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REVIEW

Management of Fibrosing Interstitial Lung Diseases

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ABSTRACT

A proportion of patients with interstitial lung diseases (ILDs), including the ILDs that are commonly associated with autoimmune diseases, develop a progressive fibrosing phenotype characterised by worsening of lung function, dyspnoea and quality of life, and early mortality. No drugs are approved for the treatment of ILDs other than idiopathic pulmonary fibrosis (IPF). At present, immunomodulatory medications are the mainstay of treatment for non-IPF ILDs. However, with the exception of systemic sclerosis-associated ILD, the evidence to suggest that immunosuppression may preserve lung function in patients with these ILDs comes only from retrospective, observational, or uncontrolled studies. In this article, we review the evidence for the treatments currently used to treat ILDs associated with autoimmune diseases and other ILDs and the ongoing trials of immunosuppressant and antifibrotic therapies in patients with these ILDs.
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Keywords: Collagen diseases; Immunosuppression; Interstitial lung disease; Respiratory; Rheumatic diseases; Treatment

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INTRODUCTION

Interstitial lung disease (ILD) encompasses a large and heterogeneous group of parenchymal lung disorders, which may be related to systemic diseases or environmental exposures or have no known cause. Some individuals with certain types of fibrosing ILD develop a progressive phenotype characterised by worsening of lung function, dyspnoea and quality of life, and early mortality [1]. Idiopathic pulmonary fibrosis (IPF), an ILD of unknown cause that predominantly affects older adults [2], is invariably progressive and is associated with a median survival of only 3–4 years [3, 4]. A progressive fibrosing phenotype has also been observed to develop in a proportion of patients with other ILDs, including ILD associated with rheumatoid arthritis (RA-ILD) [5], systemic sclerosis (SSc-ILD) [6], polymyositis/dermatomyositis [7],

chronic sarcoidosis [8], chronic hypersensitivity pneumonitis (cHP) [9], idiopathic non-specific interstitial pneumonia (iNSIP) [10] and unclassifiable ILD [11]. Irrespective of the trigger for the lung injury, progressive fibrosing ILDs show commonalities not only in disease behaviour but also in the pathogenic mechanisms that drive the fibrotic process, which culminate in irreversible loss of epithelial or endothelial barrier integrity, destruction of the lung architecture and loss of lung function [12].

No drugs are approved for the treatment of ILDs other than nintedanib and pirfenidone for IPF. No treatment guidelines have been issued by an international professional association for forms of ILD other than IPF [13, 14] and SSc-ILD [15, 16] and there is a paucity of scientific evidence to guide therapeutic decision-making even in SSc-ILD [17, 18]. Immunosuppression is the mainstay of therapy for all fibrosing ILDs other than IPF, but its efficacy and safety in the treatment of these ILDs have not been established. Of concern to many is that immunosuppression was also the "gold standard" approach to the treatment of IPF until the results of the PANTHER-IPF trial showed that combination therapy with prednisone, azathioprine and *N*-acetylcysteine (but not *N*-acetylcysteine alone) was associated with an increased risk of hospitalisations and death in this patient population [19, 20]. In this article, we review the evidence for the treatments currently used to treat ILDs that may be associated with a progressive fibrosing phenotype.

This review article is based on previously conducted studies and does not contain any studies with human participants or animals performed by either of the authors.

