Review

The role of biologics in treatment of connective tissue disease-associated interstitial lung disease

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Summary

With an increased understanding of the molecular pathways of inflammation and autoimmunity, the development of targeted biological agents has revolutionized the management of connective tissue diseases (CTDs). There has been an explosion in the development of these drugs in the last decade, targeting diseases in diverse fields including: allergic disorders, oncology, neuroinflammatory disorders, inflammatory bowel disease, macular degeneration and CTDs. In this last field, commonly applied biologics fall into two categories: cytokine inhibitors and lymphocyte-targeted therapies. The former group includes the antitumour necrosis factor alpha (TNF-α), anti-interleukin (IL)-6 receptor monoclonal antibodies and IL-1 receptor antagonists, whilst the latter encompasses the anti-CD20, B-cell depleting, monoclonal antibody (mAb), Rituximab and the anti-T-cell activation agent, Abatacept. This review will examine our developing experience in the use of these agents in the treatment of CTD-related interstitial lung diseases, with a particular focus on B-cell depletion.

Connective tissue disease-interstitial lung disease

Interstitial lung diseases (ILDs), whilst most commonly of uncertain aetiology, can be attributed to environmental exposures, or associated with connective tissue disease (CTDs) (Figure 1). This categorization is important because CTD-ILD is generally associated with a better prognosis than idiopathic interstitial pneumonias of comparable severity.\(^1\)

The concept of CTD is difficult to define, but refers to a process resulting in autoimmune-mediated organ dysfunction.\(^2\) All patients with such CTDs are at variable risk of ILD (Table 1),\(^3\) with some diseases demonstrating other patterns of pulmonary involvement, which may in some patients be the initial, or only, manifestation.

Rheumatoid arthritis (RA) has pulmonary involvement in 10–58% of patients.\(^4\) This most commonly takes the form of interstitial pneumonitis and fibrosis, however also includes rheumatoid nodules, bronchiectasis and pleural effusions or thickening. A large multicentre study of patients with RA-associated ILD in the UK found strong associations with anti-Cyclic Citrullinated Peptides (CCP) antibodies and smoking in men. RA-associated lung disease manifests with either a Usual Interstitial Pneumonia (UIP) or Non-Specific Interstitial Pneumonia (NSIP) pattern. The UIP pattern is more common and associated with more extensive/severe disease and a higher risk of all-cause mortality.\(^5\)

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Epidemiological studies show a pulmonary involvement in 40–90% of patients with Systemic Sclerosis (SSc) and 30–70% of patients with polymyositis/dermatomyositis. In the CTD spectrum, ILD is perhaps most commonly clinically and radiologically observed in SSc and myositis overlap patients. In this group, the development of interstitial pneumonia is common and often subclinical, highlighted by the finding of ILD in 90–100% of autopsy studies. Around 40–75% have abnormal physiology and 55–85% of patients have interstitial abnormalities on high-resolution computed tomography (HRCT) of the thorax.

ILD may be subclinical, being seen in 33–57% of CTD patients with no respiratory symptoms. However, 25% of patients go on to develop clinically significant lung disease within 3 years. In patients with established CTD, many of whom are managed with potent immunosuppressant’s, the cause of any interstitial abnormalities must be investigated to exclude infective, environmental or drug-related causes; these need to be excluded before the lung injury can be confidently considered to be a sequela of the CTD.

The pattern of ILD seen varies between different CTDs (Table 2). This has implications on predicting the response to treatment and also prognostication. NSIP accounts for a large proportion of disease, especially within SSc and myositis syndromes. Meanwhile, UIP represents the majority of ILD seen in RA. Pulmonary involvement in Sjögren’s syndrome is commonly associated with NSIP pattern but may present as lymphocytic interstitial pneumonia, organizing pneumonia and UIP.

In the CTD spectrum, it is increasingly apparent that risk of ILD can be assessed by defining patients-based clinicocerological phenotypes, especially those with SSc or myositis overlap. Traditional risk factors for the development of ILD in SSc include ethnicity (especially African-Americans), those with more skin involvement at presentation and those with additional organ involvement. Serological markers include the presence of anti-topoisomerase or anti-nucleolar antibodies. In the myositis overlap spectrum, a number of factors have been linked with the development and severity of ILD, including Asian ethnicity, those with severe skin involvement, minimal or no clinical muscle weakness and pyrexia. Biomarkers include hyperferritaemia and cytoplasmic or nucleolar autoantibodies including the antisynthetase group.

