/m^2 every 4 weeks for 6 cycles) followed by azathioprine or placebo was published, reporting a statistically nonsignificant 4.2% improvement in FVC in the treatment group [9]. These studies are still the basis for the current Grade A recommendation of the European League against Rheumatism (EULAR) for the use of CYC in SSc-ILD [50]. CYC was also retrospectively assessed in the treatment of rapid progressive nonspecific interstitial pneumonia (NSIP), where it led to disease stabilization [51], acute exacerbation of RA-ILD [52], and other miscellaneous progressive ILDs [53], where it was particularly effective in lymphocytic interstitial pneumonia and NSIP [53]. A recent meta-analysis reported overall improvement of FVC (but not DLCO) with CYC versus placebo in CTD-ILD without demonstrating a clear benefit compared to

MMF [54]. In inflammatory myositis-associated ILD, CYC is usually considered for salvage therapy with only very small cohort studies or anecdotal reports indicating improvement in 50% of patients [39]. When given intravenously, the protocol used in the FAST trial (0.6 g/m^2 of body surface every 4 weeks for 6 cycles [9]) is usually used with the co-administration of mesna. The same protocol is currently investigated versus RTX for CTD-ILD in the RECITAL trial [55]. Overall, CYC is one of the few conventional agents with existing RCT data to inform treatment. It is approved for therapy in SSc-ILD, but potential adverse events including solid and hematological malignancy, severe infection, and gonadal failure limit its use in the often female and younger patient population with SSc [54, 56]. CYC is used for salvage therapy with CTD-ILD, but its use must be weighed against potential implications for lung transplantation and risk of adverse events.

Targeted sDMARDs

Janus Kinase/Signal Transducer and Activator of Transcription Inhibitors

The Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway is a central point of convergence of extracellular cytokine signaling to the cell nucleus and is involved in numerous immunological and autoimmune diseases [57]. In recent years, selective JAK-1 and 2 inhibition has become approved for the treatment of several autoimmune diseases such as myelofibrosis, polycythemia vera, ulcerative colitis, and psoriatic arthritis and RA [57]. The safety profile assessed in the ORAL sequel long-term extension study found serious adverse events in the form of infections in 9% (24% of which were pneumonia) and musculoskeletal and connective tissue disorders in 5.5% of patients [58]. For the treatment of ILD, it was evaluated as a salvage therapy in rapid progressive ILD associated with anti-MDA5-amyopathic dermatomyositis despite therapy with high-dose steroids, CSA, and CYC, with a historic mortality reported up to 50% [59]. Based on a set of poor prognostic factors derived from historic controls with a mortality of 100%, 3 of 5 patients treated with tofacitinib (10 mg per day) survived and improved [60]. Encouraged by these data, a prospective single-center open-label study tested tofacitinib in 18 patients with early anti-MDA5-ADM-ILD and reported a 6-month survival of 100% compared to 78% in historic controls receiving standard of care with accompanying improvement in FVC and DLCO [61]. Despite its widespread use in RA, to date only preliminary retrospective uncontrolled data of 15 patients report significant improvement in DLCO and stabilization of fibrosis extent in high-resolution computed tomography at 12 months [62]. The recently started randomized PULMO-RA trial (NCT04311567) aims to evaluate the effects on ILD evolution in RA. In the light of early, yet promising reports of efficacy of tofacitinib in cutaneous sarcoidosis [63], a phase 1 study also aims to evaluate clinical response and expression of STAT-dependent gene expression with tofacitinib in pulmonary sarcoidosis (NCT03793439). While the results from these studies are eagerly anticipated, tofacitinib may be considered for progressive anti-MDA5-ILD despite treatment with CYC or RTX.

Biological DMARDs

Rituximab

RTX is a monoclonal antibody directed against CD20 which is expressed on pre-B and mature B lymphocytes and has been used for decades in a vast variety of autoimmune and hematological conditions with varying dosing and mode of application [64]. Treatment with RTX induces B-cell depletion by multiple mechanisms, including antibody-dependent cell-mediated toxicity, apoptosis, and complement-mediated cytotoxicity [65]. Although it directly targets B cells, therapeutic effects on T cells have also been reported. RTX is FDA (USA Food and Drug Administration) approved for the treatment of RA and granulomatosis with polyangiitis, but off-label application exists for practically every autoantibody-associated ILD. Only one single-center RCT has been completed and reported so far, including 16 patients with early SSc receiving RTX at a dose of 1,000 mg at day 0 and day 14 and at month 6, demonstrating a statistically nonsignificant trend to improved FVC [66]. Two prospective uncontrolled open-label studies in diffuse SSc with a total of 32 patients showed a favorable effect on FVC, either improving or stabilizing [67, 68], and one open-label comparative study showed improvement of FVC with RTX but not with intravenous CYC [69]. The more recent study assessed the efficacy of RTX together with MMF and also demonstrated an improvement of computed tomography (CT) graphically assessed fibrosis extent [68]. Further retrospective studies with usually mixed cohorts of SSc patients with and without evident ILD uniformly report stabilization or improvement of PFTs in the majority of patients [70–72]. For RA-ILD, one prospective open-label trial used RTX together with MTX at a dose of