CORTICOSTEROIDS

Corticosteroids are widely used as first-line therapy for ILDs other than IPF [21], but there is very little evidence to support their efficacy in treating ILD. International guidelines for the treatment of IPF provide a strong recommendation against the use of corticosteroid monotherapy other than in the treatment of acute exacerbations [13]. Among nearly 4000 patients with SSc-ILD recorded in the EUSTAR database between 2004 and 2014, glucocorticoids had been taken by 59% of patients at some point, but it is unclear what percentage of these patients were given corticosteroids with the intention to treat ILD [22]. Glucocorticoids are recommended for patients with RA if the disease remains active after treatment with disease-modifying drugs or biologics [23], but there is no evidence that glucocorticoids ameliorate RA-ILD. Corticosteroids are an established treatment for pulmonary sarcoidosis: in a Delphi consensus study, 92% of experts indicated that corticosteroids were the preferred first-line treatment [24]. There is very little evidence to support the efficacy of corticosteroids in patients with cHP. Only one randomised placebo-controlled trial has been published, which was small (n = 36) and short (8 weeks) [25]. A retrospective study of medical records from all patients with HP followed at a single centre between 2005 and 2016 found that although patients with non-fibrotic disease (n = 93) showed an improvement in lung function following initiation of corticosteroids, no benefit was observed in patients with fibrotic disease (n = 109), in whom median survival was only 9.2 years [26]. There is some evidence that corticosteroids may be beneficial in the treatment of iNSIP. In an analysis of 86 patients with iNSIP treated with corticosteroids (with or without other immunosuppressants) and followed for at least 1 year, nearly half had an improvement in forced vital capacity (FVC) of at least 10% predicted. This response appeared to be associated with lower pulmonary function at baseline, a shorter duration of respiratory symptoms, and negativity for anti-nuclear antibody [27]. It should be noted that long-term use of corticosteroids is associated with substantial morbidity, including weight gain, diabetes, cardiovascular events, cataracts and osteoporosis [28]. Decisions on whether to use, or continue to use, corticosteroids in patients with ILDs should be individualized to the patient and take into account the patient's clinical condition, including comorbidities, and the occurrence of side effects.

CYCLOPHOSPHAMIDE (CYC)

CYC is an immunosuppressant that may be delivered orally or intravenously. The latest guidelines for treatment of SSc-ILD, issued by the European League Against Rheumatism Collaborative Initiative (EULAR) in 2016, recommend the use of tailored CYC therapy, in particular for patients with progressive disease [16]. In algorithms for the treatment of SSc-ILD developed in 2016–2017, the consensus of experts was that intravenous CYC should be used as second-line induction therapy, after mycophenolate mofetil (MMF) [18]. The efficacy and safety of CYC in patients with SSc-ILD were investigated in two randomised placebo-controlled trials: the Fibrosing Alveolitis in Scleroderma Trial (FAST) and Scleroderma Lung Study I (SLS I). In FAST, in which 158 subjects were randomised to receive low-dose prednisolone plus intravenous CYC for 6 months followed by oral azathioprine for 6 months, or placebo for 1 year, there was an improvement of 2.4% in FVC % predicted with active treatment versus a decline of 3.0% with placebo [29]. In SLS I, the mean decline from baseline in FVC % predicted at 1 year was 1.0% in subjects treated with oral CYC versus 2.6% in those treated with placebo [30]. CYC is associated with side effects related to immunosuppression, such as leucopenia, haematuria and neutropenia [30], limiting its use as a long-term treatment.

FAST and SLS I are the only randomised controlled trials of CYC conducted in patients with ILDs. The use of CYC in ILDs other than SSc-ILD has been investigated only in small retrospective or uncontrolled studies. In a retrospective study of 21 patients with progressive RA-ILD, survival time was greater (72 versus 43 months) in patients treated with CYC than in patients with better baseline lung function who did not receive CYC [31]. In a retrospective analysis of 307 patients with severe ILDs, including autoimmune ILDs (37%), unclassifiable ILD (20%), and HP (19%), intravenous CYC appeared to stabilize decline in lung function in the 6–12 months after treatment [32].

AZATHIOPRINE

The immunosuppressant azathioprine is widely used as second-line therapy for ILDs other than IPF [21]. In algorithms for the treatment of SSc-ILD developed in 2016–2017, the consensus of experts was that azathioprine should be used as second-line maintenance therapy (after MMF) [18]. However, the only evidence to support the use of azathioprine in patients with SSc comes from uncontrolled open-label studies. In an open-label study in 13 patients with early diffuse SSc, of whom nine had lung involvement, patients treated with azathioprine for 1 year maintained mean FVC % predicted and diffusing capacity of the lung for carbon monoxide (DL_{CO} %) predicted at the levels achieved following 1 year's treatment with intravenous CYC [33]. In an observational study of 18 months' treatment with oral azathioprine given after 6 months' treatment with intravenous CYC in 27 patients with SSc-ILD, 8 patients (30%) had a change in FVC and/or total lung capacity (TLC) of less than 10% predicted and/or change in DL_{CO} of less than 15% predicted, while 6 (22%) had an increase in FVC and/or TLC greater than 10% predicted and/or increase in DL_{CO} of greater than 15% predicted [34].

