ACR Open Rheumatology
Vol. 3, No. 5, May 2021, pp 295–304
DOI 10.1002/acr2.11253

American College of Rheumatology
Empowering Rheumatology Professionals

REVIEW ARTICLE

Detection and Management of Interstitial Lung Diseases Associated With Connective Tissue Diseases

Flavia V. Castelino,[1] and Teng Moua[2]

Interstitial lung disease (ILD) is a common manifestation of connective tissue diseases (CTDs). A proportion of patients with CTD-ILDs develop progressive fibrosing ILD, which is characterized by worsening fibrotic abnormalities on high-resolution computed tomography scan, decline in lung function, worsening symptoms, and early mortality. Here, we review the impact of ILD in patients with CTDs, the importance of prompt diagnosis and close monitoring, and the evidence available to guide the management of CTD-ILDs. Management of patients with CTD-ILDs should be individualized and involve close collaboration between rheumatologists and pulmonologists. Immunosuppression is the mainstay of therapy for CTDs, but evidence for its effectiveness in slowing the progression of ILD is limited. Recently, nintedanib has been approved to slow decline in lung function in patients with systemic sclerosis–associated ILD and chronic fibrosing ILDs with a progressive phenotype. The results of ongoing clinical trials will help clinicians take a more evidence-based approach to the treatment of CTD-ILDs.

INTRODUCTION

Interstitial lung disease (ILD) is a common manifestation of connective tissue diseases (CTDs), including systemic sclerosis (SSc) (1), rheumatoid arthritis (RA) (2), and polymyositis/dermatomyositis (3). A proportion of patients with CTD-ILDs develop a progressive fibrosing phenotype characterized by increasing fibrotic abnormalities (eg, traction bronchiectasis and honeycombing) on high-resolution computed tomography (HRCT), decline in lung function, worsening dyspnea, and high mortality (3–5). In this article, we discuss the impact of ILD in patients with CTDs, the importance of identifying patients with progressive ILD, and the evidence available to guide the management of CTD-ILDs.

PREVALENCE AND RISK FACTORS FOR CTD-ILDS

ILD often appears early in the course of CTD and may even be the first manifestation of a CTD (1,6–9). Risk factors for the development of CTD-ILD have been identified, but CTD-ILD may develop even in patients who lack established risk factors. Estimates of the prevalence of ILD in patients with CTDs vary widely depending on the population studied and the methodology used to define ILD; definitions of ILD may be based on various degrees of abnormality on HRCT scans or impairments in lung function. Further studies of the natural history of CTD-ILDs, perhaps based on patient registries, are needed to elucidate patterns of the progression of CTD-ILDs and how likely it is that ILD detected radiographically will progress to disease that impacts morbidity and mortality.

SSc-ILD. ILD is a common manifestation of SSc and is the leading cause of death in patients with SSc (10). In a nationwide Norwegian cohort of 650 patients with SSc, 50% had ILD identified on an HRCT scan (5). Among patients in the Australian Scleroderma Cohort Study who had an HRCT scan, ILD was evident in 66% of patients (11). Risk factors for the development of ILD in patients with SSc include diffuse cutaneous disease, African American ethnicity, older age at onset, shorter disease duration, and positivity for antitopoisomerase I antibodies (1,12–14). The risk of developing ILD is greatest early in the course of the disease (1).

RA-ILD. ILD is the most common pulmonary manifestation of RA (15). The reported frequency of ILD in patients with RA depends on the patient population studied. In a nationwide Danish registry, RA-associated ILD (RA-ILD) was seen in 2.2% of patients with incident RA based on International Classification of Diseases codes (16). In a retrospective analysis of medical records from 582 patients in a US cohort, based on the

[1]Flavia V. Castelino, MD: Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts; [2]Teng Moua, MD: Mayo Clinic, Rochester, Minnesota.

Dr. Castelino reports consulting fees from Boehringer Ingelheim. No other disclosures relevant to this article were reported.

Address correspondence to Flavia V. Castelino, MD, Massachusetts General Hospital, 55 Fruit Street, Yawkey 2C-2100, Boston, MA 02114. Email: fcastelino@mgh.harvard.edu.

Submitted for publication November 10, 2020; accepted in revised form February 26, 2021.

incidence of probable ILD (abnormalities on chest computed tomography/radiograph plus terms consistent with ILD in medical record) or definite ILD (diagnosis of ILD by a pulmonologist and evidence of two of the following: ILD on chest computed tomography/radiograph and restrictive pattern on pulmonary function test [PFT] or biopsy), the lifetime risk of ILD in patients with RA was estimated to be 7.7% compared with 0.9% in matched individuals without RA (2). Risk factors for the development of ILD in patients with RA include male sex, older age, older age at RA onset, smoking, seropositivity for rheumatoid factor or anticyclic citrullinated peptide antibodies, and moderate/high disease activity (2,8,17–19).

