Zhe Wu[1,2], Philip L. Molyneaux[1,2]

p.molyneaux@imperial.ac.uk

Ask the expert

Choosing pharmacotherapy for ILD in patients with connective tissue disease

Cite as: Wu Z, Molyneaux PL. Choosing pharmacotherapy for ILD in patients with connective tissue disease. *Breathe* 2021; 17: 210114.

Interstitial lung disease (ILD) is a well-recognised complication of connective tissue diseases (CTD), leading to significant mortality and morbidity. The pathogenesis is thought to be driven by immune-mediated inflammation and subsequent architectural damage [1]. Current pharmacotherapy options predominantly focus on the use of immune suppression, although recently antifibrotic therapy has shown some promise. This article will highlight the best available evidence for treatment options in the most common forms of CTD-ILD.

Scleroderma

Of all the CTDs ILD is most prevalent in scleroderma (SSc) (70–90%) and remains the leading cause of death in SSc [2]. The most common presentation on imaging is a nonspecific interstitial pneumonia (NSIP) pattern, with a significant proportion of patients developing pulmonary hypertension. The treatment options for the latter are beyond the scope of this article but have been covered in a recent review [3].

In SSc the extent of fibrosis determines prognosis and only those with moderate-to-severe disease require treatment. A simple staging system can be employed to categorise patients as either extensive (>30% disease extent on high-resolution computed tomography (HRCT), or 10–30% disease extent on HRCT and forced vital capacity (FVC) <70% predicted) or limited disease (<30% disease extent on HRCT, or 10–30% disease extent on HRCT and FVC ≥70% predicted) [4]. Long-term steroid use above a dose of 10 mg prednisolone daily is associated with an increased risk of renal crisis and should be avoided [5], as should pulsed therapy [6]. Several randomised controlled trials (RCTs) have facilitated the current treatment approach for steroid-sparing agents. The multicentre Scleroderma Lung Study I (SLS I) demonstrated that oral cyclophosphamide (CYC) at 1–2 mg·kg^{-1} per day had a statistically significant but modest impact on FVC and total lung capacity (TLC) compared with placebo (mean improvement 2.5% and 4.1%, respectively) after 1 year of treatment, although clinically relevant improvements were also seen in dyspnoea scores, skin changes and functional status [7]. Furthermore, CT scans of patients in the placebo arm were more likely to reveal progressive fibrosis [8]. However, the benefit in FVC was not sustained at 1 year post-cessation of treatment [9]. Interestingly, a subanalysis discovered that patients with baseline FVC <70% predicted had a greater treatment effect, with FVC improvement at 12 months of 4.62%, in comparison to 0.55% in those with FVC >70% [9]. The subsequent SLS II trial compared treatment with 12 months of oral CYC *versus* 24 months of mycophenolate mofetil (MMF). The target daily dose of MMF was 3 g. Whilst equal efficacy was observed, MMF was far better tolerated with a considerably lower risk of developing leukopenia and thrombocytopenia [10]. The FAST trial used low-dose steroids in combination with six

@ERSpublications
Interstitial lung disease (ILD) is a well-recognised complication of several connective tissue diseases (CTD). This article outlines the various treatment options for the most common CTD-ILDs and discuss the ongoing research in this field. https://bit.ly/39NHwx6

CrossMark

©ERS 2021

intravenous CYC infusions (at a dose of 600 $mg \cdot m^{-2}$ per month) followed by azathioprine maintenance therapy (2.5 $mg \cdot kg^{-1}$ per day), and demonstrated beneficial effects on FVC and radiological disease extent, although these results failed to achieve statistical significance, perhaps due to small sample size [11]. In addition, the cohort studied had milder lung function impairment compared with the SLS I group. Of note, the side-effect profile of the intravenous CYC regime seemed more favourable than the oral route. The implications of this are important in real-world practice, where varying compliance or even discontinuation of treatment is common. These studies have culminated in the European League against Rheumatism (EULAR) recommending CYC in those with deteriorating pulmonary disease [12].

