

# **BIOLOGIC TREATMENTS FOR PULMONARY INVOLVEMENT IN RHEUMATIC DISEASE**

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## **ABSTRACT**

Interstitial lung disease (ILD) is a common complication of many autoimmune rheumatic diseases and has significant morbidity and mortality implications. Despite this, there is a lack of robust evidence to support treatment decisions, with many assumptions extrapolated from clinical trials in systemic sclerosis, or based on experience of treating other immune mediated inflammatory disorders. Treatment to date has typically been with steroids and synthetic disease modifying drugs, including mycophenolate and cyclophosphamide, with clinical response being variable and thus, often unpredictable.

An increased understanding of the molecular pathways responsible for propagating inflammation in connective tissue diseases (CTDs) has led to the development of targeted biological agents. These drugs have transformed the management of many autoimmune diseases and represent a key treatment strategy, particularly for patients with severe and or non-responsive disease. Since on-going inflammation in progressive CTD-ILD is likely to be due to activation of the same pathways and cytokines, there has been increasing interest in using these treatments in patients with pulmonary disease refractory to other therapies. In this chapter the evidence relating to the efficacy of biologics in treating CTD-ILD will be reviewed. Concerns around the safety of these agents will also be discussed, reflecting reports that they may indeed, on occasion, cause new ILD or accelerate pre-existing disease.

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## INTRODUCTION

Interstitial lung disease (ILD) is an umbrella term used to describe a collection of conditions where the tissue network that supports the alveoli is affected. These disorders are characterised by microscopic inflammation or fibrosis or both, resulting in impaired ventilation and in severe cases, respiratory failure. The various diseases covered by the term ILD, have common clinical, radiological and histopathological features. They are globally classified as either idiopathic interstitial pneumonias (IIP) or those secondary to specific occupations, recreational exposures, drugs or as discussed here, in the context of connective tissue disease (CTD).

The frequency of CTD associated ILD varies between individual autoimmune rheumatic diseases (Table 1), with reported rates for each disease also varying significantly. This reflects a lack of consensus about how ILD is defined, particularly as in some cases it may be diagnosed incidentally, without being clinically significant. Equally, ILD can occur as the initial, predominant or even, only manifestation of an immune mediated inflammatory disease; a condition referred to as interstitial pneumonitis with autoimmune features (IPAF) [1]. In addition, specific CTDs are associated with particular histopathological patterns with characteristic corresponding radiological features, such that a lung biopsy is infrequently necessary (Table 2).

**Table 1.** Incidence of interstitial lung disease and relative incidence of histopathological subgroups in connective tissue disease (least frequently observed (-) to most (++++)).

	Frequency of clinically significant ILD	UIP	NSIP	OP	LIP	DAD
Systemic sclerosis (SSc)	50% [2] but with some studies quoting up to 80%	++	++++	+	-	+
Polymyositis/dermatomyositis (PM/DM)	45-75% [3]–[5]	++	+++	++	-	+
Rheumatoid arthritis (RA)	18-50% [6], [7]	+++	++	+	-	+
Primary Sjögrens Syndrome (SS)	25% [8]	+	+	+	+++	-
Systemic lupus erythematosus (SLE)	3-8% [9], [10]	+	+	+	-	++

**Legend:** UIP – usual interstitial pneumonitis; NSIP – non specific pneumonitis; OP – organising pneumonia; LIP – lymphocytic interstitial pneumonitis; DAD – diffuse alveolar damage

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**Table 2.** Description of radiological features that correspond to histopathological diagnoses.

	Radiological features
UIP (Usual Interstitial Pneumonitis)	<p>Reticular change associated with traction bronchiectasis</p> <p>With or without honeycombing</p> <p>Subpleural basal predominant distribution</p> <p>Lobar volume loss</p> <p>Minimal ground glass opacification (i.e. not the dominant feature) often in areas of reticular change</p>
NSIP (Non Specific Interstitial Pneumonitis)	<p>Ground glass opacification more dominant feature</p> <p>Combined with reticular opacities</p> <p>Subpleural but may lack an apico-basilar gradient</p> <p>Typically no honeycombing although architectural distortion (traction bronchiectasis) may be present</p>
OP (Organising Pneumonia)	<p>Patchy, multifocal consolidation</p> <p>Predominantly basal, subpleural or peri-bronchovascular distribution</p> <p>Perilobular pattern may be seen</p> <p>Ill defined peribronchial or peribronchiolar nodules and bands with air bronchograms can occur</p> <p>Co-existing architectural distortion can occur i.e. traction bronchiectasis</p>
LIP (Lymphocytic Interstitial Pneumonitis)	<p>Scattered thin walled cysts typically subpleural or perivascular</p> <p>Ground glass opacification</p> <p>Interstitial thickening</p> <p>Small centrilobular or subpleural nodules</p>

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	Mid to lower lobe predominance
DAD (Diffuse Alveolar Damage)	Acutely; diffuse ground glass opacification and consolidation in a dependent distribution In the organising phase fibrotic change (including honeycombing) can develop

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There is increasing recognition that pulmonary disease is a major determinant of morbidity and mortality in CTD. In systemic sclerosis (SSc) for example, pulmonary complications (referring to ILD and pulmonary hypertension) have surpassed renal involvement as the leading cause of death [11]. Despite this, the heterogeneity of ILD coupled with the relative rarity of these diseases, means the evidence base for treatment is limited. The lack of a reliable biomarker, the difficulty in predicting the natural history of the disease and disagreement over suitable primary end points in clinical trials, are just some of the challenges facing researchers. Corticosteroids typically form the basis of initial treatment, with SSc the notable exception. Immunosuppressive agents including azathioprine, mycophenolate and cyclophosphamide are added to therapy in those requiring unacceptably high doses of steroid for maintenance, or for those who progress in spite of steroids; however, some patients demonstrate refractory disease. In reality, SSc associated ILD is the only condition for which good quality clinical trial data is available, such that treatment choices are often based on logical assumptions reflecting what is known about disease pathophysiology, together with expert opinion based on case reports/series and registry data.

The increasing use, availability and success of biological therapies to treat various autoimmune mediated diseases has led to a growing interest in the use of these drugs to treat CTD-ILD. Although the clinical manifestations of immune mediated diseases vary, there are many shared themes. There is definite evidence for a genetic component with different autoimmune diseases existing with increased frequency in certain families, as well as repeated reporting of similar environmental precipitating factors. Furthermore, the different diseases share common pathophysiological themes with certain target inflammatory cells and cytokine pathways repeatedly implicated.