Polymyositis/dermatomyositis-associated ILD. The reported prevalence of ILD in patients with myositis varies according to the subset of myositis studied and the method used to identify ILD. In a retrospective analysis of medical records from 348 patients with polymyositis/dermatomyositis, 31% had ILD on HRCT (3). ILD is particularly common in patients who have antisynthetase syndrome; an analysis of medical records from 91 anti–Jo-1–positive patients with polymyositis/dermatomyositis and antisynthetase syndrome found that 73% had ILD on HRCT (20). Among 90 anti–Jo-1–positive patients enrolled in a myositis registry, 86% had ILD on chest X-ray or HRCT (21). The presence of the melanoma differentiation–associated gene-5 antibody has also been associated with ILD. In a single-center study of 64 patients with polymyositis/dermatomyositis, all of the patients who were positive for this antibody had rapidly progressive ILD compared with 24% of the patients who were negative for this antibody (22).

Other CTD-ILDs. ILD also occurs in patients with other CTDs, including primary Sjögren syndrome (23–26), mixed CTD (MCTD) (27,28), MCTD with SSc features (11), and systemic lupus erythematosus (SLE) (29). Few data are available on the prevalence of ILD in patients with these CTDs, and the reported rates vary depending on the methodology used to identify ILD. In a meta-analysis of 6157 patients with primary Sjögren syndrome across 23 studies, the prevalence of ILD was 20% in studies conducted in Asia and 10% in studies conducted in Europe (26). In a Spanish registry of 3215 patients with SLE, diffuse ILD was present in 2% of patients (29).

Other individuals who do not meet criteria for a specific CTD but have features suggestive of an autoimmune disease may develop interstitial pneumonia (30–32). In 2015, the American Thoracic Society and European Respiratory Society published classification criteria for interstitial pneumonia with autoimmune features (IPAF), including radiological or histopathological evidence of interstitial pneumonia; exclusion of other etiologies; and some features of CTD encompassing clinical symptoms (such as Raynaud symptoms or telangiectasias), serologic features, and morphologic features (31). The criteria used to define IPAF identify a heterogeneous patient population, including some patients at an early stage of CTD-ILD, and may need further refinement (33).

IDENTIFICATION OF CTD-ILDS

Given the importance of prompt identification and treatment of ILD, screening and early diagnosis are key. If ILD is suspected or confirmed in a patient with CTD, strong consideration should be given to referring the patient to a pulmonologist. It is important to note that CTD-ILD may be present even in the absence of a restrictive defect on lung function testing (such as reduced forced vital capacity [FVC]) or symptoms (34–37) and that although patients with CTD-ILD may experience worsening of dyspnea on exertion, cough, and fatigue as fibrosis progresses (38), CTD-ILD may be asymptomatic in its early stages.

Although HRCT plays a major role in the clinical detection of ILD, there is no consensus as to what extent of fibrotic abnormalities on an HRCT scan constitute clinically significant disease. There are no established guidelines for screening patients with CTD for ILD. However, recent Delphi consensus studies in the United States (39) and Europe (40) concluded that all patients with SSc should be screened for ILD, that screening should include HRCT, PFTs, and chest auscultation, and that PFTs should be repeated regularly, whereas the frequency of repeat HRCT scans should be guided by PFTs and the presence of risk factors (Figure 1) (40). The question of which patients with RA should be screened for ILD is difficult to answer given that the high prevalence of RA would make it challenging to screen all patients with RA for ILD using HRCT but only conducting HRCT in patients with symptoms would miss a significant proportion of cases. At most centers, patients with RA who have respiratory symptoms (eg, dyspnea on exertion), impaired lung function, or crackles on chest auscultation are referred for HRCT.

Patients with CTD-ILDs show a variety of patterns on HRCT scans. Patients with SSc-ILD (41), polymyositis/dermatomyositis-associated ILD (3), or antisynthetase syndrome (9) most commonly show a nonspecific interstitial pneumonia (NSIP) pattern on HRCT scans. In patients with RA-ILD, a usual interstitial pneumonia (UIP) pattern is the most commonly observed pattern on HRCT, but some patients have an NSIP pattern (17,42,43).

It is also important that patients with ILD be screened for CTD. A retrospective analysis of 114 patients referred to an ILD clinic found that 15% of patients were diagnosed with a CTD as a consequence of evaluation for ILD (7). However, positive serologies have been reported in more than one-third of patients with non-CTD ILDs (44) and should not be regarded as diagnostic for CTD-ILD. A diagnosis of CTD-ILD should be made after multidisciplinary review of clinical, laboratory, and radiological data. A thorough multidisciplinary discussion may lead to a change in the preliminary diagnosis. A retrospective analysis of 455 patients evaluated at a tertiary ILD center in Belgium found that multidisciplinary evaluation led to a change in the preliminary diagnosis in