1,000 mg at day 0, day 15, week 24, and week 26 in a total of 10 patients, 7 of whom were evaluated at week 48, with stabilization of DLCO, FVC, and CT features of ILDs [73]. Retrospective reports also showed stabilization of PFTs [74] and most recently also in patients with progressive RA-ILD before RTX, who then improved following treatment [75]. Overall, the presence of the NSIP pattern on CT and histopathology (with CD20+ lymphocytic infiltrates) seems to increase the likelihood of therapy response, while the presence of usual interstitial pneumonia is correlated with poor response [74, 76]. The use of RTX was also described in patients with IIM associated with anti-tRNA-synthetase antibodies, often a rapid evolving and highly inflammatory condition: an open-label prospective multicentric phase II study treated 12 patients with antisynthetase syndrome-associated ILDs who were refractory to steroids and ≥ DMARDs with RTX (1,000 mg at day 0, day 15, and 6 months) with overall significant improvement in muscle strength, CK normalization, steroid reduction, and stabilization or improvement in 90% of patients [77]. Comparably large multicentric retrospective studies focusing on antisynthetase syndrome with progressive ILD showed similar efficacy [78, 79]. Results from these trials have rendered RTX the drug of choice for refractory and progressive IIM-ILD (or antisynthetase syndrome). A separate retrospective trial for patients with primary SjS-associated ILD demonstrated significant improvement of FVC and DLCO in 10 patients [80]. With other retrospective studies in mixed CTD-ILD cohorts showing overall favorable effects on PFTs [80–85], results from two currently recruiting RCTs testing RTX versus intravenous CYC (RECITAL; NCT01862926) [55] and MMF plus RTX versus MMF plus placebo (EVER-ILD; NCT02990286) in CTD-ILD are eagerly awaited. RTX is associated with the occurrence of potentially lethal infections in these patients [79], and pneumocystis pneumonia prophylaxis is usually recommended, especially when also applied to other immunosuppressive agents. In summary, RTX is considered the best therapeutic option in severe and rapidly evolving inflammatory ILDs associated with B-cell accumulation.

Tocilizumab

Tocilizumab is a humanized monoclonal antibody which acts as an IL-6 receptor antagonist. IL-6 is a pleiotropic pro-inflammatory cytokine involved in the pathogenesis of RA but is also associated with ILD progression in SSc [86, 87]. Tocilizumab is widely used in and approved for the treatment of moderate to severe RA, systemic juvenile idiopathic arthritis, and giant cell arteritis [88]. Two recent multicentric RCTs have evaluated tocilizumab in patients with SSc and a mean FVC and DLCO at baseline of >80% ofpredicted, where FVC loss was an exploratory endpoint. In the "faSScinate" trial, 87 patients were randomized and demonstrated an attenuated decline in FVC with a difference of 136 mL at week 24 (p = 0.037) [89]. Similar effects were seen in the open-label phase of the study in patients who switched from placebo to tocilizumab after week 48 [90]. In the preliminary results from the phase III "Focused" trial including 212 patients, a significant reduction in FVC decline (−0.6 vs. −3.9%) in favor of tocilizumab versus placebo was reported [91]. Both studies recruited patients with early disease onset and also showed a significant effect of tocilizumab treatment (preserved FVC) in SSc patients who were not considered to be suffering from ILD at baseline. Both studies used tocilizumab subcutaneously at a dose of 162 mg weekly and reported serious infections in 16% under treatment versus 5% (placebo). Of note, CCL18 levels, which are correlated with inflammatory activity and survival of SSc-ILD [92, 93], were significantly suppressed in patients receiving tocilizumab [89]. While these data are promising with regard to prevention of progressive ILD in SSc, little to no data exist regarding the effect of tocilizumab on other clinically significant and progressive ILDs. One multicentric retrospective study in 28 patients with RA-ILD who received at least one dose of tocilizumab reported the majority of patients had stable or improving FVC and DLCO (both 76%). Of interest, most of the patients recruited into this trial had early disease with a median baseline FVC of 99% [94]. In conclusion, tocilizumab provides a promising treatment option for patients with SSc and potentially RA-ILD and might be effective particularly in early disease with higher levels of inflammatory activity. Given the widespread use of tocilizumab for RA, prospective studies are warranted to assess the true influence on ILD course and best timing.

