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Ask the expert

Choosing pharmacotherapy for ILD in patients with connective tissue disease

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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

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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

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.

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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.

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