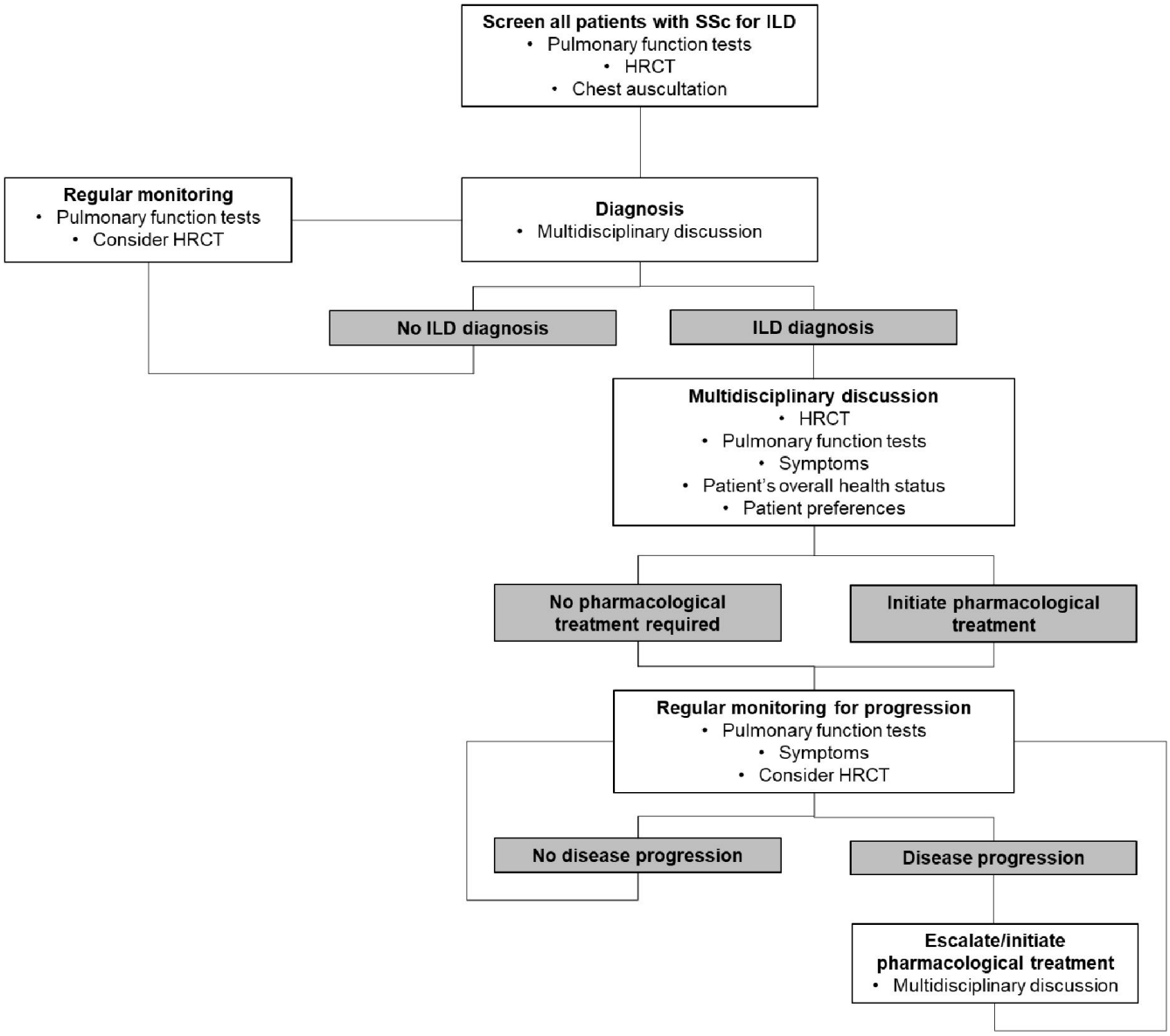

Figure 1. Suggested algorithm for screening for, monitoring and treating systemic sclerosis (SSc)–associated interstitial lung disease (ILD). Reproduced from Hoffmann-Vold et al (40). HRCT, high-resolution computed tomography.

42% of cases (45). Similarly, at a US tertiary care clinic, multidisciplinary evaluation led to a change in diagnosis in 54% of patients referred with idiopathic pulmonary fibrosis (IPF) or a CTD-ILD (46).

PROGRESSION OF CTD-ILDS

The course of CTD-ILD is variable and unpredictable. A proportion of patients with CTD-ILD develop a progressive fibrosing phenotype characterized by increasing fibrosis on HRCT, decline in lung function, worsening symptoms, and high mortality.

SSc-ILD. In a nationwide Norwegian cohort, 33% of 391 patients with SSc-ILD had severe progression of ILD (defined as a decline in FVC >10% predicted or a decline in FVC ≥5% to ≤10% predicted with a decline in diffusing capacity of the lungs for carbon monoxide [DLco] ≥15% predicted) over a mean follow-up of 6 years (5). Among 122 patients with FVC greater than 80% predicted at baseline, 10-year survival was 56% in patients who had any fibrosis on HRCT scan at baseline versus 80% in those who did not (5). An increase in the extent of fibrosis on HRCT scan and/or a decline in FVC are associated with mortality. In a seminal study conducted at a UK referral center, extensive ILD, defined as more than 30% extent of fibrosis on HRCT or 10% to 30% extent of fibrosis on HRCT with FVC of less than 70% predicted, was strongly predictive of mortality (hazard ratio 3.46; 95% confidence interval 2.19-5.46) (47). A further study showed that a relative decline in FVC of 10% or greater or a relative decline in FVC of 5% to9% with a relative decline in DLco of greater than 15% at 1 year was predictive of mortality over a 15-year follow-up (48).