As well as the predictable challenges of studying drug efficacy in orphan diseases, progress in this area has been further complicated by the emergence of autoimmune phenomena (including ILD) in response to some biological agents. In this chapter current experience of using these treatments in CTD-ILD, including the possible development of new or worsening ILD in response to therapy, will be covered.

The biological treatments discussed fall into two broad categories; lymphocyte targeted therapies or cytokine inhibitors. The former refers to the anti CD20 B cell depleting monoclonal antibody, rituximab and anti T cell activation agent, abatacept, whilst the latter includes tumour necrosis factor (TNF) blockers, IL6 receptor monoclonal antibodies and IL1 receptor antagonists.

### **PATHOGENESIS OF CTD-ILD**

The pathogenesis of ILD due to autoimmune disease is complex and involves cellular and biological players from both the innate and adaptive immune responses. The lung pathology is characterised by degrees of inflammation and fibrosis that vary, not only between diseases, but also between individuals with the same disease. The events that lead to ILD can be considered in three phases illustrated schematically in Figure 1. In an *initiating phase*, there is lung endothelial or epithelial damage. This may result from autoimmunity, such as antibody mediated cellular toxicity (Type II hypersensitivity) or deposition of antigen-antibody complexes and activation of complement (Type III hypersensitivity); or by an environmental stimulus such

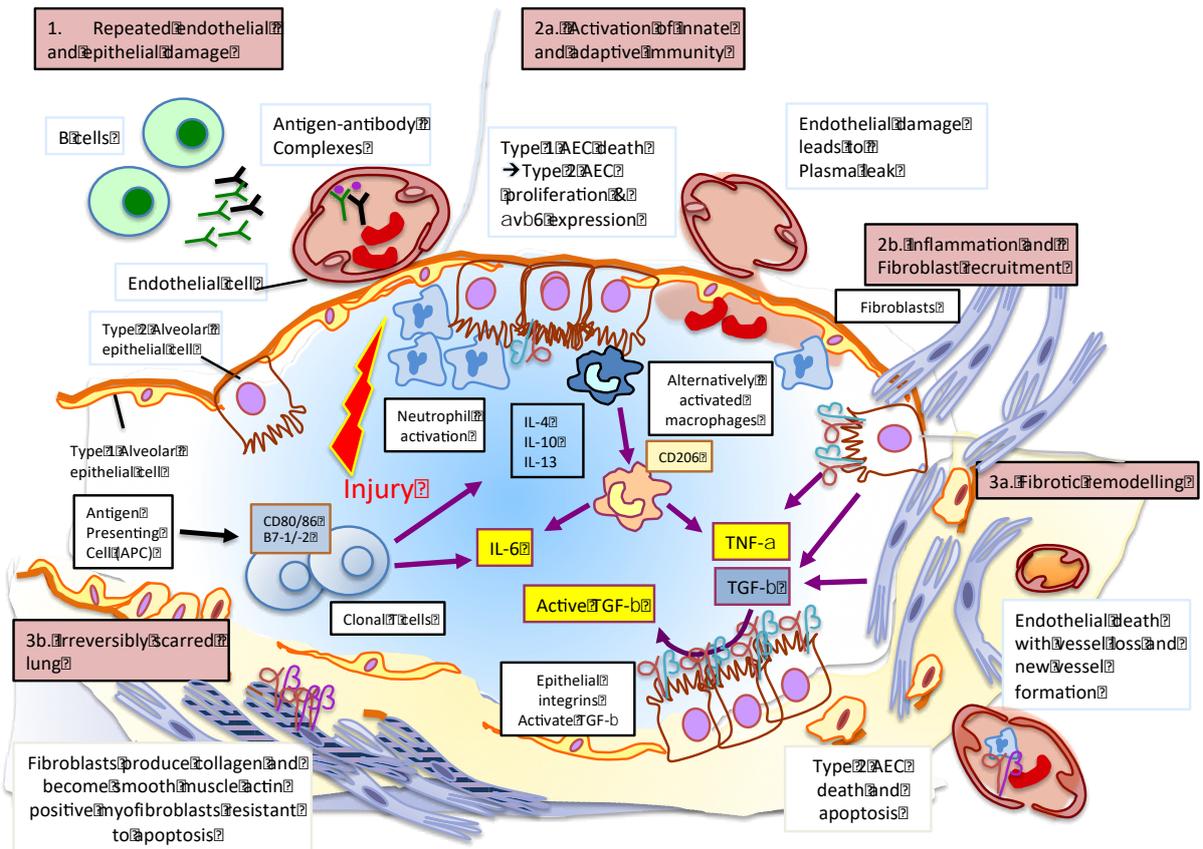
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as severe infection or a systemic / inhaled toxin. In each of these scenarios, a complex interplay between host and environmental factors results in a vigorous inflammatory response.

There is an increasing interest in the role of neutrophils in driving the subsequent adaptive immune response. T cells produce cytokines, IL4, IL10 and IL13, that drive monocytes, recruited from the blood, and lung resident macrophages towards an alternatively activated macrophage (AAM) phenotype that produce, amongst other cytokines, high levels of IL6 and TGF- $\beta$ . In this *inflammatory phase* the key mediators are TNF- $\alpha$  (produced by the epithelium and AAMs) and IL6 (Neutrophils, T cells and AAMs). There is loss of the normal lung architecture and disruption of the basement membrane across which gas exchange takes place. With further epithelial damage and apoptosis, comes up-regulation of epithelial integrins such as  $\alpha$ v $\beta$ 6. This robust inflammatory response overlaps with a *reparative phase* in which resolution of inflammation and fibroproliferative repair dominate driven by high levels of TGF- $\beta$ . Released in an inactive form, this cytokine requires an activation step facilitated by  $\alpha$ v integrins that bind the RGD motif of pro-TGF- $\beta$  and promote its cleavage and activation. Locally activated TGF- $\beta$  drives the recruitment of fibroblasts and a feed-forward cycle of further TGF- $\beta$  production. Under these conditions, fibroblasts differentiate into myofibroblasts that express high levels of integrin  $\alpha$ v $\beta$ 5, are resistant to apoptosis and lay down collagen matrix. Once collagen has been laid down in the lung, where the architecture is already distorted, gas exchange is no longer efficient. There is a change in the vasculature of the lung parenchyma with both fall-out of blood vessels and neoangiogenesis driven by local production of vascular endothelial growth factors. Although this is a simplification of a complex series of events, it is clear that early interruption of the abnormal mechanisms at play may allow a return of the lung architecture to normal; once the inflammation and fibrosis have continued unchecked and irreversible fibrosis ensues the chances of full recovery are reduced. At this stage the clinical aim is merely to prevent further loss of lung function.