In recent times, the era of antifibrotic use for idiopathic pulmonary fibrosis (IPF) has led to an interest in using these agents for non-IPF fibrotic lung disease. The SENSCIS trial evaluated the efficacy and safety of nintedanib in SSc-ILD *versus* standard therapy. The study enrolled 576 subjects with more than 10% fibrosis, approximately half of whom were receiving MMF at baseline [13]. The relative reduction of FVC decline on nintedanib was 44%, similar to the rates seen in IPF trials. However, no treatment effect was observed on dyspnoea, quality of life or skin manifestations. Nintedanib was well tolerated with over four-fifths of those in the active arm completing the full treatment period. Subsequently, *post-hoc* analysis revealed that nintedanib had similar effects on the relative reduction in FVC decline between both MMF and non-MMF groups (40% and 46%, respectively) [14]. The optimal timing of the introduction of antifibrotic therapy, however, remains unknown. Meanwhile, small early phase studies of pirfenidone in SSc-ILD have demonstrated favourable safety and tolerability [15, 16], prompting the ongoing SLS III study which will evaluate the effect of combined MMF and pirfenidone *versus* MMF monotherapy (clinicaltrials.gov identifier: NCT03221257).

Biological agents have also been examined. Rituximab (RTX), an agent that depletes B-cells, has shown promise in several small studies [17–19]. RECITAL is a multicentre RCT comparing RTX (two doses 14 days apart) with monthly intravenous CYC infusions (six doses) for the treatment of a range of CTDs including SSc, with the results eagerly awaited [20]. Tocilizumab, an anti-interleukin (IL)-6 agent, has shown a possible stabilising effect on FVC in two RCTs (namely the faSScinate and focuSSced trials), although the existence of ILD at baseline was not screened for at enrolment [21, 22]. Thus, the participants had minimal lung function impairment and the efficacy of anti-IL-6 agents in those with moderate-to-severe ILD requires further evaluation.

Interestingly, SSc-like features can overlap with systemic lupus erythematosus (SLE) [23]. The presence of an overlap syndrome, longer duration of SLE diagnosis and older age is associated with poorer prognosis [24, 25]. However, ILD is uncommon in SLE and few studies have evaluated the therapeutics [26] or long-term prognosis [27].

Rheumatoid arthritis

The prevalence of ILD in rheumatoid arthritis (RA) is estimated at 5–10% and this figure is rising with the increasing screening of patients with RA [28–30]. The predominant CT pattern is usual interstitial pneumonia (UIP) followed by NSIP, the former of which confers a poorer prognosis [31]. The treatment of RA-ILD remains a poorly studied field, although it is widely accepted that steroids should be the first-line agent. The current literature, based on observational studies and case series, provides inconclusive evidence for steroid-sparing therapy, although RTX has shown some promise [32]. Given both the radiological and genetic overlap between RA-ILD and IPF [33], it was of no surprise that RA-ILD patients were included in the INBUILD study which investigated the efficacy of nintedanib for multiple subtypes of ILD with a progressive phenotype [34]. Although the study was not powered to specifically analyse the effect in RA patients, the overall signal was positive and it is likely that in the future those patients with RA and a more fibrotic UIP type picture may receive antifibrotic therapy earlier in their disease course.

One of the main areas of historic controversy in the treatment of CTD-ILD is the link between methotrexate (MTX) and ILD in RA patients. While MTX-induced pneumonitis is a real entity, it is uncommon, the onset is usually within 12 months of initiation and the appearances on CT are inflammatory rather than fibrotic [35]. Only a handful of older, low quality, original publications suggest MTX being associated with fibrotic ILD and these studies were conducted before the widespread use of CT scanning [35]. Much larger and robust studies have recently refuted the link and in fact suggest MTX use may delay the onset of ILD. Juge *et al.* [36] examined MTX exposure across RA patients with ILD (n=410) *versus* patients without (n=673), demonstrating that MTX use was associated with a lower risk of developing RA-ILD (OR 0.43, 95% CI 0.26–0.69). This finding was validated in a multicentre prospective cohort study of over 2000 newly diagnosed RA subjects [37]. In this cohort higher rates of RA-ILD were found in those who had never taken MTX (4.8%) compared with those who had (2.5%), and MTX use was associated with a longer time to the development of ILD. Several other studies have further supported these findings [38–41]; therefore, MTX should no longer be routinely discontinued in the rheumatoid patient with well-controlled joint disease who develops ILD.

Idiopathic inflammatory myopathies

The idiopathic inflammatory myopathies (IIMs) are a group of disorders including polymyositis, dermatomyositis and anti-synthetase syndrome (ASS). The most common ILD patterns are NSIP and organising pneumonia, which can often coexist. While the heterogeneous nature of the IIMs means the decision to treat varies, it is worth noting that patients with the anti-MDA5 antibody subtype often develop a clinically amyopathic and rapidly progressive phenotype akin to acute interstitial pneumonia and will often require similarly aggressive and combined treatment approaches [42].