It has not been established whether the fibrotic pattern on HRCT or biopsy (eg, UIP versus NSIP) affects outcomes in patients with SSc-ILD.

RA-ILD. In a single-center study of 167 patients with RA-ILD, the proportion of patients with FVC of less than 50% predicted increased from 14% at diagnosis of ILD to 22% after 5 years, whereas the proportion with DLco of less than 40% predicted increased from 29% to 40% (Figure 2) (4). ILD has a major impact on mortality in patients with RA. In the national Danish registry of patients with RA, 5-year mortality was 39.0% in patients with ILD compared with 18.2% in those without ILD (16). An analysis of US medical claims found that, among 750 patients with incident RA-ILD, 35.9% died within 5 years of diagnosis (49). A greater extent of fibrosis on HRCT scan and/or a decline in FVC are predictors of mortality in patients with RA-ILD. A prospective analysis of 169 patients with RA-ILD found that patients with more than 20% extent of ILD on HRCT scan at presentation had a more than twofold increased risk of death over the next 14 years than patients with a smaller extent of ILD (17). In patients with RA-ILD, a UIP pattern on HRCT scan or biopsy is associated with higher mortality than other fibrotic patterns (17,50,51). A meta-analysis of data from 1256 patients with RA-ILD across 10 studies estimated that the relative risk of death in patients with a UIP pattern compared with other patterns on HRCT or histology was 1.66 (51). Other studies have suggested that patients with RA-ILD and UIP have as poor a prognosis as patients with IPF (52,53).

Other CTD-ILDs. Other CTD-ILDs have been less extensively studied than SSc-ILD and RA-ILD but may also develop a progressive fibrosing phenotype (3,24). In a retrospective analysis of medical records from 107 patients with polymyositis/dermatomyositis-associated ILD seen at four university hospitals, 16% had worsened symptoms and/or a decline in FVC of 10% predicted or greater and/or a decline in DLco 15% predicted or greater over a median follow-up 34 months (3).

MONITORING AND MANAGEMENT OF CTD-ILDS

It is important that progression of fibrosing ILD is detected in a timely manner given its implications for patient counseling and treatment. All patients who develop ILD should be closely monitored for disease progression with regular PFTs and with HRCT scans as appropriate. In an online survey of 486 physicians with experience in managing progressive fibrosing ILDs, most of the respondents performed PFTs every 3 to 6 months and HRCT scans every 6 to 12 months (54). Input from a radiologist is valuable, as features evident on HRCT scans may be relevant to prognosis (55).

There is no accepted algorithm for the initiation or escalation of pharmacotherapy in patients with CTD-ILDs. Therapeutic decisions should be based on multidisciplinary discussion and take into account the patient's overall health status, risk factors for progression of ILD, and patients' preferences about their treatment. Comanagement of patients by pulmonologists, rheumatologists, and other health care professionals should involve discussion (live, phone, or virtual) of how the patient is progressing and responding to therapy. Regular monitoring, including laboratory tests, is needed when patients are receiving immunosuppression to ensure that side-effects can be managed appropriately (56,57).

Immunomodulatory therapies for SSc-ILD. Algorithms have been proposed for the initiation of treatment for SSc-ILD on the basis of HRCT findings, lung function, and symptoms (39,40,58). The use of mycophenolate and cyclophosphamide in the treatment of SSc-ILD is supported by evidence from randomized controlled trials (59–61). The Scleroderma Lung Study (SLS) I was conducted in 158 patients with SSc-ILD with onset

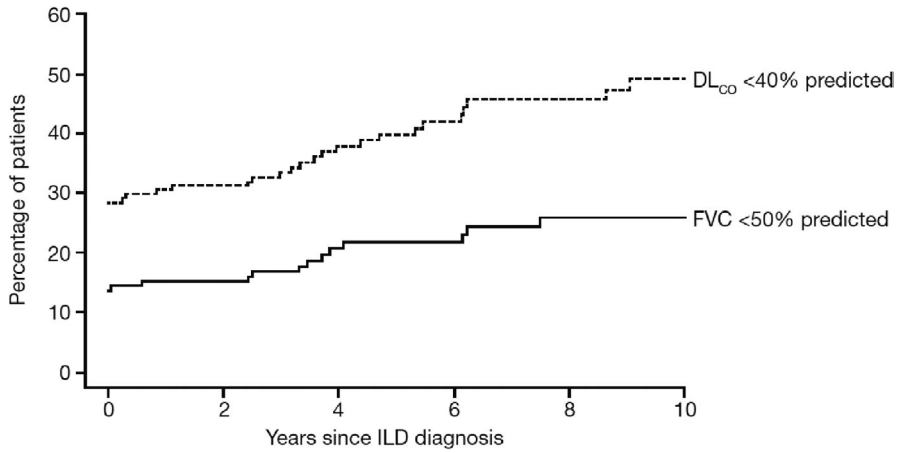

Figure 2. Proportion of patients with diffusing capacity of the lungs for carbon monoxide (DLco) of less than 40% predicted and forced vital capacity (FVC) of less than 50% predicted by time since diagnosis of rheumatoid arthritis–associated interstitial lung disease. Adapted with permission from Zamora-Legoff et al (4).