Tumor Necrosis Factor-α Inhibitors

Tumor necrosis factor (TNF)-α is a key cytokine in the Th1 pathway eventually leading to granulomatous inflammation. The most applied TNF-α inhibitor in ILD is infliximab, which is administered intravenously with a dose of 3 or 5 mg per kg body weight at weeks 0, 2, and 6 and every 4–8 weeks thereafter. The main area of application is as off-label third-line therapy in steroid-dependent pulmonary sarcoidosis, where it was evaluated in a randomized double-blind placebo-controlled trial with improvement in FVC in the infliximab group [95]. Infliximab easily penetrates to the CNS, making it very ef-

fective in neurosarcoidosis [96]. Infliximab is contraindicated in severe heart failure, and infections occur in up to 36% of patients in a multicenter retrospective analysis [97]. Of note, infectious complications differ from other immunosuppressive therapies and are usually mild [98]. In particular, viral infections such as herpes zoster and warts are more common in patients treated with infliximab [99]. There is an increased risk of activation of latent tuberculosis, but this has been very rarely reported in sarcoidosis [98, 100]. Adalimumab, which is a fully human anti-TNF antibody, was also successfully evaluated in an open-label trial with efficacy in 82% of patients in terms of improvement of FVC, 6-min walking test, and steroid-dose reduction [101]. Adalimumab is administered subcutaneously usually at 40 mg weekly. The role of TNF-alpha blockade for other autoimmune ILDs is unclear, but a recent review regarding TNF-alpha blockade in RA-ILD showed high reporting of adverse events (87.5%) with a reported mortality rate of 35% and little evidence of potential benefits in this patient cohort in the absence of RCTs [102].

Abatacept

Abatacept belongs to the selective co-stimulation modulators as a recombinant fusion protein comprising the extracellular domain of human cytotoxic T lymphocyte-associated protein 4 which inhibits T-cell activation by specifically binding to CD80 and CD86 on antigen-presenting cells [103]. It is approved for treatment of active RA. A first study to report retrospective multicentric registry data reported stabilization or improvement of FVC and DLCO in >80% of 63 evaluated patients with RA-ILD treated with 10 mg per kg body weight on day 0 and day 15 and thereafter 4 weekly [104]. Seventeen percent of patients discontinued abatacept due to adverse events, including 3 with serious infections. A recent retrospective cohort study with 44 patients in RA-ILD reported similar positive effects in PFTs with no severe adverse events [105]. Currently, 2 prospective trials are in recruitment using abatacept: the APRIL trial (NCT03084419) assesses the course of PFTs in an open-label single-arm trial in patients with RA-ILD as a feasibility trial to inform a larger study. The ATtackMy-ILD phase 2 study (NCT03215927) is a placebo-controlled randomized trial for myositis-associated ILD at a dose of 125 mg s.c. weekly. With the results from these trials still pending, abatacept is a promising agent in IIM-ILD and RA-ILD, but its effect on clinical and radiological subtypes, especially in the latter, remains to be determined.

Conclusion

For many systemic diseases and especially in the context of CTDs, progressive ILD is still the main driver of mortality [106, 107]. Despite this negative prognostic implication, the majority of evidence to inform treatment decisions is based on retrospective or small prospective studies [56]. Currently recruiting studies (Table 2) will shed light on new treatment modalities, hopefully leading to approval of these agents by the authorities and improved long-term outcomes. A variety of immunomodulatory agents are currently under investigation for IPF which have not yet been approved for CTDs, but which are reviewed elsewhere [108], are beyond the scope of this article. In the light of emerging evidence for efficacy of antifibrotic drugs in autoimmune disease-associated ILD [109], further research to inform choice of treatment modality regarding anti-inflammatory or antifibrotic drugs or both is urgently warranted.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

There was no specific funding for this project. Dr. Seeliger is supported by PRACTIS – Clinician Scientist Program of Hannover Medical School, funded by the German Research Foundation (DFG, ME 3696/3-1).

Author Contributions

B.S. conducted the literature research and prepared the initial draft of the manuscript. A.P. critically revised the manuscript. Both authors approved of the final version of the manuscript.

References

1 Lederer DJ, Martinez FJ. Idiopathic pulmonary fibrosis. N Engl J Med. 2018;378(19):1811–23.
2 Raghu G, Raghu G, Anstrom KJ, King TE, Lasky JA, Martinez FJ. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. N Engl J Med. 2012;366(21):1968–77.
3 Spagnolo P, Tzouvelekis A, Bonella F. The management of patients with idiopathic pulmonary fibrosis. Front Med. 2018;5:148.
4 Fischer A, Antoniou KM, Brown KK, Cadranel J, Corte TJ, Du Bois RM, et al. An official European respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. Eur Respir J. 2015;46(4):976–87.