As with other CTD-ILDs steroids are the first-choice therapy, but recurrence is common and the addition of a second-line agent is often required to achieve remission. Unfortunately, no RCTs have studied this patient group. Nonetheless, a systematic review conducted by Ge *et al.* [43] concluded that intravenous CYC for 6–12 months improved lung function and CT appearances in over half of patients and recovered muscle strength in four-fifths. RTX has shown promise in a small pilot study of 10 subjects with ASS who relapsed after initial immunosuppressive therapy, defined in this cohort as having one of either muscle symptoms, elevated creatine kinase or lung function decline [44]. RTX either stabilised or improved lung function in the majority of patients (nine out of 10). Another single-centre retrospective case series evaluating the long-term efficacy of RTX in 34 ASS patients (median follow up 52 months) reported improvement in median FVC by 24% and diffusing capacity of the lung for carbon monoxide by 17% [45]. However, given the nature of the study, pre-and post-RTX immunosuppressive regimes were not standardised. In this regard, the previously mentioned RECITAL trial will address this issue. With regards to oral agents, MMF and azathioprine may be useful in stabilising pulmonary indices and allow tapering of steroid dosage [46, 47]. The calcineurin inhibitor tacrolimus has been shown to have a role as add-on therapy to steroids and also in conjunction with other immunosuppressive agents [48]. Despite its anecdotal use in rapidly progressive disease, the role of immunoglobulins and plasmapheresis remains unknown [49, 50]. Given the high mortality, there is an urgent need to discover treatments for this cohort [51, 52].

Conclusion

Broadly, the choice of pharmacotherapy can be divided into two categories: those that aim to arrest decline *versus* treatments for achieving ongoing stability. Close surveillance of lung function is therefore essential, in guiding treatment initiation and assessment of response. The body of evidence that exists for CTD-ILD is limited and treatment regimens are often drawn from specific diseases and extrapolated across the entire spectrum of CTD-ILD. Nevertheless, recent studies have seen more robust methodologies which have born important advances. MTX use is unlikely to predispose the development of fibrotic ILD in RA. The use of antifibrotics is a promising field, but throws up further questions about the timing of treatment initiation, and whether its use lies with concomitant immunosuppression or as a stand-alone therapy.

Affiliations

Zhe Wu[1,2], Philip L. Molyneaux[1,2]

[1]National Heart and Lung Institute, Imperial College London, London, UK. [2]Royal Brompton and Harefield Hospitals, Guy's and St Thomas' NHS Foundation Trust, London, UK.

Conflict of interest

Z. Wu has nothing to disclose. P.L Molyneaux reports grants or contracts from AstraZeneca outside the submitted work. Consulting fees from Hoffman-La Roche, Boehringer Ingelheim, and AstraZeneca outside the submitted work. Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Boehringer Ingelheim and Hoffman-La Roche, outside the submitted work.

References

1. Wells AU, Denton CP. Interstitial lung disease in connective tissue disease—mechanisms and management. *Nat Rev Rheumatol* 2014; 10: 728–739.
2. Wallace B, Vummidi D, Khanna D. Management of connective tissue diseases associated interstitial lung disease: a review of the published literature. *Curr Opin Rheumatol* 2016; 28: 236–245.
3. Lee MH, Bull TM. The role of pulmonary arterial hypertension-targeted therapy in systemic sclerosis. *F1000Research* 2019; 8: 2124.
4. Goh NSL, Desai SR, Veeraraghavan S, *et al.* Interstitial lung disease in systemic sclerosis: a simple staging system. *Am J Respir Crit Care Med* 2008; 177: 1248–1254.
5. Steen VD, Medsger TA. Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. *Arthritis Rheum* 1998; 41: 1613–1619.
6. Teixeira L, Mouthon L, Mahr A, *et al.* Mortality and risk factors of scleroderma renal crisis: a French retrospective study of 50 patients. *Ann Rheum Dis* 2008 Jan 1; 67: 110–116.