of first non-Raynaud symptom 7 years or less before screening, active alveolitis on bronchoalveolar lavage fluid and/or ground-glass opacity on HRCT scan, and an exertional dyspnea grade of 2 or more on the Mahler Dyspnea Index (60). The mean decline from baseline in FVC percentage predicted after 1 year was 1.0% in patients treated with oral cyclophosphamide compared with 2.6% in those who received placebo (60). However, a between-group difference in FVC was no longer present 1 year after patients had stopped taking the study drug (62). The SLS II was conducted in 142 patients with SSc-ILD with onset of first non-Raynaud symptom 7 years or less before screening, ground-glass opacity on HRCT, and exertional dyspnea grade of 2 or more on the Mahler Baseline Dyspnea Index (61). Patients treated with mycophenolate for 2 years had similar improvements in FVC compared with those who received oral cyclophosphamide for 1 year followed by placebo for 1 year (61). A recent randomized placebo-controlled trial of mycophenolate in 41 patients with SSc and mild ILD, defined as FVC of 70% predicted or more at baseline, found no difference in FVC decline after 6 months' treatment with mycophenolate (63).

Other than mycophenolate and cyclophosphamide, no immunosuppressant has shown efficacy as a treatment for SSc-ILD in a randomized double-blind controlled trial. Tocilizumab has been investigated as a treatment for SSc in two randomized placebo-controlled trials, FaSScinate and FocuSSced (64,65). Patients in these trials had diffuse cutaneous SSc with onset of first non-Raynaud symptom 5 years or less before screening, modified Rodnan skin score (mRSS) of 15 to 40 (FaSScinate) or 10 to 35 (FocuSSced), and active disease defined based on duration of SSc, changes in mRSS or skin involvement in the previous 6 months, the presence of tendon friction rubs, and elevated acute-phase reactant levels (64,65). Both trials failed to meet the primary endpoint (change from baseline in modified Rodnan skin score) but suggested that tocilizumab may have a benefit on lung function (64,65). A number of open-label or observational studies have suggested that patients with SSc treated with rituximab show preservation or improvement in lung function (66–69). Although glucocorticoids have been used in combination with other immunosuppressive agents in small trials, there is no evidence that corticosteroids are effective at slowing SSc-ILD progression. Further, there is concern with prolonged use of high-dose corticosteroids in patients with SSc because of an increased risk of scleroderma renal crisis (70).

Autologous hematopoietic stem cell transplantation (HSCT) is recommended in treatment guidelines issued by the European League Against Rheumatism for patients with rapidly progressive SSc at risk of organ failure following a careful assessment of a patient's risk-benefit profile (71). Three major trials have compared HSCT with cyclophosphamide in patients with diffuse cutaneous SSc (dcSSc) and internal organ involvement. ASSIST (American Scleroderma Stem Cell Versus Immune Suppression Trial), a single-center study, found that patients with diffuse cutaneous SSc and internal organ involvement treated with HSCT compared with intravenous cyclophosphamide for 6 months had improvement in mRSS and FVC at 12 months (72). The ASTIS (Autologous Stem Cell Transplantation International Scleroderma) trial, a multicenter study conducted in Europe and Canada, and the SCOT **(**Scleroderma: Cyclophosphamide or Transplantation) trial, a multicenter study conducted in North America, found improved long-term event-free and overall survival with HSCT compared with cyclophosphamide (73,74). HSCT may be considered at expert centers for patients with severe cutaneous disease who have been refractory to treatment; however, studies focused specifically on ILD have not been done.

Immunomodulatory therapies for RA-ILD. The choice of immunomodulatory therapy to treat RA-ILD is challenging in the absence of randomized controlled trials or guidelines. Corticosteroids are recommended for the treatment of RA if the disease remains active after treatment with disease-modifying drugs or biologics (75) and are commonly used to treat RA-ILD (54), but there is no evidence to support their efficacy in slowing the progression of ILD. Observational studies have suggested that rituximab (76,77) and abatacept (78,79) may slow the progression of RA-ILD, but no randomized controlled trials have been completed.

Immunomodulatory therapies for myositis-associated ILD. Corticosteroids are generally the first-line therapy for polymyositis/dermatomyositis-associated ILD, but there are no published studies to support their efficacy. Uncontrolled or retrospective studies with small sample sizes have been conducted on other therapies including intravenous cyclophosphamide (80,81), cyclosporine (82–84), tacrolimus (85,86), and infliximab (87). Retrospective analyses have indicated potential benefits of rituximab (88–90), tacrolimus, or cyclosporine (91) in patients with antisynthetase syndrome–related ILD.