5 Smolen JS, van der Heijde D, Machold KP, Aletaha D, Landewé R. Proposal for a new nomenclature of disease-modifying antirheumatic drugs. Ann Rheum Dis. 2014;73(1):3–5.
6 Maltzman JS, Koretzky GA. Azathioprine: old drug, new actions: old drug, new actions. J Clin Invest. 2003;111(8):1122–4.
7 Sanderson JD. TPMT testing before starting azathioprine or mercaptopurine: surely just do it? Gastroenterology. 2015;149(4):850–3.
8 Relling MV, Schwab M, Whirl-Carrillo M, Suarez-Kurtz G, Pui CH, Stein CM, et al. Clinical pharmacogenetics implementation consortium guideline for thiopurine dosing based on TPMT and NUDT15 genotypes: 2018 update. Clin Pharmacol Ther. 2019;105(5):1095–105.
9 Hoyles RK, Ellis RW, Wellsbury J, Lees B, Newlands P, Goh NS, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. Arthritis Rheum. 2006;54(12):3962–70.
10 Nadashkevich O, Davis P, Fritzler M, Kovalenko W. A randomized unblinded trial of cyclophosphamide versus azathioprine in the treatment of systemic sclerosis. Clin Rheumatol. 2006;25(2):205–12.
11 Bérezné A, Ranque B, Valeyre D, Brauner M, Allanore Y, Launay D, et al. Therapeutic strategy combining intravenous cyclophosphamide followed by oral azathioprine to treat worsening interstitial lung disease associated with systemic sclerosis: a retrospective multicenter open-label study. J Rheumatol. 2008;35(6):1064–72.
12 Oldham JM, Lee C, Valenzi E, Witt LJ, Adegunsoye A, Hsu S, et al. Azathioprine response in patients with fibrotic connective tissue disease-associated interstitial lung disease. Respir Med. 2016;121:117–22.
13 Huapaya JA, Silhan L, Pinal-Fernandez I, Casal-Dominguez M, Johnson C, Albayda J, et al. Long-term treatment with azathioprine and mycophenolate mofetil for myositis-related interstitial lung disease. Chest. 2019;156(5):896–906.
14 Mira-Avendano IC, Parambil JG, Yadav R, Arrossi V, Xu M, Chapman JT, et al. A retrospective review of clinical features and treatment outcomes in steroid-resistant interstitial lung disease from polymyositis/dermatomyositis. Respir Med. 2013;107(6):890–6.
15 Vorselaars ADM, Wuyts WA, Vorselaars VMM, Zanen P, Deneer VHM, Veltkamp M, et al. Methotrexate vs azathioprine in second-line therapy of sarcoidosis. Chest. 2013;144(3):805–12.
16 Wang W, Zhou H, Liu L. Side effects of methotrexate therapy for rheumatoid arthritis: a systematic review. Eur J Med Chem. 2018;158:502–16.
17 Imokawa S, Colby TV, Leslie KO, Helmers RA. Methotrexate pneumonitis: review of the literature and histopathological findings in nine patients. Eur Respir J. 2000;15(2):373–81.
18 Sathi N, Chikura B, Kaushik VV, Wiswell R, Dawson JK. How common is methotrexate pneumonitis? A large prospective study investigates. Clin Rheumatol. 2012;31(1):79–83.
19 Fragoulis GE, Conway R, Nikiphorou E. Methotrexate and interstitial lung disease: controversies and questions. A narrative review of the literature. Rheumatology. 2019;58(11):1900–6.
20 Kiely P, Busby AD, Nikiphorou E, Sullivan K, Walsh DA, Creamer P, et al. Is incident rheumatoid arthritis interstitial lung disease associated with methotrexate treatment? Results from a multivariate analysis in the ERAS and ERAN inception cohorts. BMJ Open. 2019;9(5):e028466.
21 Baughman RP, Winget DB, Lower EE. Methotrexate is steroid sparing in acute sarcoidosis: results of a double blind, randomized trial. Sarcoidosis Vasc Diffuse Lung Dis. 2000;17(1):60–6.
22 Culver DA, Judson MA. New advances in the management of pulmonary sarcoidosis. BMJ. 2019;367:l5553.
23 Cohen SB, Iqbal I. Leflunomide. Int J Clin Pract. 2003;57(2):115–20.
24 Conway R, Low C, Coughlan RJ, O'Donnell MJ, Carey JJ. Leflunomide use and risk of lung disease in rheumatoid arthritis: a systematic literature review and metaanalysis of randomized controlled trials. J Rheumatol. 2016;43(5):855–60.