There is also a group of patients for whom their ILD can be the first presentation of CTD. This is particularly seen in patients with the antisynthetase syndrome in the myositis-overlap spectrum. In one cohort, 15% of new patients referred to a tertiary referral centre met diagnostic criteria for CTDs. In some patients, ILD may be their only manifestation of their CTD. How such patients should be investigated and managed remains the subject...
In fact there is a body of evidence that the lung may be the site of initiation of the inflammatory process in RA, and possibly other CTDs including myositis overlap. There are no histopathological findings that are pathognomonic for CTD. Multicompartment (parenchyma, airway, vascular or pleural) involvement on the biopsy is often very suggestive of CTD-ILD; lymphoid follicles and aggregates, perivascular collagen, eosinophilic infiltration and pleural inflammation all suggest the diagnosis. NSIP is seen in many forms of CTD-ILD in conjunction with ground-glass abnormalities. Pleural and pericardial effusions and pericardial thickening are patterns often seen on the radiological imaging. These radiological and histopathological findings are seen in other interstitial lung disease but seem to have a better prognosis in CTD-ILD patients.

Given that a large proportion of patients with CTD-ILD will have subclinical or minimally symptomatic disease, the decision to treat is determined by the clinical impairment, disease course/progression and comorbidities suffered by the patient. Therapy is generally reserved for more severe and progressive disease phenotypes, based on a constellation of both subjective and objective measures of respiratory function.

### Management of CTD-ILD

Except for SSc, there are no controlled clinical trial data available to guide decision making in CTD-ILD. This is a heterogeneous group of patients, so available data is hard to generalize and recruitment to trials is challenging. In addition, there are few therapeutic options available, with significant toxicity accompanying those that could be of benefit. Most available data are from registries, case series or individual case reports. Cyclophosphamide has been studied in a randomized, controlled trial in symptomatic scleroderma-associated lung disease, demonstrating significant, although modest, benefit in this group as measured by forced vital capacity (FVC) and also quality-of-life scores.15

As with other areas of ILD research, clinical outcomes have not been clearly defined. While consensus has been difficult, a recent working group statement has identified a core set of measures, including lung physiology, walk distance, imaging, survival, dyspnoea, cough and health-related quality-of-life measures and progression free survival as suitable for use in multicentre clinical trials for both CTD-ILD and idiopathic pulmonary fibrosis.16 Appropriately validated clinical endpoints for use in clinical trials in this field are an evolving area and further research is needed.

Although subclinical ILD is fairly commonly identified in CTD patients, not all of these are treated. This decision must be predicated on the clinical state of the patient and evidence of progression, with FVC, the extent of fibrosis and active inflammation suggestive of capacity for reversibility on HRCT commonly used. A full discussion must be held, including the known toxicity profile of the treatments and the presumed natural history of the condition to inform the patient’s choice and consent.

Currently accepted initial treatments in CTD-ILD include corticosteroids, azathioprine and mycophenolate mofetil for mild disease, while cyclophosphamide has been used in refractory or rapidly progressive disease. This area is reviewed by Fischer and du Bois,3 and is beyond the scope of this article.

### Biologics and CTD-ILD

#### Rituximab

Rituximab is a chimeric mAb with high affinity for the CD20 surface antigen, expressed on B and pre-B lymphocytes, originally applied in the treatment of lymphoma. It is derived from mouse mAb 2B8 following replacement of the heavy and light chain constant regions with their equivalents from a human IgG1 mAb. Administration results in depletion of B cells from the peripheral circulation for Table 2

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<td>Systemic lupus erythematosus</td>
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<td>Primary Sjogren’s syndrome</td>
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COP, cryptogenic organizing pneumonia; DAD, diffuse alveolar damage; DAH, diffuse alveolar haemorrhage; LIP, lymphocytic interstitial pneumonia; NSIP, non-specific interstitial pneumonia; UIP, usual interstitial pneumonia.

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up to 6–9 months. The mechanism of B-cell killing by rituximab is believed to depend on its antibody-dependent cell-mediated cytotoxicity including its ability to induce apoptosis and inhibit proliferation. This represents the rationale for its use in immune-mediated diseases.

There is evidence of benefit with use of rituximab in a number of immune-mediated diseases, including anti-neutrophil cytoplasmatic antibody-associated vasculitis\(^{17}\) and RA\(^{18}\). The shared immune dysfunction underlying these conditions has led to exploration of its use in CTD-ILD.

The first report of successful treatment of scleroderma-associated ILD was in 2008, with further experience reported in a cohort of eight patients, in whom the FVC and diffusing capacity of carbon monoxide (DL\(_{CO}\)) increased significantly more than a matched group who received standard treatment.\(^{19}\)

Further experience has been reported in treatment of the anti-synthetase syndrome, where 11 patients with severe and progressive ILD who had failed cyclophosphamide treatment demonstrated stabilization of their lung disease as based on FVC, DL\(_{CO}\) and also HRCT appearances.\(^{20}\)

Keir et al.\(^{21}\) have reported their experience in a more diverse cohort of ILD. They report 50 consecutive patients whose ILD, of various aetiologies, was progressive despite immunosuppressive therapy, including cyclophosphamide and intravenous corticosteroids. The median change in FVC in the 6–12 months following treatment was 6.7%, with stability of DL\(_{CO}\). The subgroup of patients \((n = 33)\) with CTD-ILD demonstrated a median improvement of 8.9% in FVC. Ten patients died from progression of their ILD despite this treatment and one underwent transplantation. Two patients developed pneumonia and nine lower respiratory tract infection after treatment with rituximab, suggesting that in their experience, based on the poor prognosis in untreated patients, the balance of risk favours treatment with B-cell suppression.