Antifibrotic therapy for the treatment of SSc-ILD and chronic fibrosing ILDs with a progressive phenotype. Nintedanib has been approved by the Food and Drug Administration and other regulatory bodies for the treatment of IPF and chronic fibrosing ILDs with a progressive phenotype and for reducing the rate of decline in FVC in patients with SSc-ILD. The randomized placebo-controlled safety and efficacy of nintedanib in systemic sclerosis (SENSCIS) trial was conducted in 576 patients with SSc-ILD with onset of first non-Raynaud symptom 7 years or less before screening, FVC of 40% predicted or greater, and fibrotic ILD of 10% or greater extent on HRCT (based on assessment of the whole lung), of whom 279 were taking mycophenolate at baseline (92). Nintedanib reduced the rate of decline in FVC (ml/year) over 52 weeks by 44% versus placebo (92). In the randomized, placebo-controlled INBUILD trial, conducted in 663 subjects with non-IPF chronic fibrosing ILDs that had progressed within the previous 2 years despite management in clinical practice, nintedanib slowed the rate of decline in FVC (ml/year) over 52

weeks by 57% versus placebo (93). Approximately one-quarter (25.6%) of the patients in this trial had autoimmune disease–related ILDs (93). Although the INBUILD trial was not powered to study individual ILDs, subgroup analyses suggested that there was no heterogeneity in the rate of FVC decline across subgroups by ILD diagnosis (94) nor in the effect of nintedanib across these subgroups (Figure 3) (95). Across patient groups, the adverse events associated with nintedanib were predominantly gastrointestinal events, particularly diarrhea (92,93,96).

Investigational therapies for the treatment of CTD-ILDs. Trials of potential therapies for CTD-ILDs include SLS III, which is investigating the antifibrotic therapy pirfenidone plus mycophenolate versus mycophenolate alone in patients with SSc-ILD (NCT03221257); the rituximab versus cyclophosphamide in connective tissue disease-ILD (RECITAL) trial of rituximab versus cyclophosphamide in patients with severe and/or progressive ILD associated with SSc, myositis, or MCTD (97); the evaluation of efficacy and safety of rituximab With mycophenolate mofetil in patients With interstitial lung diseases (EvER-ILD) trial of rituximab added to mycophenolate versus mycophenolate alone in patients with CTD-ILD or idiopathic ILD plus NSIP (NCT02990286); the abatacePt in rheumatoid arthritis-ILD (APRIL) trial of abatacept in patients with RA-ILD (NCT03084419); and the treatment for rheumatoid arthritis and interstitial lung disease 1 (TRAIL1) study of pirfenidone in patients with RA-ILD (98). The results of these trials will help clinicians take a more evidence-based approach to the treatment of patients with CTD-ILDs.

Lung transplant. Patients with CTD-ILDs who have not responded to treatment should be considered for lung transplantation (99). In a retrospective review of records from 10 patients with RA-ILD and 17 patients with SSc-ILD who underwent lung transplantation at a single center, cumulative survival rates 1 year after transplant were 67% in the patients with RA-ILD and 82% in the patients with SSc-ILD (100). The patients with RA-ILD (but not SSc-ILD) showed significant improvements in symptoms following transplant (100). Another single-center study found that 1-year survival after lung transplant in 15 patients with CTD-ILDs was 80% and that survival rates over 60 months were similar to those observed in age- and sex-matched patients with IPF (101).

A holistic approach. Nonpharmacological therapies such as supplemental oxygen, pulmonary rehabilitation, and patient support can be important aspects of the care of patients with CTD-ILDs. A recent Delphi consensus exercise concluded that oxygen should be recommended for patients with fibrosing ILDs who have severe resting hypoxemia or exertional desaturation, particularly in those with symptoms or exercise limitation (102). Pulmonary rehabilitation can improve exercise performance, symptoms, and quality of life (103,104). It is important to screen patients with CTD for pulmonary arterial hypertension (PAH). Guidelines from the European Society of Cardiology and European Respiratory Society recommend screening asymptomatic patients with SSc for PAH at diagnosis using echocardiography, followed by annual screening with echocardiography and DLco (105). Echocardiography is also recommended in the evaluation of PAH symptoms in patients with other CTDs. Effective management of extrapulmonary manifestations of CTD and of comorbidities is important to maximize patient's quality of life and improve outcomes (106). Anti-reflux therapy is commonly used by patients with SSc (107), although its benefits in those without evidence of acid reflux disease remains unclear. Influenza and pneumococcal vaccinations should be provided to reduce the risk of infections. Supportive/palliative care should be considered part of patient