25 Baughman RP, Lower EE. Leflunomide for chronic sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2004;21(1):43–8.
26 Sahoo DH, Bandyopadhyay D, Xu M, Pearson K, Parambil JG, Lazar CA, et al. Effectiveness and safety of leflunomide for pulmonary and extrapulmonary sarcoidosis. Eur Respir J. 2011;38(5):1145–50.
27 Rojas-Serrano J, González-Velásquez E, Mejía M, Sánchez-Rodríguez A, Carrillo G. Interstitial lung disease related to rheumatoid arthritis: evolution after treatment. Reumatol Clin. 2012;8(2):68–71.
28 Del Papa N, Vitali C. Management of primary Sjögren's syndrome: recent developments and new classification criteria. Ther Adv Musculoskelet Dis. 2018;10(2):39–54.
29 Broen JCA, van Laar JM. Mycophenolate mofetil, azathioprine and tacrolimus: mechanisms in rheumatology. Nat Rev Rheumatol. 2020;16(3):167–78.
30 Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med. 2016;4(9):708–19.
31 Volkmann ER, Tashkin DP, Li N, Roth MD, Khanna D, Hoffmann-Vold AM, et al. Mycophenolate mofetil versus placebo for systemic sclerosis-related interstitial lung disease: an analysis of scleroderma lung studies I and II. Arthritis Rheumatol. 2017;69(7):1451–60.
32 Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med. 2019;380(26):2518–28.
33 Fischer A, Brown KK, Du Bois RM, Frankel SK, Cosgrove GP, Fernandez-Perez ER, et al. Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease. J Rheumatol. 2013;40(5):640–6.
34 Fiddler CA, Simler N, Thillai M, Parfrey H. Use of mycophenolate mofetil and azathioprine for the treatment of chronic hypersensitivity pneumonitis-A single-centre experience. Clin Respir J. 2019;13(12):791–4.
35 Morisset J, Johannson KA, Vittinghoff E, Aravena C, Elicker BM, Jones KD, et al. Use of mycophenolate mofetil or azathioprine for the management of chronic hypersensitivity pneumonitis. Chest. 2017;151(3):619–25.
36 McCoy SS, Mukadam Z, Meyer KC, Kanne JP, Meyer CA, Martin MD, et al. Mycophenolate therapy in interstitial pneumonia with autoimmune features: a cohort study. Ther Clin Risk Manag. 2018;14:2171–81.
37 Schiff M, Beaulieu A, Scott DL, Rashford M. Mycophenolate mofetil in the treatment of adults with advanced rheumatoid arthritis: three 24-week, randomized, double-blind, placebo- or ciclosporin-controlled trials. Clin Drug Investig. 2010;30(9):613–24.
38 Sadeleer LJde, Hermans F, Dycker Ede, Yserbyt J, Verschakelen JA, Verbeken EK, et al. Impact of BAL lymphocytosis and presence of honeycombing on corticosteroid treatment effect in fibrotic hypersensitivity pneumonitis: a retrospective cohort study. Eur Respir J. 2020;55(4):1901983.
39 Barba T, Fort R, Cottin V, Provencher S, Durieu I, Jardel S, et al. Treatment of idiopathic inflammatory myositis associated interstitial lung disease: a systematic review and meta-analysis. Autoimmun Rev. 2019;18(2):113–22.
40 Wilkes MR, Sereika SM, Fertig N, Lucas MR, Oddis CV. Treatment of antisynthetase-associated interstitial lung disease with tacrolimus. Arthritis Rheum. 2005;52(8):2439–46.
41 Labirua-Iturburu A, Selva-O'Callaghan A, Martínez-Gómez X, Trallero-Araguás E, Labrador-Horrillo M, Vilardell-Tarrés M. Calcineurin inhibitors in a cohort of patients with antisynthetase-associated interstitial lung disease. Clin Exp Rheumatol. 2013;31(3):436–9.
42 Cavagna L, Caporali R, Abdì-Alì L, Dore R, Meloni F, Montecucco C. Cyclosporine in anti-Jo1-positive patients with corticosteroid-refractory interstitial lung disease. J Rheumatol. 2013;40(4):484–92.
43 Miyake S, Ohtani Y, Sawada M, Inase N, Miyazaki Y, Takano S, et al. Usefulness of cyclosporine A on rapidly progressive interstitial pneumonia in dermatomyositis. Sarcoidosis Vasc Diffuse Lung Dis. 2002;19(2):128–33.