**Figure 1.** Pathological Mechanisms involved in Interstitial Lung Disease in the context of autoimmune rheumatic diseases.

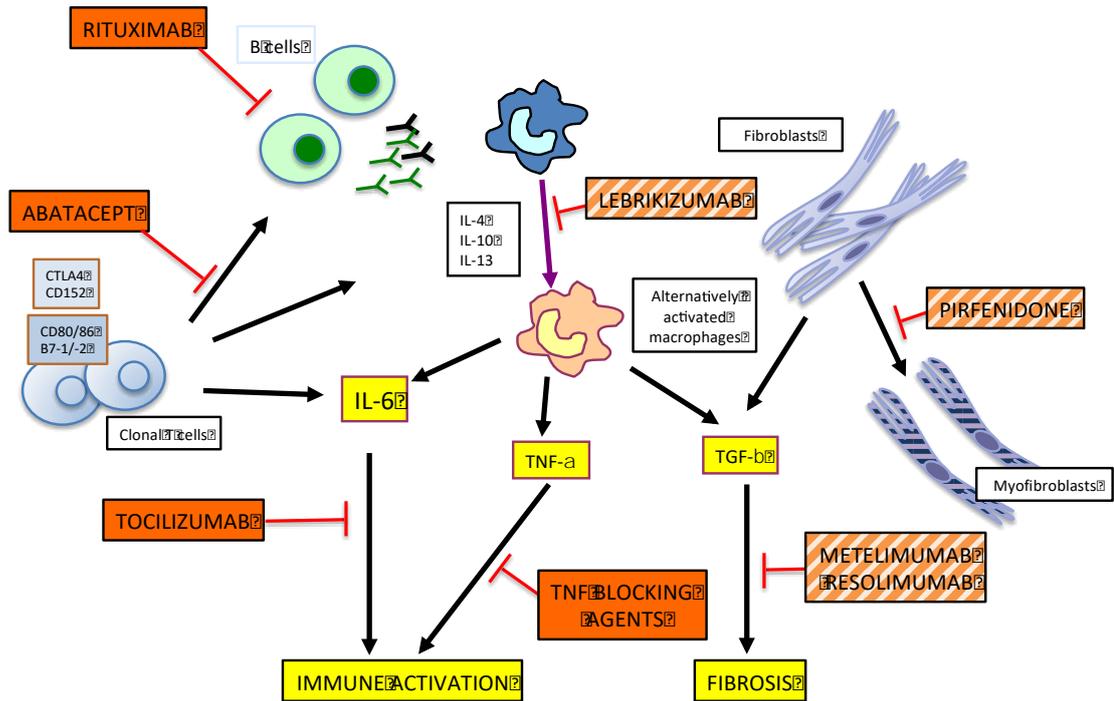
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Attempts to interrupt this cycle of inflammation and fibro-proliferative repair form the basis of the therapies considered in this article and shown in Figure 2. Those shown in orange boxes are considered in the article below; those shown in hatched boxes although theoretically beneficial have yet to be proven in a clinical setting and include the anti-IL13 agent lebrikizumab, the TGF- $\beta$  inhibitor resolimumab and metelimumab and the anti-fibrotic pirfenidone, whose mode of action, though not well understood, appears to, amongst other things, to prevent the effects of TGF- $\beta$  on fibroblasts.

**Figure 2.** Drug targets in ILD associated with autoimmune rheumatic diseases.

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Drugs in clinical practice are shown in orange boxes; those that are not yet used clinically for this indication are shown in hatched boxes.

### INDIVIDUAL BIOLOGICAL AGENTS

Evidence for individual biological agents is described in the following text. The greatest amount of data exists for rituximab and results of that data are also presented in Table 3.

#### RITUXIMAB

Rituximab is a chimeric monoclonal antibody with a high affinity for the CD20 surface antigen expressed on B and pre B lymphocytes and results in B cell depletion. It is derived from a mouse monoclonal antibody following replacement of the heavy and light chain constant regions with their equivalent from the human IgG1 monoclonal antibody. It was originally developed and used to successfully treat lymphomas, but now has proven efficacy in treating the articular manifestations of rheumatoid arthritis (RA) as well as having a role in the management of ANCA vasculitis and idiopathic thrombocytopenic purpura (ITP).

Excess B cell accumulation in lung biopsies of ILD patients has been described in several pre clinical studies. One group demonstrated increased CD20+ B cell infiltrates in lung biopsies from 35 patients with RA-ILD [12] compared to 21 patients with idiopathic interstitial pneumonias and 11 non ILD cases. The RA-ILD

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samples showed marked formation of peri-bronchiolar B cell follicles, diffuse tissue infiltration with plasma cells and increased B cell cellularity. Equally, in SSc B cells have been repeatedly implicated as having a pathogenic role. In one animal model, B cells demonstrated chronic hyperactivity and augmented CD19 signaling, an important regulator of B cell maturation, with CD19 deficiency attenuating skin fibrosis [13]. Furthermore, in patients with SSc, peripheral blood B cells specifically overexpress CD19 and are chronically activated [14] with lung biopsies from these patients also demonstrating excess B cell infiltration arranged in lymphoid aggregates [15].

Two uncontrolled studies have explored the potential clinical efficacy of rituximab in SSc, although the primary endpoints were related to skin manifestations. In the first, skin fibrosis clinically and histologically improved significantly [16]. In the second although no overt clinical benefit was observed, skin biopsies did show a reduction in the myofibroblast score and patients were clinically stable [17]. In these studies lung function was documented pre and post treatment and shown to be stable at 24 weeks, although significant ILD was one of the exclusion criteria and only 50% of patients (across both groups) had any ILD, all of which was mild.

When specifically considering SSc associated interstitial lung disease (SSc-ILD) several case reports have shown success in otherwise refractory disease [18], [19]. Furthermore, in a case controlled trial [20] the effects of RTX in 14 patients with SSc-ILD was evaluated. All the patients had a predictable autoantibody profile (Scl 70 positive), diffuse cutaneous disease and significant ILD on the basis of high resolution CT (HRCT) appearances and pulmonary function tests (PFTs). They were then randomized to receive either four weekly pulses of rituximab (repeated at 6 months) or placebo in addition to any established medication (predominantly mycophenolate). At 1 year there was a significant increase in forced vital capacity (FVC) and diffusing capacity of carbon monoxide (DLCO) from baseline in the rituximab group whilst no change was seen in the control arm. In addition, direct comparison of FVC change showed significant improvement in the treatment group when compared to standard therapy ( $p=0.002$ ). In an extension study [21] 8 of the original patients received further courses of rituximab at 12 and 18 months, completing a total of 2 years of follow up. The lung function tests of these patients demonstrated a linear improvement over time with interestingly the most striking response seen in the two individuals with the shortest disease duration.