The evidence for the efficacy of azathioprine in other ILDs is also very limited. There is some evidence from uncontrolled open-label trials that azathioprine may stabilize lung function in patients with pulmonary sarcoidosis [35, 36]. In a retrospective study of 55 patients with sarcoidosis who had not responded to, or had contraindications to, corticosteroids, forced expiratory volume in 1 s (FEV_1 %) predicted, VC % predicted and DL_{CO} % predicted increased in those who completed 1 year of azathioprine (mean ± SD increases of 10.0 ± 14.5, 7.8 ± 14.7 and 13.4 ± 27.2, respectively) [36]. In a retrospective analysis of 19 patients with cHP, treatment with azathioprine was associated with an improvement in DL_{CO} % predicted, but not FVC % predicted, after 1 year [37]. Adverse effects of azathioprine reported in patients with ILD include infections, gastrointestinal effects and elevated transaminases [36, 38].

METHOTREXATE

Methotrexate is an immunosuppressant that may be delivered orally, or by intramuscular, subcutaneous, intravenous, or intrathecal injection. Methotrexate is recommended in EULAR guidelines as a treatment for skin manifestations in patients with early diffuse SSc [15] and is widely used in patients with SSc [22], but there is no evidence that it is effective in treating SSc-ILD. Methotrexate is approved for the treatment of RA, but has not been shown to ameliorate RA-ILD. It should also be noted that methotrexate has been reported as a rare cause of lung injury [39, 40]. Other adverse events associated with methotrexate include gastrointestinal disorders (e.g. stomatitis, dyspepsia, abdominal pain, nausea) and elevations in liver enzymes. Methotrexate was recommended as second-line therapy (after corticosteroids) by experts participating in a Delphi panel on the treatment of pulmonary sarcoidosis [24]. A retrospective analysis of patients with sarcoidosis who had not responded to, or had contraindications to, corticosteroids showed a mean ± SD increase in FEV_1 % predicted, VC % predicted and DL_{CO} % predicted of 7.6 ± 14.4, 9.2 ± 13.1 and 6.6 ± 11.0, respectively, in those who completed 1 year of methotrexate [36].

MYCOPHENOLATE MOFETIL (MMF)

MMF is an immunosuppressant that may be delivered orally or by intravenous infusion. In the randomised controlled SLS II, treatment with oral MMF for 2 years resulted in similar improvements in FVC as oral CYC for 1 year followed by placebo for 1 year (absolute changes of 2.88% predicted and 2.19%, respectively; no significant difference between groups). MMF was better tolerated than CYC, with fewer premature withdrawals due to adverse events (35% versus 42%), fewer treatment-related serious adverse events (4% versus 10%), and lower rates of leucopenia (41% versus 6%) and thrombocytopenia (6% versus 0%) [41]. No recommendation for or against the use of MMF was included in the treatment guidelines for SSc-ILD issued by EULAR in 2016 [16], which did not consider the results of SLS II. However, in algorithms developed by expert consensus in 2016–2017, the consensus of experts was that MMF should be used as first-line induction therapy and first-line maintenance therapy for SSc-ILD [18]. In a recent Delphi consensus study conducted in the USA, clinicians with expertise in managing SSc-ILD supported the use of MMF as first-line therapy for SSc-ILD [42].

No randomised controlled trials of MMF have been performed in ILDs other than SSc-ILD, but there is some evidence from retrospective studies that MMF may have benefits on other ILDs. In a retrospective analysis of medical records from 125 patients with various connective tissue disease (CTD)-ILDs (including 35% with SSc-ILD, 26% with polymyositis/dermatomyositis-related ILD, 15% with lung-dominant CTD, 14% with RA-ILD), treatment with MMF was associated with improvements in FVC % predicted of 4.9%, 6.1% and 7.3% at 1, 2 and 3 years after initiation of MMF, and improvements in DL_{CO} % predicted of 6.3% and 7.1% after 1 and 2 years, respectively [43]. In a retrospective analysis of 51 patients with cHP, administration of MMF was associated with an improvement in DL_{CO} % predicted of 4.2%, but no significant improvement in FVC % predicted, after 1 year [37].