7. Tashkin DP, Elashoff R, Clements PJ, *et al.* Cyclophosphamide versus placebo in scleroderma lung disease. *N Engl J Med* 2006; 354: 2655–2666.
8. Goldin J, Elashoff R, Kim HJ, *et al.* Treatment of scleroderma-interstitial lung disease with cyclophosphamide is associated with less progressive fibrosis on serial thoracic high-resolution CT scan than placebo: findings from the scleroderma lung study. *Chest* 2009; 136: 1333–1340.
9. Tashkin DP, Elashoff R, Clements PJ, *et al.* Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. *Am J Respir Crit Care Med* 2007; 176: 1026–1034.
10. Tashkin DP, Roth MD, Clements PJ, *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: 708–719.
11. Hoyles RK, Ellis RW, Wellsbury J, *et al.* A multicenter, prospective, randomised, 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: 3962–3970.
12. Kowal-Bielecka O, Fransen J, Avouac J, *et al.* Update of EULAR recommendations for the treatment of systemic sclerosis. *Ann Rheum Dis* 2017; 76: 1327–1339.
13. Distler O, Highland KB, Gahlemann M, *et al.* Nintedanib for systemic sclerosis–associated interstitial lung disease. *N Engl J Med* 2019; 380: 2518–2528.
14. Highland KB, Distler O, Kuwana M, *et al.* Efficacy and safety of nintedanib in patients with systemic sclerosis-associated interstitial lung disease treated with mycophenolate: a subgroup analysis of the SENSCIS trial. *Lancet Respir Med* 2021; 9: 96–106.
15. Khanna D, Albera C, Fischer A, *et al.* An open-label, phase II study of the safety and tolerability of pirfenidone in patients with scleroderma-associated interstitial lung disease: the LOTUSS trial. *J Rheumatol* 2016; 43: 1672–1679.
16. Acharya N, Sharma SK, Mishra D, *et al.* Efficacy and safety of pirfenidone in systemic sclerosis-related interstitial lung disease—a randomised controlled trial. *Rheumatol Int* 2020; 40: 703–710.
17. Daoussis D, Liossis S-NC, Tsamandas AC, *et al.* Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. *Rheumatology* 2010; 49: 271–280.
18. Jordan S, Distler JHW, Maurer B, *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: 1188–1194.
19. Daoussis D, Melissaropoulos K, Sakellaropoulos G, *et al.* A multicenter, open-label, comparative study of B-cell depletion therapy with Rituximab for systemic sclerosis-associated interstitial lung disease. *Semin Arthritis Rheum* 2017; 46: 625–631.
20. Saunders P, Tsipouri V, Keir GJ, *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: 275.
21. Khanna D, Denton CP, Lin CJF, *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: 212–220.
22. Khanna D, Lin CJF, Furst DE, *et al.* Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2020; 8: 963–974.
23. Mathai SC, Danoff SK. Management of interstitial lung disease associated with connective tissue disease. *BMJ* 2016; 352: h6819.
24. Mittoo S, Fell C. Pulmonary manifestations of systemic lupus erythematosus. *Semin Respir Crit Care Med* 2014; 35: 249–254.
25. Bertoli AM, Vila LM, Apte M, *et al.* Systemic lupus erythematosus in a multiethnic US Cohort LUMINA XLVIII: factors predictive of pulmonary damage. *Lupus* 2007; 16: 410–417.
26. Amarnani R, Yeoh S-A, Denneny EK, *et al.* Lupus and the lungs: the assessment and management of pulmonary manifestations of systemic lupus erythematosus. *Front Med* 2021; 7: 610257.
27. Weinrib L, Sharma OP, Quismorio FP. A long-term study of interstitial lung disease in systemic lupus erythematosus. *Semin Arthritis Rheum* 1990; 20: 48–56.
28. Olson AL, Swigris JJ, Sprunger DB, *et al.* Rheumatoid arthritis–interstitial lung disease–associated mortality. *Am J Respir Crit Care Med* 2011; 183: 372–378.
29. Raimundo K, Solomon JJ, Olson AL, *et al.* Rheumatoid arthritis–interstitial lung disease in the United States: prevalence, incidence, and healthcare costs and mortality. *J Rheumatol* 2019; 46: 360–369.
30. Hyldgaard C, Hilberg O, Pedersen AB, *et al.* A population-based cohort study of rheumatoid arthritis-associated interstitial lung disease: comorbidity and mortality. *Ann Rheum Dis* 2017; 76: 1700–1706.
31. Yunt ZX, Chung JH, Hobbs S, *et al.* High resolution computed tomography pattern of usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease: relationship to survival. *Respir Med* 2017; 126: 100–104.
32. Fui A, Bergantini L, Selvi E, *et al.* Rituximab therapy in interstitial lung disease associated with rheumatoid arthritis. *Intern Med J* 2020; 50: 330–336.
33. Juge P-A, Lee JS, Ebstein E, *et al.* MUC5B promoter variant and rheumatoid arthritis with interstitial lung disease. *N Engl J Med* 2018; 379: 2209–2219.
34. Wells AU, Flaherty KR, Brown KK, *et al.* Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. *Lancet Respir Med* 2020; 8: 453–460.
35. Dawson JK, Quah E, Earnshaw B, *et al.* Does methotrexate cause progressive fibrotic interstitial lung disease? A systematic review. *Rheumatol Int* 2021; 41: 1055–1064.
36. Juge PA, Lee JS, Lau J, *et al.* Methotrexate and rheumatoid arthritis associated interstitial lung disease. *Eur Respir J* 2021; 57: 2000337.
37. Kiely P, Busby AD, Nikiphorou E, *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: e028466.
38. Kur-Zalewska J, Kisiel B, Kania-Pudło M, *et al.* A dose-dependent beneficial effect of methotrexate on the risk of interstitial lung disease in rheumatoid arthritis patients. *PLoS ONE* 2021; 16: e0250339.
39. Robles-Pérez A, Luburich P, Bolivar S, *et al.* A prospective study of lung disease in a cohort of early rheumatoid arthritis patients. *Sci Rep* 2020; 10: 15640.
40. Li L, Liu R, Zhang Y, *et al.* A retrospective study on the predictive implications of clinical characteristics and therapeutic management in patients with rheumatoid arthritis-associated interstitial lung disease. *Clin Rheumatol* 2020; 39: 1457–1470.
41. Ibfelt EH, Jacobsen RK, Kopp TI, *et al.* Methotrexate and risk of interstitial lung disease and respiratory failure in rheumatoid arthritis: a nationwide population-based study. *Rheumatology* 2021; 60: 346–352.
42. Chen Z, Cao M, Plana MN, *et al.* Utility of anti-melanoma differentiation-associated gene 5 antibody measurement in identifying patients with dermatomyositis and a high risk for developing rapidly progressive interstitial lung disease: a review of the literature and a meta-analysis. *Arthritis Care Res (Hoboken)* 2013; 65: 1316–1324.
43. Ge Y, Peng Q, Zhang S, *et al.* Cyclophosphamide treatment for idiopathic inflammatory myopathies and related interstitial lung disease: a systematic review. *Clin Rheumatol* 2015; 34: 99–105.
44. Allenbach Y, Guiguet M, Rigolet A, *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: e0133702.