There have also been several reports describing the successful use of rituximab for ILD associated with anti synthetase syndrome, a form of polymyositis/dermatomyositis where 70-80% of patients have ILD. In one retrospective case series [22] 11 patients with severe ILD were treated with rituximab. In this cohort the lung function prior to treatment (where available) demonstrated a definite deterioration, with 64% of the patients achieving a greater than 10% improvement in FVC and/or a greater than 15% improvement in DLCO 6 months after therapy. Amongst the remaining patients, 2 still improved but by a less convincing categorical percentage change, whilst 2 deteriorated in spite of treatment and 1 died secondary to pneumocystis jirovecii infection. In a follow on study [23] of the same patients, plus a further 13 treated at the same centre, there were significant improvements in lung function over more than 4 years of follow up. Again the most pronounced improvements were seen in those who received treatment within 12 months of diagnosis.

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Similarly, Marie *et al* [24] described 7 patients with deteriorating anti synthetase syndrome associated ILD refractory to steroids, cytotoxics and/or intravenous immunoglobulins who were then treated with rituximab. In these patients there was a significant improvement in median FVC and DLCO 1 year after rituximab therapy as well as a universal improvement in symptoms and imaging, that at follow up, was either stable (n=2) or improved (n=5).

Finally, in a retrospective case series of 50 patients with severe progressive immune mediated ILD, rituximab was shown to be a viable rescue therapy [25]. The patients in this report had a variety of underlying diseases, including 33 with a defined CTD. These patients had severe lung disease as defined by a median FVC of 44%, median DLCO of 24.5% and resting hypoxia, with 4 being mechanically ventilated at the time of rituximab administration. In these patients there was a demonstrable deterioration in lung function, in spite of treatment with cyclophosphamide or mycophenolate, prior to rituximab. Paired pulmonary function tests 6-12 months following one course of treatment (1g at baseline repeated at 14 days) resulted in an improvement in FVC with stabilisation of DLCO. It is worth noting that in results similar to the previous series the response to treatment was unsurprisingly not universal; whilst 85% of CTD-ILD patients responded, 5 patients continued to deteriorate in spite of treatment. The authors evaluated possible predictors of response and discovered a lesser decline in FVC prior to treatment and a trend towards a better preserved FVC were positive predictors of response, perhaps hinting yet again that earlier intervention with biological therapy is more likely to result in a positive clinical outcome.

There clearly remains a need for further, more robust data in support of rituximab, however these studies do suggest a potential role for its use in specifically treating CTD-ILD, irrespective of extra-thoracic disease activity. Moreover, these are patients with severe and progressive disease in whom treatment options are extremely limited. For these patients lung transplant may be the only remaining option, but in reality is only possible for a few highly selected patients. The currently recruiting RECITAL study comparing cyclophosphamide and rituximab as treatments for CTD-ILD (NCT01862926) will potentially provide more data on the subject.

It is worth considering that whilst the current studies suggest B cells may be important, it is unlikely that this is simply related to blocking autoantibody production. There is data, for instance from systemic lupus erythematosus, that these cells have a role in regulating T cell behaviour and that the B cell line that repopulate following successful depletion tend to be antigenically inexperienced and hence there may be a mechanism by which the immune dysregulation, which characterizes these diseases, is effectively reset. Should rituximab become an established treatment option in the future the timing of repeat treatments will need to be considered. B cell depletion (based on peripheral blood measures) in patients receiving rituximab (for other indications) persists for 6-9 months after dosing, however, it is not consistent across all patients and does not always correspond to clinical disease activity, perhaps adding weight to the concept of immune system “resetting”. These observations make standardised treatment protocols difficult to determine and it is likely significant resources will need to be deployed to detect any suggestion of disease “reactivation” or relapse.

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**Table 3.** Studies assessing efficacy of rituximab in CTD-ILD.

Clinical Trial	Study design	Connective tissue disease studied	Endpoint or measured parameters	Outcome/Comments
<b>Daoussis <i>et al.</i> (10)</b>	Open label, randomised controlled; rituximab (n=8) vs. standard therapy (n=6)	Systemic sclerosis	(1) change in PFTs (baseline, 24 weeks and 1 year) (2) modified Rodnan skin score at baseline and 1 year.	<p>Significant increase in FVC with RTX; 68.13% +/-19.69 at baseline vs. 75.63% +/- 19.73 at 1 year; p=0.0018.</p> <p>Significant increase in DLCO with RTX; 52.25% +/-20.71 at baseline vs. 62 +/-23.21 at 1 year; p=0.017).</p> <p>Median improvement in FVC was 10.25% with RTX vs. a mean deterioration of -5.04% in the control group..</p> <p>Significant improvement in HAQ at 1 year vs. baseline in RTX group; no change in the standard therapy group</p>
<b>Daoussis <i>et al.</i> (11)</b>	Extension study of the 8 original patients who received rituximab (10) Two additional cycles given at 12 and 18 months with follow up at 2 years	Systemic sclerosis	Lung function parameters.	<p>Significant increase in FVC at 2 years compared to baseline 77.13% (+/-7.13) vs. 68.13% (+/-6.96), p&lt;0.0001</p> <p>Median percentage improvement in FVC at 2 years was 12.79% (8.76-25.12%)</p> <p>Early disease (n=2) had the most striking response with increases in FVC of 27.94% and 29.03%</p> <p>Significant increase in DLCO 63.13 % (+/-7.65) vs. baseline of 52.25% (+/-7.32), p&lt;0.001</p> <p>Median percentage improvement in DLCO at 2 year 19.47% (3.81-27.15)</p>