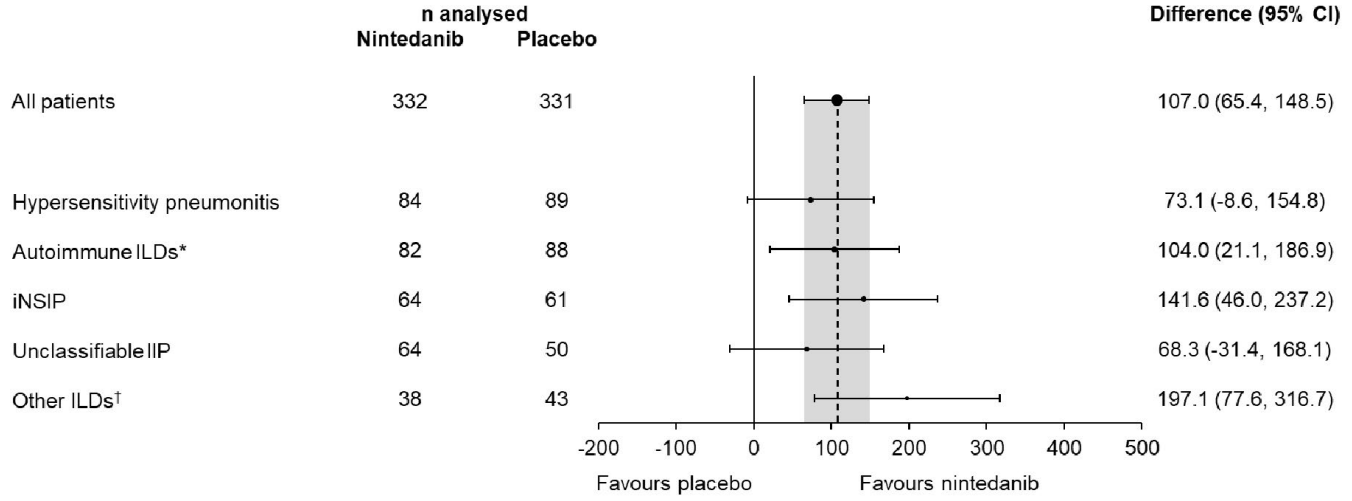

Figure 3. Rate of decline in forced vital capacity (mL/year) over 52 weeks in patients with progressive fibrosing interstitial lung diseases (ILDs) treated with nintedanib versus placebo in subgroups by ILD diagnosis. Reproduced from Wells et al (95). CI, confidence interval; IIP, idiopathic interstitial pneumonia; NSIP, nonspecific interstitial pneumonia.

care throughout the course of the disease, not only as the patient nears the end of their life (108).

CONCLUSION

ILD is a significant cause of morbidity and mortality in patients with CTDs. It is important that patients with progressive CTD-ILD are identified in clinical practice so that they can be monitored and managed appropriately. The management of patients with CTD-ILDs should be individualized and involve close collaboration between rheumatologists and pulmonologists. With the exception of SSc-ILD, the effectiveness of immunosuppression in reducing the progression of ILD remains unclear. Recently, nintedanib has been approved for use in patients with SSc-ILD and chronic fibrosing ILDs with a progressive phenotype. Although algorithms have been proposed for monitoring and managing patients with SSc-ILD, there remains a need for evidence-based clinical guidelines to improve the monitoring and management of patients with CTD-ILDs. Ongoing randomized controlled trials will provide further data to inform an evidence-based approach to the care of patients with CTD-ILDs.

A plain language summary of this article is available at https://www.usscicomms.com/respiratory/castelino_and_moua_review.

ACKNOWLEDGMENTS

Writing support was provided by Elizabeth Ng, BSc, and Wendy Morris, MSc, of FleishmanHillard Fishburn, which was contracted and funded by Boehringer Ingelheim Pharmaceuticals. Boehringer Ingelheim Pharmaceuticals was given the opportunity to review the article for medical and scientific accuracy as well as intellectual property considerations.