44 Takada K, Nagasaka K, Miyasaka N. Polymyositis/dermatomyositis and interstitial lung disease: a new therapeutic approach with T-cell-specific immunosuppressants. Autoimmunity. 2005;38(5):383–92.
45 Go DJ, Park JK, Kang EH, Kwon HM, Lee YJ, Song YW, et al. Survival benefit associated with early cyclosporine treatment for dermatomyositis-associated interstitial lung disease. Rheumatol Int. 2016;36(1):125–31.
46 Kameda H, Nagasawa H, Ogawa H, Sekiguchi N, Takei H, Tokuhira M, et al. Combination therapy with corticosteroids, cyclosporin A, and intravenous pulse cyclophosphamide for acute/subacute interstitial pneumonia in patients with dermatomyositis. J Rheumatol. 2005;32(9):1719–26.
47 Cottin V, Barba T, Mainbourg S, Nasser M, Valenzuela C, Lega J-C. Pulmonary involvement in inflammatory myopathies. In: Wuyts WA, Cottin V, Spagnolo P, Wells AU, editors. Pulmonary manifestations of systemic diseases. Sheffield, UK: European Respiratory Society; 2019. p. 68–89.
48 Subramanian R, Pathak H, Ravindran V. Safety of cyclophosphamide therapy in autoimmune rheumatic diseases. Indian J Rheumatol. 2019;14(2):127.
49 Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med. 2006;354(25):2655–66.
50 Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A, Allanore Y, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis. 2017;76(8):1327–39.
51 Corte TJ, Ellis R, Renzoni EA, Hansell DM, Nicholson AG, Du Bois RM, et al. Use of intravenous cyclophosphamide in known or suspected, advanced non-specific interstitial pneumonia. Sarcoidosis Vasc Diffuse Lung Dis. 2009;26(2):132–8.
52 Ota M, Iwasaki Y, Harada H, Sasaki O, Nagafuchi Y, Nakachi S, et al. Efficacy of intensive immunosuppression in exacerbated rheumatoid arthritis-associated interstitial lung disease. Mod Rheumatol. 2017;27(1):22–8.
53 Schupp JC, Köhler T, Müller-Quernheim J. Usefulness of cyclophosphamide pulse therapy in interstitial lung diseases. Respiration. 2016;91(4):296–301.
54 Barnes H, Holland AE, Westall GP, Goh NS, Glaspole IN. Cyclophosphamide for connective tissue disease-associated interstitial lung disease. Cochrane Database Syst Rev. 2018;1:CD010908.
55 Saunders P, Tsipouri V, Keir GJ, Ashby D, Flather MD, Parfrey H, et al. Rituximab versus cyclophosphamide for the treatment of connective tissue disease-associated interstitial lung disease (RECITAL): study protocol for a randomised controlled trial. Trials. 2017;18(1):275.
56 Jee AS, Corte TJ. Current and emerging drug therapies for connective tissue disease-interstitial lung disease (CTD-ILD). Drugs. 2019;79(14):1511–28.
57 Muller R. JAK inhibitors in 2019, synthetic review in 10 points. Eur J Intern Med. 2019;66:9–17.
58 Wollenhaupt J, Lee EB, Curtis JR, Silverfield J, Terry K, Soma K, et al. Safety and efficacy of tofacitinib for up to 9.5 years in the treatment of rheumatoid arthritis: final results of a global, open-label, long-term extension study. Arthritis Res Ther. 2019;21(1):89.
59 Ye S, Chen XX, Lu XY, Wu MF, Deng Y, Huang WQ, et al. Adult clinically amyopathic dermatomyositis with rapid progressive interstitial lung disease: a retrospective cohort study. Clin Rheumatol. 2007;26(10):1647–54.
60 Kurasawa K, Arai S, Namiki Y, Tanaka A, Takamura Y, Owada T, et al. Tofacitinib for refractory interstitial lung diseases in antimelanoma differentiation-associated 5 gene antibody-positive dermatomyositis. Rheumatology. 2018;57(12):2114–9.
61 Chen Z, Wang X, Ye S. Tofacitinib in amyopathic dermatomyositis-associated interstitial lung disease. N Engl J Med. 2019;381(3):291–3.
62 Bejarano M, Tamborenea MN, Goñi MA, Saldarriaga L, Pisoni C, Salinas RG, et al. AB0418 interstitial lung disease in patients with rheumatoid arthritis treated with tofacitinib. In: Abstracts Accepted for Publication. BMJ Publishing Group Ltd and European League Against Rheumatism; 062019. 1672.1–1672.