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<b>Sem <i>et al.</i> (12)</b>	Retrospective case series (n=11)	Anti-synthetase syndrome	Lung function at baseline, 3 and 6 months. HRCT Serum anti Jo-1 (or anti-PL-12) and serum creatine kinase.	In the 8 patients with gradual onset ILD, 5 displayed a >10% improvement FVC and >15% DLCO, 2 improved but by a lesser degree and 1 demonstrated a decline in FVC In the 3 with acute onset ILD (< 1 month) FVC improved by >10% in 1, however 1 worsened and the 1 patient died
<b>Andersson <i>et al.</i> (13)</b>	Retrospective cases series (n=24)	Anti synthetase syndrome	Lung function. HRCT. Median follow up 52 months.	Median percentage predicted FVC increased from 58% (15-60) to 72% (38-105), p<0.018 Median percentage predicated DLCO increased from 41% (15-60%) to 48% (15-84%) 7 of the 24 had >30% increase in all PFTs Most pronounced effects in those with disease duration < 12 months Extent of ILD on HRCT decreased in the majority of patients 21% (7 out of 34) died during the observation period with the most common adverse event infection although mortality rate across whole patient cohort was 32%
<b>Marie <i>et al.</i> (14)</b>	Retrospective case series of patients with ILD refractory to standard therapy	Antisynthetase syndrome	Change in FVC and DLCO prior to RTX and 6 and 12 months after treatment	Significant improvement in FVC (p=0.03) and DLCO (p= 0.00002). Median FVC at baseline 66% (35-76%) increasing to 74% (57-108%) and median DLCO from 39% (20-57%) to 59% (49-72%). Clinical resolution/improvement of ILD allowed a tapering of the daily steroid dose from a median daily dose of 20mg (range 7-30mg) at baseline to 9mg (range 3-15mg) at 1 year (p=0.015).

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<b>Allenbach et al</b>	Open label prospective multi-centre phase II trial in patients refractory to prednisolone and at least 2 immunosuppressants (n=10)	Anti-synthetase syndrome with myoisits and ILD	Primary endpoint was muscular involvement Secondary endpoints (1) CK levels (2) FVC and or DLCO (3) decreased need for immunosuppressive therapy at 12 months following 1 <sup>st</sup> of 2 cycles 6 months apart	Improvement in ILD as measured by PFTS in 50% of patients (N=5), 4 demonstrated stabilisation and 1 declined 6 out of 10 were able to reduced IS
<b>Keir et al. (16)</b>	Retrospective assessment of case series of patients with severe progressive ILD (n=50)	CTD-ILD (33); Idiopathic inflammatory myopathy (10) SSc (8) UCTD (9) MCTD (2) RA (2) SLE (1) Sjogren's (1)	Change in paired pulmonary function data at 6-12 months Patients defined as responders (stable or categorical improvement) or non responders (continued categorical decline or death)	Median decline in FVC of -13.3% (-47.2 to 4.5%) and DLCO of -18.8% (-47.8 to 0%) prior to RTX In the 6-12 months following RTX FVC improved by 8.9% (-9.1% to 45.5%) and DLCO stabilised (median change of 0%, range -24% to 76.2%; p<0.01). 28 (85%) patients were classified as responders; 18 with stabilisation of PFTs and 10 with a categorical improvement. Strongest response in ILD associated with idiopathic inflammatory myopathy
<b>RECITAL (NCT01862926)</b>	Randomised double blind controlled trial comparing rituximab	Severe or progressive CTD-ILD; SSc, PM.DM or MCTD	Primary endpoint of absolute change in FVC over 48 weeks.	Currently recruiting

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against intravenous  
cyclophosphamide

Secondary endpoints;  
change in (1) DLCO (2)  
health related quality of life  
scores (3) global disease  
activity score (4)  
progression free survival  
using a composite endpoint  
of mortality, transplant,  
treatment failure or decline  
in FVC >10%

**Legend:** PFTs - pulmonary function tests; FVC – forced vital capacity; RTX – rituximab; DLCO – diffusing capacity of the lungs for carbon monoxide; HAQ - health assessment questionnaire; HRCT – high resolution CT scan; CK – creatine kinase; SSc – systemic sclerosis; UCTD – undifferentiated connective tissue disease; MCTD – mixed connective tissue disease; RA – rheumatoid arthritis; SLE – systemic lupus erythematosus; PM – polymyositis; DM – dermatomyositis.

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### ABATACEPT

Abatacept is a fully human soluble fusion protein made up of cytotoxic T lymphocyte antigen 4 (CTLA-4) and the Fc portion of IgG1 (CTLA4-Ig). The CTLA-4 component is a physiological antagonist of the T cell co-stimulatory molecule CD28 (also known as B7). By binding to this molecule it prevents the interaction between CD28 on the T cell and CD80/86 on the antigen presenting cell, thus blocking T cell activation and resulting in immunological anergy.

Abatacept therapy already has an established role in treating the articular features of RA where CD28 expression is increased, with a mean expression greatest in patients with clinically active disease [26]. It's role in treating CTD-ILD is not fully established but would seem logical given that excess, activated T cells in ILD may promote fibrosis and endothelial damage through cytotoxic effects and through the production of soluble mediators. Certainly, activated T cells are increased in the lung interstitium and bronchoalveolar fluid from SSc patients with active ILD [27]. Furthermore, serum CTLA-4 levels have been shown to be elevated in patients with diffuse cutaneous systemic sclerosis (dcSSc) and are associated with greater frequency and severity of pulmonary fibrosis in this cohort [28].

In the pre clinical setting animal data has provided further evidence, with a CD28 deficient mouse model demonstrating markedly reduced fibrosis with decreased production of relevant chemokines and cytokines [29]. As previously intimated CTD-ILD knowledge frequently evolves from similar diseases and in hypersensitivity pneumonitis, a form of non CTD-ILD, there is an influx of activated T cells with up-regulated expression of B7 molecules. In a mouse model of this disease, administration of CTLA4-Ig markedly decreased lung inflammation with significantly fewer inflammatory cells in the bronchoalveolar lavage fluid and lung tissue, coupled with decreased production of IL-4, IL-10, and IFN-gamma [30], [31].

In terms of clinical experience of using abatacept in CTD-ILD only case reports exist with the majority commenting on safety rather than efficacy, reflecting concerns about the use of alternative biological agents in patients with ILD. Mera-Varela *et al.* [32] presented their experience with the drug in 4 patients who either developed ILD or had progression of underlying ILD whilst receiving TNF blockers. In all cases a switch to abatacept resulted in significant improvement in their joint disease and no further progression of respiratory disease measured both objectively (with lung function and imaging) and in terms of symptoms. A further case report of a 62 year old male with treatment refractory sero-negative RA has been published which suggested that treatment with abatacept not only halted progression of lung function deterioration but in fact resulted in some parameters improving [33]. The paucity of similar positive results, in other words cases where there is an improvement rather than a lack of deterioration, underpins one of the key messages when managing CTD-ILD. Unlike articular disease the goal of treatment is often to induce stability and whilst improving function is desirable, it is not realistic when established fibrosis is present. The currently recruiting ASSET study will potentially provide more insight into the efficacy of abatacept in CTD-ILD. It is a phase

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2 study comparing abatacept versus placebo in dcSSc with one of the secondary outcomes measures being change in per cent predicted FVC from baseline to 52 weeks (NCT02161406).