45. Andersson H, Sem M, Lund MB, *et al*. Long-term experience with rituximab in anti-synthetase syndrome-related interstitial lung disease. *Rheumatology* 2015; 54: 1420–1428.
46. Mira-Avendano IC, Parambil JG, Yadav R, *et al*. A retrospective review of clinical features and treatment outcomes in steroid-resistant interstitial lung disease from polymyositis/dermatomyositis. *Respir Med* 2013; 107: 890–896.
47. Huapaya JA, Silhan L, Pinal-Fernandez I, *et al*. Long-term treatment with azathioprine and mycophenolate mofetil for myositis-related interstitial lung disease. *Chest* 2019; 156: 896–906.
48. Kurita T, Yasuda S, Oba K, *et al*. The efficacy of tacrolimus in patients with interstitial lung diseases complicated with polymyositis or dermatomyositis. *Rheumatology* 2015; 54: 39–44.
49. Bakewell CJ, Raghu G. Polymyositis associated with severe interstitial lung disease: remission after three doses of IV immunoglobulin. *Chest* 2011; 139: 441–443.
50. Omotoso BA, Ogden MI, Balogun RA. Therapeutic plasma exchange in antisynthetase syndrome with severe interstitial lung disease. *J Clin Apher* 2015; 30: 375–379.
51. Nagasaka K, Harigai M, Tateishi M, *et al*. Efficacy of combination treatment with cyclosporin A and corticosteroids for acute interstitial pneumonitis associated with dermatomyositis. *Mod Rheumatol* 2003; 13: 231–238.
52. Kameda H, Nagasawa H, Ogawa H, *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: 1719–1726.