In contrast to this data, an analysis of 20 patients with a range of CTD-ILDs treated with rituximab for whom lung function data were available from our centre has demonstrated no improvement in FVC, DL\(_{CO}\) or total lung capacity, although these remained stable. Interestingly, a subgroup analysis of nine patients with myositis managed in this way demonstrated an improvement in FVC \((P = 0.011)\). DL\(_{CO}\) and 6-min walk distance remained unchanged.\(^{22}\)

Robust clinical trials are urgently needed to inform decision making in this area; the only registered study has yet to start recruiting (ClinicalTrials.gov Identifier: NCT01862926).

Experience of B-cell depletion with rituximab in other conditions has highlighted the incidence of induction of ILD in patients with lymphoma, in addition to cases in patients with RA.\(^{23}\) Further reports of complications have included acute respiratory distress syndrome and culture-negative bronchopneumonia. This highlights the dangers accompanying use of this potent immunosuppressive therapy and the gaps in our understanding of the mechanism underlying its possible benefits.

### Anti-tumour necrosis factor alpha- agents

The most commonly used biologic therapies used in CTDs have been anti-tumour necrosis factor alpha (TNF-\(\alpha\)) agents. TNF is a proinflammatory mediator implicated in a wide range of inflammatory and autoimmune conditions. It is a key component of the host response to infection, however dysregulated activity is felt to underlie some of the pathogenetic mechanisms in CTDs. Agents targeting this process were amongst the first biologic agents approved in CTDs, and they have subsequently been applied in a wide range of conditions, including RA, inflammatory bowel disease and several inflammatory arthritides.

The profibrotic mechanisms of TNF have led some to postulate a possible role for these agents in the management of CTD-ILD. With increasing experience, however, an increasing weight of evidence suggests a high risk of induction of ILD in patients treated with anti-TNF-\(\alpha\) agents.\(^{24}\) An analysis of >8000 patients with CTDs managed with infliximab suggested no increased incidence of ILD,\(^{25}\) however this excluded those with pre-existing pulmonary disease, so a role in exacerbation of this cannot be excluded. There is, in addition to this risk of ILD, a risk of other non-infectious pulmonary side effects, with the role of anti-TNF agents in precipitating granulomatous disease increasingly established.

### Newer agents in the treatment of CTD

Several newer biologic agents are now being used in CTD and RA, however the role of these in related ILD remains unclear. The anti-IL6 mAb, Tocilizumab, has been implicated in exacerbation of pre-existing ILD related to RA, and also in the causation of pneumonitis.\(^{26}\) A case report of possible therapeutic benefit in CTD-ILD in an adolescent patient has been published\(^{27}\); however, experience is lacking for this agent in ILD.

The IL1 receptor antagonist, Anakinra, appears to be a much safer biologic agent, with no literature suggestive of non-infectious pulmonary
complications of its use. There is, however, little to suggest therapeutic benefit.

A final category of biologic agent, of particular interest in the field of interstitial lung disease presently, is the tyrosine kinase inhibitors. The recent publication of the INPULSIS clinical trials showing benefit of nintedanib in Idiopathic Pulmonary Fibrosis cannot translate to the area of CTD-ILD. Experience of this group of drugs is mostly in oncology, with a wide range of pulmonary complications reported. One small study has examined the use of Imatinib in SSc-associated ILD, however this was significantly limited by adverse events, and no benefit was seen. There is currently no literature to support a possible therapeutic role. Given the wide diversity of the human kinome and our increasing understanding of the pathogenetic mechanisms underlying both CTD and ILDs, it is possible that targeted and specific use of these agents may hold future therapeutic benefit.

Conclusions

Experience of immunosuppressive therapies in the management of CTD-ILD is an evolving field, with little robust clinical trial based data to guide decision-making. These are drugs with significant side-effect profiles, placing patients at risk of both infectious and noninfectious complications.

The use of B-cell depletion with the anti-CD20 mAb rituximab has been driven mostly by failure of other treatments to modify the course of deteriorating disease. The rationale for use is based on our knowledge of the underlying disease processes, which is incomplete, supported with case series and extrapolated data to suggest possible benefit. This is an agent that is employed when all other options have been explored, with ongoing decline despite this.

It remains to be established which CTD-ILD patients are most likely to benefit from Rituximab, with the likelihood that response will not be universal in this heterogeneous group. Robust clinical trials are urgently needed.

Conflict of interest: None declared.

References