### **TUMOUR NECROSIS FACTOR BLOCKERS**

A longstanding interest in TNF alpha as a target reflects no shortage of evidence indicating that expression of this master cytokine is increased in the lungs of ILD patients, localising particularly to the epithelium and macrophages. A causative role for it in the pathogenesis of pulmonary fibrosis is strengthened by observations that blocking TNF signalling attenuates bleomycin induced fibrosis [34]–[37].

Several case reports of CTD-ILD (RA, SSc and DM) have demonstrated a sustained improvement in respiratory symptoms with stabilisation of lung function tests [38], [39] or even an improvement in some physiological parameters [40][41] when using infliximab. In a retrospective case series of 14 patients with DM associated ILD, 71.4% demonstrated an increase in motor strength, reduced rashes and an improvement in lung CT appearances with adalimumab [42]. The remaining 4 patients, however, died of respiratory failure, although they all had more severe hypoxaemia compared to the responders, suggesting that earlier intervention may be associated with a greater chance of response.

Despite these reports the role of TNF blockers as a therapy for ILD has been significantly hampered by numerous reports of new or worsening ILD as a response to these agents, an observation discussed in more detail elsewhere in this chapter.

### **TOCILIZUMAB**

Tocilizumab is a fully humanised monoclonal antibody that binds to and inhibits IL6 receptors. IL6 has been implicated in the disease pathogenesis of various autoimmune diseases with a wealth of data demonstrating that it is both pro-inflammatory [43]–[45] and profibrotic with an increase in collagen and glycosaminoglycan production from human dermal fibroblasts induced by IL6 [46].

In SSc patients IL6 has been shown to be overexpressed in skin, serum [47] and bronchoalveolar lavage fluid. Serum levels positively correlate with severity of skin disease [48]. Furthermore, IL6 inhibition has been associated with prevention and reversal of skin fibrosis in a murine scleroderma model [49]. A positive correlation between IL6 and HRCT scores [50] has also been demonstrated, suggesting that IL6 induced inflammation is associated with more aggressive pulmonary disease. De Santis *et al* [51] reported similar findings with elevated IL6 levels predictive of a decline in FVC and/or DLCO within the first year and of death within 30 months.

The clinical experience of using the drug to treat ILD is, however, scarce. In a published case report [52] a 15 year old girl with an undifferentiated systemic inflammatory condition associated with progressive interstitial lung disease, refractory to steroids, synthetic disease modifying drugs, TNF blockers and anakinra, was then treated with tocilizumab, leading to an improvement in respiratory symptoms, oxygenation and a reduction in ground glass opacification on CT which was then sustained for 2.5 years. In another case report experience of using tocilizumab to treat organising pneumonia associated with Sjögrens

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was reported [53]. A 55 year old man with clinical findings consistent with the disease was initially treated with oral prednisolone demonstrating a rapid improvement in respiratory symptoms and infiltrates on CT imaging, however, as the dose was reduced both methotrexate and rituximab were ineffective at controlling both pulmonary and arthritis symptoms. At this stage tocilizumab was added to prednisolone and methotrexate with a rapid improvement in symptoms, normalisation of lung function tests and successful reduction in steroid dose.

A more recent proof of concept study the use of tocilizumab in SSc was investigated [54]. Eighty seven patients with active diffuse cutaneous disease and elevated acute phase reactants (in this instance platelets and C reactive protein) were randomised to receive subcutaneous tocilizumab or placebo for 48 weeks. At the mid point evaluation there was a numerically favourable effect on the modified skin scores favouring tocilizumab, an effect which was even greater at 48 weeks. Over the course of the study 27% of patients in the placebo arm showed a decline of more than 10% in FVC compared with 3.3% in the tocilizumab group ( $p=0.009$ ). Adverse events were high for both groups (88.4% of the treatment arm and 90.9% of the placebo group) with infection more commonly associated with tocilizumab ( $n=6$  versus 1) with one pulmonary infection resulting in death whilst non-infectious side effects were more frequently observed with placebo ( $n=10$  versus 5). As a result of these findings a confirmatory phase 3 clinical trial assessing benefit on skin, but also evaluation pulmonary disease response is underway (NCT01532869).

### **ANAKINRA**

Anakinra is a recombinant interleukin 1 receptor antagonist, blocking the activity of IL1, a cytokine produced in response to inflammatory stimuli. It has proven efficacy in RA articular disease, reducing radiological progression [55] and providing greater benefit than traditional DMARDs alone [56], [57] .

In an animal model of pulmonary fibrosis administration of an IL1 receptor antagonist completely prevented collagen deposition day 15 after instillation of a profibrotic drug and globally decreased the proportion of damaged lung on histopathological samples [58].

In humans IL1 inhibitory activity has been shown to be diminished in healthy smokers, patients with sarcoidosis and idiopathic pulmonary fibrosis, compared with healthy nonsmokers suggesting that this may be relevant in other chronic inflammatory lung diseases [59]. Furthermore, in other forms of ILD, namely asbestosis and silicosis, Nalp3 inflammasome activation has been shown to lead to IL1 secretion and Nalp3 knockout mice show reduced production of this cytokine with diminished recruitment of intrapulmonary inflammatory cells [60]. At present there is minimal clinical experience of using this agent except for a case report demonstrating partial response, however, the rationale underpinning its potential may result to further use in the future.

### **NEW OR WORSENING ILD IN RESPONSE TO BIOLOGICAL THERAPY**

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Autoimmune disease appearing as a result of biological agents was first described in RA patients treated with a TNF blocker [61]. Since then the number and diversity of autoimmune diseases triggered by biological agents has accumulated in line with their increasing use. Cases of new ILD in association with all the first generation TNF blockers have been reported [62], [63]. Results from post marketing surveillance for the 3 TNF blockers in common use are presented in Table 4.

**Table 4.** Incidence of new ILD from post surveillance of the TNF blockers

TNF blocker	Number of RA patients evaluated	Number/% developing ILD	Reference
Infliximab	5000	25/0.5%	Takeuchi T <i>et al</i> [64]
Etanercept	7091	42/0.6%	Koike T <i>et al</i> [65]
Adalimumab	3000	17/0.6%	Koike T [66]

There are also a considerable number of case reports describing new onset or worsening of pre-existing ILD in response to biological treatments with an alternative mechanism of action including tocilizumab, rituximab and abatacept [67]–[73]. The sometimes serious nature of these reactions were highlighted by Ostor *et al* [74] who reported four fatalities from sudden deterioration of previously present, but asymptomatic ILD, soon (3-10 weeks) after receiving infliximab. How exactly these treatments might cause such serious respiratory complications is not known, but theories include causing idiosyncratic drug reactions, modifying a pre existing ILD into a more injurious phenotype or by increasing susceptibility to infection which potentially leads to an exuberant inflammatory host defence. In the case of the TNF blockers, experimental studies have shown that TNF may have both pro and anti-fibrotic effects and potentially it is the balance or rather imbalance of these two opposing roles that may result in either prevention or acceleration of pulmonary inflammation.