63 Damsky W, Thakral D, Emeagwali N, Galan A, King B. Tofacitinib treatment and molecular analysis of cutaneous sarcoidosis. N Engl J Med. 2018;379(26):2540–6.
64 Musette P, Bouaziz JD. B cell modulation strategies in autoimmune diseases: new concepts. Front Immunol. 2018;9:622.
65 Pecoraro A, Crescenzi L, Galdiero MR, Marone G, Rivellese F, Rossi FW, et al. Immunosuppressive therapy with rituximab in common variable immunodeficiency. Clin Mol Allergy. 2019;17:9.
66 Boonstra M, Meijs J, Dorjée AL, Marsan NA, Schouffoer A, Ninaber MK, et al. Rituximab in early systemic sclerosis. RMD Open. 2017;3(2):e000384.
67 Lafyatis R, Kissin E, York M, Farina G, Viger K, Fritzler MJ, et al. B cell depletion with rituximab in patients with diffuse cutaneous systemic sclerosis. Arthritis Rheum. 2009;60(2):578–83.
68 Fraticelli P, Fischetti C, Salaffi F, Carotti M, Mattioli M, Pomponio G, et al. Combination therapy with rituximab and mycophenolate mofetil in systemic sclerosis. A single-centre case series study. Clin Exp Rheumatol. 2018;113(36 Suppl 4):142–5.
69 Sircar G, Goswami RP, Sircar D, Ghosh A, Ghosh P. Intravenous cyclophosphamide vs rituximab for the treatment of early diffuse scleroderma lung disease: open label, randomized, controlled trial. Rheumatology. 2018;57(12):2106–13.
70 Jordan S, Distler JH, Maurer B, Huscher D, van Laar JM, Allanore Y, et al. Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma Trial and Research (EUSTAR) group. Ann Rheum Dis. 2015;74(6):1188–94.
71 Giuggioli D, Lumetti F, Colaci M, Fallahi P, Antonelli A, Ferri C. Rituximab in the treatment of patients with systemic sclerosis. Our experience and review of the literature. Autoimmun Rev. 2015;14(11):1072–8.
72 Bosello SL, De Luca G, Rucco M, Berardi G, Falcione M, Danza FM, et al. Long-term efficacy of B cell depletion therapy on lung and skin involvement in diffuse systemic sclerosis. Semin Arthritis Rheum. 2015;44(4):428–36.
73 Matteson EL, Bongartz T, Ryu JH, Crowson CS, Hartman TE, Dellaripa PF. Open-label, pilot study of the safety and clinical effects of rituximab in patients with rheumatoid arthritis-associated interstitial pneumonia. OJRA. 2012;2(3):53–8.
74 Md Yusof MY, Kabia A, Darby M, Lettieri G, Beirne P, Vital EM, et al. Effect of rituximab on the progression of rheumatoid arthritis-related interstitial lung disease: 10 years' experience at a single centre. Rheumatology. 2017;56(8):1348–57.
75 Fui A, Bergantini L, Selvi E, Mazzei MA, Bennett D, Pieroni MG, et al. Rituximab therapy in interstitial lung disease associated with rheumatoid arthritis. Intern Med J. 2020;50(3):330–6.
76 Peng M, Wang W, Qin L, Liu H, Qin M, Zheng W, et al. Association between nonspecific interstitial pneumonia and presence of CD20+ B lymphocytes within pulmonary lymphoid follicles. Sci Rep. 2017;7(1):16912.
77 Allenbach Y, Guiguet M, Rigolet A, Marie I, Hachulla E, Drouot L, et al. Efficacy of rituximab in refractory inflammatory myopathies associated with anti- synthetase auto-antibodies: an open-label, phase II trial. PLoS One. 2015;10(11):e0133702.
78 Doyle TJ, Dhillon N, Madan R, Cabral F, Fletcher EA, Koontz DC, et al. Rituximab in the treatment of interstitial lung disease associated with antisynthetase syndrome: a multicenter retrospective case review. J Rheumatol. 2018;45(6):841–50.
79 Andersson H, Sem M, Lund MB, Aaløkken TM, Günther A, Walle-Hansen R, et al. Long-term experience with rituximab in anti-synthetase syndrome-related interstitial lung disease. Rheumatology. 2015;54(8):1420–8.
80 Chen M-H, Chen C-K, Chou H-P, Chen M-H, Tsai C-Y, Chang D-M. Rituximab therapy in primary Sjögren's syndrome with interstitial lung disease: a retrospective cohort study. Clin Exp Rheumatol. 2016;34(6):1077–84.
81 Sharp C, McCabe M, Dodds N, Edey A, Mayers L, Adamali H, et al. Rituximab in autoimmune connective tissue disease-associated interstitial lung disease. Rheumatology. 2016;55(7):1318–24.