RITUXIMAB

Rituximab is an intravenous anti-CD20 monoclonal antibody that elicits immunosuppressant effects via depletion of peripheral B cells. It is approved for use in combination with methotrexate for the treatment of patients with severe active RA (in the EU) or moderately to severely active RA (in the USA) and an inadequate response to tumour necrosis factor-α antagonist therapy. While no randomised double-blind controlled trials of rituximab as a treatment for ILD have been completed, several retrospective or open-label studies have shown preservation or improvement in lung function in patients with CTD-ILDs treated with rituximab [44–51]. In an open-label study of 60 patients with SSc-ILD who were randomised to receive rituximab or CYC for 6 months, mean

FVC improved from 61.3% to 67.5% predicted in the rituximab group compared with a decline from 59.3% to 58.1% predicted in the CYC group [49]. In a retrospective assessment of 50 patients with severe progressive ILD, there was a median improvement in FVC of 6.7% predicted after 6–12 months' treatment with rituximab compared with a median decline in FVC of 14.3% predicted in the previous 6–12 months [46]. In an observational study of 56 patients with RA-ILD, the median relative change in FVC was 1.2% predicted in the 6–12 months after initiation of rituximab compared with a decline of 2.4% predicted in the 6–12 months before treatment [48]. In algorithms developed by expert consensus in 2016–2017, rituximab was recommended as third-line induction therapy (after MMF and CYC) for the treatment of SSc-ILD [18]. Randomised double-blind controlled trials of rituximab in patients with ILDs are ongoing (Table 1).

TOCILIZUMAB

Tocilizumab is an interleukin-6 receptor antagonist with immunosuppressant and anti-inflammatory effects that is delivered via intravenous infusion or subcutaneous injection. Tocilizumab is approved for use in combination with methotrexate in the treatment of severe active RA, but has not been investigated as a treatment for RA-ILD. The efficacy and safety of tocilizumab in patients with SSc (but not necessarily SSc-ILD) have been investigated in two randomised controlled trials. In the faSScinate trial, there was no significant difference between tocilizumab and placebo on the primary endpoint, mean change from baseline in modified Rodnan skin score (mRSS) at week 24, but an exploratory analysis of changes in FVC % predicted suggested a potential benefit of tocilizumab on lung function [52]. Over 48 weeks, similar proportions of patients in each group withdrew because of an adverse event (14% with tocilizumab versus 11% with placebo) but serious infections were more common with tocilizumab than placebo (16% versus 5%, respectively) [52]. In the focuSSced trial, which involved 210 patients with SSc, there was no significant difference between tocilizumab and placebo on the primary endpoint of change in mRSS at week 48, but exploratory analyses of changes in FVC % predicted suggested that tocilizumab may ameliorate loss of lung function. The mean change from baseline in FVC at week 48 was − 0.4% predicted in the tocilizumab group versus − 4.6% predicted in the placebo group, while the proportion of patients with an FVC decline of greater than 10% predicted at week 48 was 5.4% versus 16.5% in these treatment groups, respectively [53].

HAEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

The latest guidelines issued by EULAR include a recommendation for use of autologous HSCT to treat patients with rapidly progressive SSc at risk of organ failure, but highlight that HSCT should only be performed after careful evaluation of the benefit and risks for the individual patient [16]. This recommendation was based on the results of two randomised trials: Autologous Stem Cell Transplantation International Scleroderma (ASTIS) and Scleroderma: Cyclophosphamide or Transplantation (SCOT). The ASTIS trial compared HSCT with CYC in patients with diffuse cutaneous SSc and renal, pulmonary or cardiac involvement. In the first 12 months, 8 of the 79 patients in the HSCT group and none of the 77 patients in the CYC group died from treatment-related causes. However, at month 12, HSCT was associated with significantly greater event-free survival than CYC (HR 0.52 [95% CI 0.28, 0.96]). Significant improvements were observed with HSCT versus CYC in FVC % predicted (6.3% versus − 2.8%) and total lung capacity % predicted (5.1% versus − 1.3%) at month 24. Grade 3 or 4 adverse events were reported by 63% and 37% of patients in the HSCT and CYC groups, respectively [54]. The SCOT trial compared HSCT with CYC in 75 subjects with diffuse cutaneous SSc and renal or pulmonary involvement. At month 72, event-free survival was greater with HSCT than CYC (74% versus 47%), as was overall survival (86% versus 51%) [55]. In 2018, a task force of the American