In an analysis of registry data from the BIOGEAS project, Ramos-Casals *et al* [75] reviewed 800 cases of autoimmune disease (all forms, not just pulmonary) appearing after the use of biologic agents. Amongst all the cases 118 were due to ILD, predominantly following infliximab and etanercept. The mean time of developing ILD after starting the therapy was 14.7 weeks with the majority manifesting within 6 weeks of initiating treatment. In all cases the biological agent was stopped and over 80% of patients were then treated with steroids or an alternative immunosuppressant, with subsequent resolution in just over a third. 78% of the recorded deaths were due to ILD (N=14 of a total of 18 deaths), 12% of the total number of patients developing ILD as a complication of their treatment. Perhaps even more importantly death was predominantly seen in patients with pre-existing ILD (11 of the 14 who died).

One difficulty with appraising the currently available data, with regard ILD risk, is that these observations are from case reports or registry data and bias is likely to exist. Since safety signals have been published in relation to TNF blockers and RA-ILD since 2004, clinicians are less inclined to prescribe these drugs in

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patients with pre-existing pulmonary fibrosis. Indeed ILD has been included as an “undesirable effect” on the specific product characteristics (SPC) for the three TNF blocking agents. This has potentially resulted in more patients with ILD receiving standard therapy and since the presence of ILD is a major contributor of death, the mortality rate in this cohort will have risen.

Indeed, several authors have presented evidence suggesting that there is no increased risk of ILD with biologics. Wolfe *et al* [76] were unable to associate the use of biological treatments with hospitalisation for ILD, with only one case in their cohort (a total of 260 per 100,00 patient years) demonstrating a possible temporal association with the administration of infliximab. What is more clear is that ILD itself is a strong predictor of increased all-cause mortality in RA patients (mortality odds ratio 2.12) irrespective of the treatment given [77]. An observational study using data from the BSRBR (British Society for Rheumatology Biologics Register) examined the influence of TNF blockers on mortality in patients with established RA-ILD [77]. Of the 13883 patients identified, 367 had pre-existing ILD as identified by their physician; 68 were then treated with standard therapy, whilst 299 were treated with anti TNF therapy (biologic naïve). The mortality rate in the group with pre existing ILD treated with a biologic was 23% versus 21% in those who received standard treatment (median follow up 3.8 and 2.1 years respectively). Amongst these patients, ILD was cited as the cause of death in 21% of the patients who died and were treated with TNF blockers compared with 7% in the DMARD group. For patients who had no pre-existing ILD, ILD was given as the cause of death in 14 patients treated with TNF blockers (2% of deaths, 0.13% of the total number treated) versus 2 patients in the comparison group (1% of the deaths, 0.05% of the total number of patients in this cohort). After adjustment for age, gender and other potential cofounders the adjusted mortality rate ratio was 0.81 (0.38 to 1.73) for the TNF treated cohort, suggesting no increased mortality in this group.

Curtis *et al* [78] evaluated the ILD incidence and exacerbation of pre-existing disease amongst users of abatacept, rituximab and tocilizumab compared with anti TNF agents in a cohort of RA patients. These patients had previously discontinued a different biologic agent and hence represented a group with more refractory disease. They used two different methods to define ILD, one with a high specificity and the other with a high sensitivity, acknowledging the inherent difficulties with ILD diagnosis. Overall ILD incidence rates ranged from 1.8 to 6.4 per 1000 patient years. The authors concluded that there was no significant difference in the risk of ILD incidence between patients exposed to TNF blocking agents compared to biologics with an alternative mechanism of action. The proportion of patients with newly diagnosed ILD ranged from 0.1% to 0.4%; whilst the frequency of ILD exacerbations in patients with pre-existing ILD ranged from 4.1-8.4% at rates between 65.8 to 127.7 per 1000 patient years.

Similarly Herrinton *et al* [79] identified 38 cases of newly diagnosed ILD amongst 8417 patients with autoimmune diseases. Of those patients treated with a TNF blocker, 0.5% were diagnosed with ILD over follow up, versus 0.3% of those who received standard treatment. Nearly all the cases of ILD occurred in patients with RA where the incidence rate was 7 times higher than for the other autoimmune diseases, however the adjusted hazard ratio (1.03; 95% CI [0.51–2.07]) did not suggest any increased risk with TNF blockers compared to standard treatment with methotrexate. It is worth remembering, however, that existing

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ILD patients were not included in this analysis and observations from other authors would suggest it is these individuals where the risk is greatest.

Ultimately, whilst there are reports of both new ILD and progression of pre existing disease in response to all currently licenced biologics making firm conclusions is not possible based on current evidence, particularly for diseases other than RA. These outcomes are rare and generally based on observational or retrospective data where there is no formal, matched comparator arm. Since ILD is a complication of these diseases it is of course feasible that the new ILD cases may have occurred irrespective of the treatment. Equally, the natural history of existing ILD is often unpredictable and it is difficult to know whether observed progression is related to treatment or indeed disease activity.

### **CONCLUSION**

There are many considerations when determining a management plan for a patient with CTD-ILD. The first is whether indeed the disease requires treatment. Given that a significant number of patients will have subclinical, or minimally significant disease, the decision to treat will be informed by the course of the disease, as well as non-pulmonary, patient factors. In some cases, reassurance combined with sequential long-term observation is appropriate. Therapy is generally given to those with either significant, severe disease at diagnosis or those with a progressive phenotype based on the severity of functional impairment indicated by symptoms, lung physiology measures/FVC decline, HRCT appearances and in some cases, BAL cytology. In the absence of strong trial evidence it would seem most appropriate to appraise each patient on a case by case basis taking into consideration these various factors, as well as the presence of articular disease and response to previous therapies. A potential algorithm for managing these patients is summarised in Figure 3.