82 Chartrand S, Swigris JJ, Peykova L, Fischer A. Rituximab for the treatment of connective tissue disease-associated interstitial lung disease. Sarcoidosis Vasc Diffuse Lung Dis. 2016; 32(4):296–304.
83 Duarte AC, Cordeiro A, Fernandes BM, Bernardes M, Martins P, Cordeiro I, et al. Rituximab in connective tissue disease-associated interstitial lung disease. Clin Rheumatol. 2019;38(7):2001–9.
84 Fitzgerald DB, Moloney F, Twomey M, O'Connell JO, Cronin O, Harty L, et al. Efficacy and safety of rituximab in connective tissue disease related interstitial lung disease. Sarcoidosis Vasc Diffuse Lung Dis. 2015; 32(3):215–21.
85 Keir GJ, Maher TM, Ming D, Abdullah R, de Lauretis A, Wickremasinghe M, et al. Rituximab in severe, treatment-refractory interstitial lung disease. Respirology. 2014;19(3):353–9.
86 Lauretis Ade, Sestini P, Pantelidis P, Hoyles R, Hansell DM, Goh NSL, et al. Serum interleukin 6 is predictive of early functional decline and mortality in interstitial lung disease associated with systemic sclerosis. J Rheumatol. 2013;40(4):435–46.
87 Muangchan C, Pope JE. Interleukin 6 in systemic sclerosis and potential implications for targeted therapy. J Rheumatol. 2012;39(6): 1120–4.
88 Scott LJ. Tocilizumab: a review in rheumatoid arthritis. Drugs. 2017;77(17):1865–79.
89 Khanna D, Denton CP, Jahreis A, van Laar JM, Frech TM, Anderson ME, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. Lancet. 2016; 387(10038):2630–40.
90 Khanna D, Denton CP, Lin CJF, van Laar JM, Frech TM, Anderson ME, et al. Safety and efficacy of subcutaneous tocilizumab in systemic sclerosis: results from the open-label period of a phase II randomised controlled trial (faSScinate). Ann Rheum Dis. 2018;77(2):212–20.
91 Khanna D, Lin CJF, Kuwana M, Allanore Y, Batalov A, Butrimiene I, et al. Efficacy and safety of tocilizumab for the treatment of systemic sclerosis: results from a phase 3 randomized controlled trial [abstract]: presented at the American College of Rheumatology (ACR)/Association of Rheumatology Professionals (ARHP) annual meeting, Chicago, IL, USA, 19–24 October 2018. Arthritis Rheumatol. 2018 [cited 2020 Mar 31];70(Suppl 10).
92 Prasse A, Pechkovsky DV, Toews GB, Schäfer M, Eggeling S, Ludwig C, et al. CCL18 as an indicator of pulmonary fibrotic activity in idiopathic interstitial pneumonias and systemic sclerosis. Arthritis Rheum. 2007;56(5):1685–93.
93 Volkmann ER, Tashkin DP, Kuwana M, Li N, Roth MD, Charles J, et al. Progression of interstitial lung disease in systemic sclerosis: the importance of pneumoproteins Krebs von den Lungen 6 and CCL18. Arthritis Rheumatol. 2019;71(12):2059–67.
94 Manfredi A, Cassone G, Furini F, Gremese E, Venerito V, Atzeni F, et al. Tocilizumab therapy in rheumatoid arthritis with interstitial lung disease: a multicenter retrospective study. Intern Med J. 2020;50(9):1085–90.
95 Baughman RP, Drent M, Kavuru M, Judson MA, Costabel U, Du Bois R, et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. Am J Respir Crit Care Med. 2006;174(7):795–802.
96 Gelfand JM, Bradshaw MJ, Stern BJ, Clifford DB, Wang Y, Cho TA, et al. Infliximab for the treatment of CNS sarcoidosis: a multi-institutional series. Neurology. 2017;89(20): 2092–100.
97 Jamilloux Y, Cohen-Aubart F, Chapelon-Abric C, Maucort-Boulch D, Marquet A, Pérard L, et al. Efficacy and safety of tumor necrosis factor antagonists in refractory sarcoidosis: a multicenter study of 132 patients. Semin Arthritis Rheum. 2017;47(2):288–94.
98 Hostettler KE, Studler U, Tamm M, Brutsche MH. Long-term treatment with infliximab in patients with sarcoidosis. Respiration. 2012;83(3):218–24.
99 Kim SY, Solomon DH. Tumor necrosis factor blockade and the risk of viral infection. Nat Rev Rheumatol. 2010;6(3):165–74.
100 Zhang Z, Fan W, Yang G, Xu Z, Wang J, Cheng Q, et al. Risk of tuberculosis in patients treated with TNF-α antagonists: a systematic review and meta-analysis of randomised controlled trials. BMJ Open. 2017; 7(3):e012567.
101 Sweiss NJ, Noth I, Mirsaeidi M, Zhang W, Naureckas ET, Hogarth DK, et al. Efficacy results of a 52-week trial of adalimumab in the treatment of refractory sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2014;31(1): 46–54.
102 Huang Y, Lin W, Chen Z, Wang Y, Huang Y, Tu S. Effect of tumor necrosis factor inhibitors on interstitial lung disease in rheumatoid arthritis: angel or demon? Drug Des Devel Ther. 2019;13:2111–25.
103 Blair HA, Deeks ED. Abatacept: a review in rheumatoid arthritis. Drugs. 2017;77(11): 1221–33.
104 Fernández-Díaz C, Loricera J, Castañeda S, López-Mejías R, Ojeda-García C, Olivé A, et al. Abatacept in patients with rheumatoid arthritis and interstitial lung disease: a national multicenter study of 63 patients. Semin Arthritis Rheum. 2018;48(1):22–7.
105 Cassone G, Manfredi A, Atzeni F, Venerito V, Vacchi C, Picerno V, et al. Safety of abatacept in italian patients with rheumatoid arthritis and interstitial lung disease: a multicenter retrospective study. J Clin Med. 2020; 9(1):277.
106 Palm O, Garen T, Berge Enger T, Jensen JL, Lund MB, Aaløkken TM, et al. Clinical pulmonary involvement in primary Sjogren's syndrome: prevalence, quality of life and mortality: a retrospective study based on registry data. Rheumatology. 2013;52(1): 173–9.
107 Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Risk of serious infection in patients with rheumatoid arthritis-associated interstitial lung disease. Clin Rheumatol. 2016;35(10):2585–9.
108 Somogyi V, Chaudhuri N, Torrisi SE, Kahn N, Müller V, Kreuter M. The therapy of idiopathic pulmonary fibrosis: what is next? Eur Respir Rev. 2019;28(153):190021.
109 Collins BF, Raghu G. Antifibrotic therapy for fibrotic lung disease beyond idiopathic pulmonary fibrosis. Eur Respir Rev. 2019; 28(153):190022.