Table 1 Ongoing or recently completed randomised double-blind controlled trials of drugs in patients with fibrosing ILDs

ClinicalTrials.gov identifier (trial name)	Patient population	Sample size	Drug under investigation	Lung function endpoint/s
NCT02597933 (SENSCIS®) [90]	SSc-ILD	576	Nintedanib	Rate of decline in FVC over 52 weeks (mL/year) (primary endpoint)
NCT02999178 (INBUILD®) [91]	Progressive fibrosing ILDs other than IPF	663	Nintedanib	Rate of decline in FVC over 52 weeks (mL/year) (primary endpoint)
NCT03099187 [92]	Unclassifiable progressive fibrosing ILD (with progression defined as deterioration in FVC > 5% or significant symptomatic worsening in last 6 months)	252	Pirfenidone	Rate of decline in FVC (mL) over 24 weeks (primary endpoint)
NCT02808871 (TRAIL1)	RA-ILD	≈ 270	Pirfenidone	Proportion of patients with decline in FVC ≥ 10% predicted or death at week 52 (primary endpoint)
NCT03221257 (SLS III)	SSc-ILD	≈ 150	Pirfenidone plus MMF (vs MMF alone)	Change in FVC % predicted at month 18 (primary endpoint)
NCT03260556 (PirFS)	Progressive fibrotic sarcoidosis	≈ 60	Pirfenidone	Change in FVC at month 48 (secondary endpoint)
NCT02958917	Fibrotic HP (with no evidence of improvement in disease severity over preceding year)	≈ 40	Pirfenidone	Change in FVC % predicted from baseline at week 52 (primary endpoint)
NCT02990286 (EvER-ILD)	CTD-ILD or IPAF or idiopathic ILD, plus NSIP based on HRCT or histology, plus lack of response to immunosuppressant therapy for ILD	≈ 122	Rituximab plus MMF (vs MMF alone)	Change in FVC % predicted from baseline at week 24 (primary endpoint) and change in DL_{CO} from baseline at week 24 (secondary endpoint)
NCT01862926 (RECITAL) [93]	Severe and/or progressive ILD associated with SSc, idiopathic inflammatory myositis (including anti-synthetase syndrome), or MCTD	≈ 116	Rituximab vs IV CYC	Changes in FVC (mL) from baseline at week 24 (primary endpoint) and 48 (secondary endpoint)

As per ClinicalTrials.gov on 29 April 2019. Comparator is placebo unless otherwise stated
CTD-ILD connective tissue disease-associated ILD, *IPAF* interstitial pneumonia with autoimmune features, *MCTD* mixed connective tissue disease, *NSIP* non-specific interstitial pneumonia

Society for Blood and Marrow Transplantation recommended autologous HSCT as standard of care for patients with severe SSc, with close collaboration between expert rheumatologists and transplant physicians to identify eligible patients [56].

LUNG TRANSPLANTATION

Given its very poor prognosis, lung transplantation should be considered for patients with IPF at an early stage of disease [13, 57]. Lung transplantation should also be considered for patients with severe autoimmune ILDs who have not responded to treatment and have no contraindications [57], but the prevalence of contraindications means that only a minority of patients are eligible. Many patients with SSc-ILD are not referred for transplant because of concerns that oesophageal dysmotility and gastroparesis may increase the risk of aspiration and transplant rejection. However, successful transplantation is possible in carefully selected patients with SSc-ILD. In a retrospective analysis of data from a single US centre, survival after lung transplant in 72 patients with SSc referred between 2005 and 2013 was 81% at 1 year and 66% at 5 years [58]. Post-transplant survival rates of 93%, 76%, and 60% after 1, 3, and 5 years were reported in a retrospective analysis of 30 patients with SSc-ILD who underwent lung or heart–lung transplant at 14 centres between 1993 and 2016 [59]. Data on post-transplant survival in patients with other ILDs are limited to small short-term studies [60–62]. In an analysis of five patients with ILD associated with idiopathic inflammatory myopathy, all patients survived for 1 year after transplant. Among a cohort of 37 patients with non-IPF ILDs (14 with HP, 9 with RA, 6 with SSc, 3 with systemic lupus erythematosus), the 1-, 2- and 5-year survival rates after lung transplant were 86%, 63% and 57% [61]. A recent analysis of 15 patients with autoimmune ILDs (5 with polymyositis/dermatomyositis, 4 with RA, 3 with SSc) who underwent lung transplant at a Korean centre showed a 1-year survival rate of 80% [62].