At present, if the pulmonary disease is the dominant clinical problem it is likely treatment with more conventional, non biological therapy will remain first line, with mycophenolate or azathioprine, or alternatively cyclophosphamide (+/- methylprednisolone) if the disease is severe or rapidly progressive. The use of biologics will be reserved for those patients who fail to respond to these treatments or in those who have co-existing severe articular disease. Having said this some of the current data hints that earlier intervention, when function is better preserved, might result in more impressive outcomes and the results of future studies may well add weight to this argument, such that biological agents will be used sooner and more frequently. In terms of selecting specific agents, currently the largest evidence base is for rituximab, however, it is feasible that as new evidence emerges drugs with alternative mechanisms of action may be increasingly used.

In addition, combination therapy (to include a biological agent or agents) may become more commonplace with physicians adopting an approach more akin to oncology, focussing on multiple mediators and pathways, simultaneously targeting them. ILD pathogenesis shares common themes with cancer biology including response to growth signals, abnormal fibroblast behaviour and altered cellular signalling and

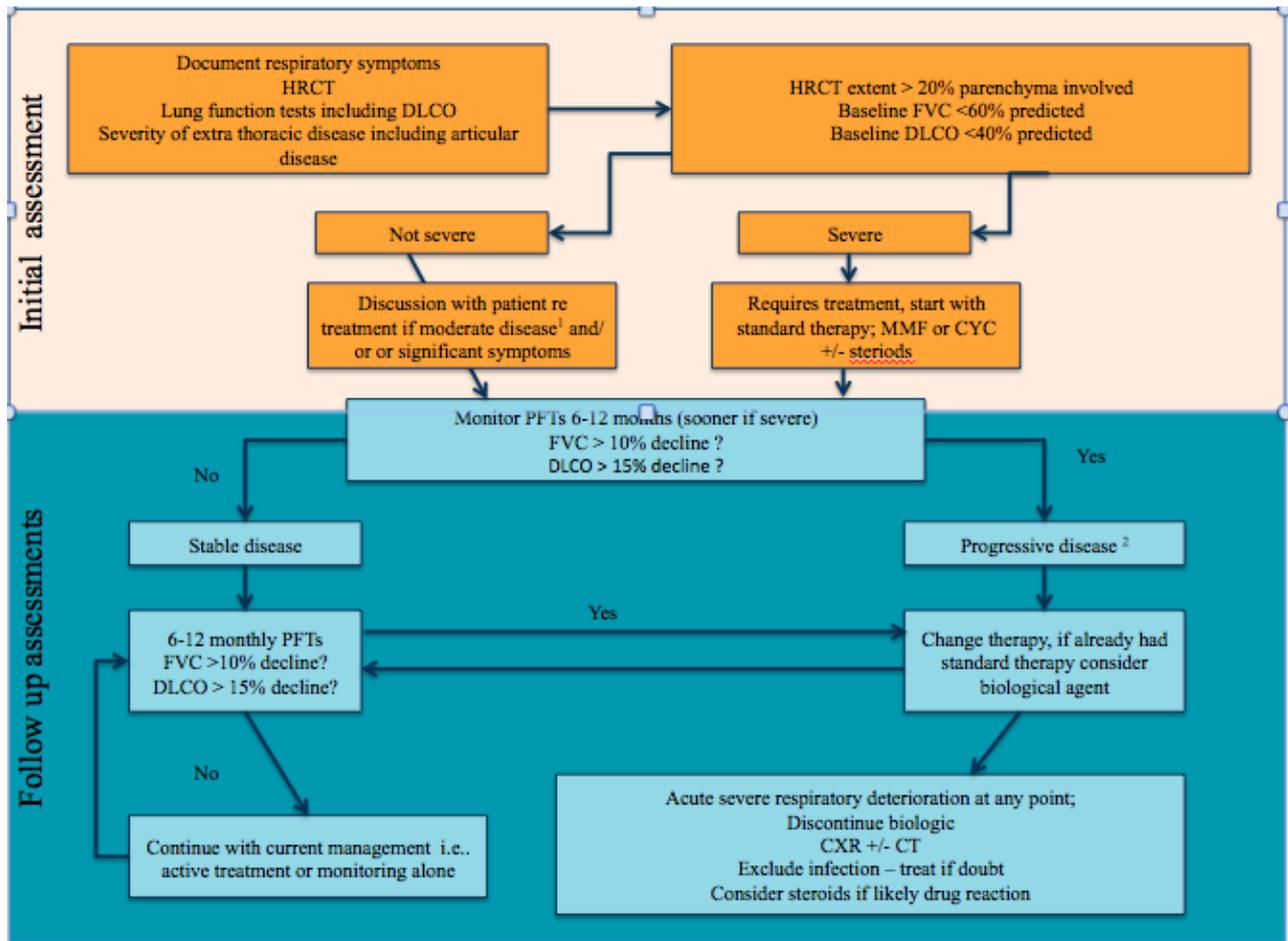
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communication. In both disease groups, multiple pathways are implicated in propagating disease and in pulmonary fibrosis the balance of these potentially varies between individuals, providing a possible explanation for the different histological patterns, range of clinical manifestations and response to treatments that we see in clinical practice. Personalised medicine, already used to treat some cancers, would allow for individualised treatment on the basis of a patient's predominant pathogenic pathway. This may become possible as our understanding of pathogenesis improves and with the availability of validated and commercially available biomarkers. In the future predicting response to treatments using these tools and applying pharmacogenomics may drastically alter our approach to treatment. There will, however, need to be careful consideration in terms of maintaining effective host defence particular if combination therapy is used.

There remains controversy about the safety of TNF blockers or indeed other biological agents in the presence of pre-existing ILD. It is the authors' view that if a patient has severe debilitating disease, either thoracic or extra thoracic, biological agents should not, on the basis of current evidence, be withheld due to concerns about causing exacerbations. Put simply, if it is felt that the disease left untreated will have significant morbidity or mortality implication, treatment should be undertaken but with careful, specialist directed monitoring. The greatest body of evidence for potential harm relates to TNF blockers in patients who have established ILD, thus one might postulate that where alternatives are available it would seem ideal to use a non TNF agent in these patients. Having said this the absence of evidence does not have the same meaning as evidence of no harm and the same close monitoring for adverse events is recommended irrespective of the drug used.

**Figure 3.** Potential treatment algorithm for managing CTD-ILD

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**Legend:** <sup>1</sup> “Moderate disease” defined as FVC 60-80% predicted. <sup>2</sup>Progressive disease” should include exclusion of infection or other potential cause for lung function decline. HRCT – high resolution CT; DLCO – diffusion capacity of lungs; FVC – forced vital capacity; MMF – mycophenolate; CYC – cyclophosphamide; PFTs – pulmonary function tests.

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