ANTIFIBROTIC THERAPIES

Fibrosing ILDs show commonalities in pathogenic pathways [63]. Some ILDs, such as those related to CTDs, are initially inflammatory disorders, in which endothelial injury triggers an excessive fibro-proliferative response under certain conditions. Other ILDs are primarily fibro-proliferative disorders in which fibrosis results from pathological alterations to the lung epithelium [64–66]. In progressive fibrosing ILDs, repetitive injuries at epithelial or endothelial sites lead to cell destruction and unregulated repair. Fibroblasts orchestrated to the site of injury are activated to become myofibroblasts, which secrete excessive amounts of extracellular matrix, resulting in increased tissue stiffness, which further activates and stimulates fibroblasts [64, 67, 68]. Macrophages and lymphocytes recruited to the site of injury release pro-fibrotic mediators, such as transforming growth factor β1, connective tissue growth factor and platelet-derived growth factor [68]. These processes result in a self-sustaining and progressive process of fibrosis. It has been postulated that, irrespective of the initial injury, once fibrosis has become progressive, a therapy that acts on fibrotic pathways is required to slow disease progression. This provides a rationale for investigating the drugs known to slow disease progression in patients with IPF—pirfenidone and nintedanib—as treatments for other forms of fibrosing ILD.

In patients with IPF, pirfenidone reduces lung function decline with a side effect profile characterised mainly by gastrointestinal events and rash [69]. The open-label LOTUSS study suggested that pirfenidone also had an acceptable safety and tolerability profile in subjects with SSc-ILD, but no conclusions could be drawn about its effects on lung function because of the lack of a comparator group [70]. The efficacy and safety of pirfenidone in subjects with SSc-ILD (in combination with MMF versus MMF alone), unclassifiable progressive fibrosing ILD, RA-ILD, fibrotic sarcoidosis and fibrotic HP are currently being investigated in clinical trials (Table 1).

Nintedanib has been shown to slow lung function decline and reduce the risk of acute exacerbations in patients with IPF, with side effects that are mainly gastrointestinal [71, 72]. Nintedanib is an intracellular inhibitor of tyrosine kinases, which blocks processes fundamental to the pathogenesis of fibrosis, including the proliferation, migration and differentiation of fibroblasts, the deposition of extracellular matrix and the release of pro-fibrotic mediators [73, 74]. Nintedanib has demonstrated antifibrotic and anti-inflammatory effects in animal models resembling aspects of fibrosing ILDs, including those with an immunological trigger [73, 75–79]. The efficacy and safety of nintedanib in subjects with SSc-ILD and in subjects with progressive fibrosing ILDs other than IPF have been investigated in the SENSCIS® and INBUILD® trials, respectively (Table 1). The primary endpoint in both these trials is the annual rate of decline in FVC (mL/year) assessed over 52 weeks.

CHOICE OF TREATMENT

Clearly the first step in selecting an appropriate treatment for a patient with ILD is to ensure that they have received the correct diagnosis. Multidisciplinary team discussion to integrate clinical, radiological and laboratory data is the gold standard for making a differential diagnosis of ILD [80]. In the absence of adequate scientific evidence to guide treatment decisions for patients with fibrosing ILDs other than IPF, clinicians must rely on the limited data available, expert opinion and their clinical experience. Some treatment options, based on our clinical experience and recommendations published by experts in the field, are shown in Table 2. Other than nintedanib and pirfenidone for the treatment of IPF, none of these therapies is approved for the treatment of ILD, nor supported by a robust evidence base. Not all patients with ILD require drug treatment. In some patients, it may be appropriate not to initiate therapy but to ensure that patients are closely monitored for disease progression. However, patients with progressive disease warrant consideration of drug therapy. All patients with IPF, which is invariably progressive and has a very poor prognosis, should be offered treatment with nintedanib or pirfenidone to slow the progression of their disease.

OVERALL CARE OF PATIENTS WITH FIBROSING ILDS

All patients with fibrosing ILDs should receive supportive care. Measures to alleviate symptoms and preserve quality of life should be initiated early and tailored to the needs of the patient [81]. Pulmonary rehabilitation or exercise training can improve exercise capacity and quality of life in patients with ILDs, particularly if started when the patient's physiology is less impaired [82, 83]. The use of supplementary oxygen in patients with ILD and hypoxia can help to alleviate dyspnoea and improve quality of life [84]. Vaccines should be recommended to reduce the risk of respiratory infections. Prophylactic antibiotics may also be considered to reduce the risk of infections and associated hospitalisations [85]. For patients with HP, a thorough investigation for the inciting antigen should be performed and, if the antigen can be identified, the patient advised of the importance of antigen avoidance [86]. Management of extra-pulmonary manifestations of disease and identification and treatment of comorbidities can improve patient outcomes [87–89].

CONCLUSIONS

There is a lack of robust evidence to guide the management of patients with fibrosing ILDs other than IPF. Immunomodulatory medications are the mainstay of treatment, but there is very limited evidence to support their efficacy or safety as treatments for ILDs other than SSc-ILD. Progressive fibrosing ILDs show commonalities in underlying pathogenetic mechanisms, suggesting that drugs that slow the progression of IPF may also have utility in slowing the progression of other progressive fibrosing ILDs. Ongoing trials will provide valuable insights into the potential use of immunomodulatory

Table 2 Pharmacological treatment options for ILDs

Type of ILD	Treatment options
IPF	Nintedanib or pirfenidone
SSc-ILD	Induction therapy:
	1st line: MMF or cyclophosphamide
	2nd line: MMF or cyclophosphamide
	3rd line: rituximab
	Maintenance therapy:
	1st line: MMF
	2nd line: azathioprine
RA-ILD	Rituximab
	MMF or cyclophosphamide (in combination with therapy to treat articular manifestations)
ILD associated with polymyositis/ dermatomyositis	Induction therapy:
	1st line: high-dose corticosteroids with oral taper
	2nd line: rituximab or cyclophosphamide
	Maintenance therapy: mycophenolate or azathioprine
MCTD-ILD	If dominant histopathologic subtype is NSIP or UIP, treat as per SSc-ILD
	If dominant histopathologic subtype is OP, treat as per ILD associated with polymyositis/dermatomyositis
IPAF	If dominant histopathologic subtype is NSIP or UIP, treat as per SSc-ILD
	If dominant histopathologic subtype is OP, treat as per ILD associated with polymyositis/dermatomyositis
Hypersensitivity pneumonitis[a]	Patients with signs of inflammation: trial of immunosuppression (corticosteroids tapered to low dose ± cytotoxic agent)
Pulmonary sarcoidosis	1st line: corticosteroids
	2nd line: methotrexate, azathioprine
	3rd line: infliximab, leflunomide, hydroxychloroquine
	4th line: thalidomide
Unclassifiable ILD	Treat according to working diagnosis but undertake regular reassessment and refine diagnosis according to treatment response and/or the emergence of new symptoms, clinical signs or radiological features

Nintedanib and pirfenidone are approved for the treatment of IPF. Other than these, none of the drugs shown in this table is approved for the treatment of any ILD

IPAF interstitial pneumonia with autoimmune features, *IPF* idiopathic pulmonary fibrosis, *MCTD* mixed connective tissue disease, *MMF* mycophenolate mofetil, *NSIP* non-specific interstitial pneumonia, *OP* organising pneumonia, *RA-ILD* rheumatoid arthritis-associated ILD, *UIP* usual interstitial pneumonia

[a] In addition to drug therapy, avoidance of exposure to the inciting antigen where it can be identified is a key element of the management of hypersensitivity pneumonitis

and antifibrotic agents in the management of fibrosing ILDs with a progressive phenotype.

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