AUTHOR CONTRIBUTIONS

Drs. Castelino and Moua drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

REFERENCES

1. Jaeger VK, Wirz EG, Allanore Y, Rossbach P, Riemekasten G, Hachulla E, et al. Incidences and risk factors of organ manifestations in the early course of systemic sclerosis: a longitudinal EUSTAR Study. PLoS One 2016;11:e0163894.
2. Bongartz T, Nannini C, Medina-Velasquez YF, Achenbach SJ, Crowson CS, Ryu JH, et al. Incidence and mortality of interstitial lung disease in rheumatoid arthritis: a population-based study. Arthritis Rheum 2010;62:1583–91.
3. Marie I, Hatron PY, Dominique S, Cherin P, Mouthon L, Menard JF. Short-term and long-term outcomes of interstitial lung disease in polymyositis and dermatomyositis: a series of 107 patients. Arthritis Rheum 2011;63:3439–47.
4. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Progressive decline of lung function in rheumatoid arthritis-associated interstitial lung disease. Arthritis Rheumatol 2017;69:542–9.
5. Hoffmann-Vold AM, Fretheim H, Halse AK, Seip M, Bitter H, Wallenius M, et al. Tracking impact of interstitial lung disease in systemic sclerosis in a complete nationwide cohort. Am J Respir Crit Care Med 2019;200:1258–66.
6. Fathi M, Dastmalchi M, Rasmussen E, Lundberg IE, Tornling G. Interstitial lung disease, a common manifestation of newly diagnosed polymyositis and dermatomyositis. Ann Rheum Dis 2004;63:297–301.
7. Mittoo S, Gelber AC, Christopher-Stine L, Horton MR, Lechtzin N, Danoff SK. Ascertainment of collagen vascular disease in patients presenting with interstitial lung disease. Respir Med 2009;103:1152–8.
8. Koduri G, Norton S, Young A, Cox N, Davies P, Devlin J, et al. Interstitial lung disease has a poor prognosis in rheumatoid arthritis: results from an inception cohort. Rheumatology (Oxford) 2010;49:1483–9.
9. Zamora AC, Hoskote SS, Abascal-Bolado B, White D, Cox CW, Ryu JH, et al. Clinical features and outcomes of interstitial lung disease in anti-Jo-1 positive antisynthetase syndrome. Respir Med 2016;118:39–45.
10. Elhai M, Meune C, Boubaya M, Avouac J, Hachulla E, Balbir-Gurman A, et al. Mapping and predicting mortality from systemic sclerosis. Ann Rheum Dis 2017;76:1897–1905.
11. Fairley JL, Hansen D, Proudman S, Sahhar J, Ngian GS, Walker J, et al. Clinical characteristics and survival in systemic sclerosis-mixed connective tissue disease and systemic sclerosis-overlap syndrome. Arthritis Care Res (Hoboken) 2020. E-pub ahead of print.
12. Steen V, Domsic RT, Lucas M, Fertig N, Medsger TA. A clinical and serologic comparison of African-American and Caucasian patients with systemic sclerosis. Arthritis Rheum 2012;64:2986–94.
13. Nihtyanova SI, Schreiber BE, Ong VH, Rosenberg D, Moinzadeh P, Coghlan JG, et al. Prediction of pulmonary complications and long-term survival in systemic sclerosis. Arthritis Rheumatol 2014;66:1625–35.
14. Nihtyanova SI, Sari A, Harvey JC, Leslie A, Derrett-Smith EC, Fonseca C, et al. Using autoantibodies and cutaneous subset to develop outcome-based disease classification in systemic sclerosis. Arthritis Rheumatol 2020;72:465–76.
15. Myasoedova E, Crowson CS, Turesson C, Gabriel SE, Matteson EL. Incidence of extraarticular rheumatoid arthritis in Olmsted County, Minnesota, in 1995–2007 versus 1985–1994: a population-based study. J Rheumatol 2011;38:983–9.
16. Hyldgaard C, Hilberg O, Pedersen AB, Ulrichsen SP, Løkke A, Bendstrup E, et al. A population based cohort study of rheumatoid arthritis-associated interstitial lung disease: comorbidity and mortality. Ann Rheum Dis 2017;76:1700–6.
17. Kelly CA, Saravanan V, Nisar M, Arthanari S, Woodhead FA, Price-Forbes AN, et al. Rheumatoid arthritis-related interstitial lung disease: associations, prognostic factors and physiological and radiological characteristics–a large multicentre UK study. Rheumatology (Oxford) 2014;53:1676–82.
18. Doyle TJ, Patel AS, Hatabu H, Nishino M, Wu G, Osorio JC, et al. Detection of rheumatoid arthritis-interstitial lung disease is enhanced by serum biomarkers. Am J Respir Crit Care Med 2015;191:1403–12.
19. Sparks JA, He X, Huang J, Fletcher EA, Zaccardelli A, Friedlander HM, et al. Rheumatoid arthritis disease activity predicting incident clinically apparent rheumatoid arthritis-associated interstitial lung disease: a prospective cohort study. Arthritis Rheumatol 2019;71:1472–82.
20. Marie I, Josse S, Hatron PY, Dominique S, Hachulla E, Janvresse A, et al. Interstitial lung disease in anti-Jo-1 patients with antisynthetase syndrome. Arthritis Care Res (Hoboken) 2013;65:800–8.
21. Richards TJ, Eggebeen A, Gibson K, Yousem S, Fuhrman C, Gochuico BR, et al. Characterization and peripheral blood biomarker assessment of anti-Jo-1 antibody-positive interstitial lung disease. Arthritis Rheumatol 2009;60:2183–92.

22. Chen Z, Cao M, Plana MN, Liang J, Cai H, Kuwana M, et al. Utility of anti–melanoma differentiation–associated gene 5 antibody measurement in identifying patients with dermatomyositis and a high risk for developing rapidly progressive interstitial lung disease: a review of the literature and a meta-analysis. Arthritis Care Res (Hoboken) 2013;65:1316–24.
23. Nannini C, Jebakumar AJ, Crowson CS, Ryu JH, Matteson EL. Primary Sjogren's syndrome 1976–2005 and associated interstitial lung disease: a population-based study of incidence and mortality. BMJ Open 2013;3:e003569.
24. Palm O, Garen T, Berge Enger T, Jensen JL, Lund MB, Aaløkken TM, et al. Clinical pulmonary involvement in primary Sjögren's syndrome: prevalence, quality of life and mortality—a retrospective study based on registry data. Rheumatology (Oxford) 2013;52:173–9.
25. Sambataro G, Ferro F, Orlandi M, Sambataro D, Torrisi SE, Quartuccio L, et al. Clinical, morphological features and prognostic factors associated with interstitial lung disease in primary Sjögren's syndrome: a systematic review from the Italian Society of Rheumatology. Autoimmun Rev 2020;19:102447.
26. He C, Chen Z, Liu S, Chen H, Zhang F. Prevalence and risk factors of interstitial lung disease in patients with primary Sjögren's syndrome: a systematic review and meta-analysis. Int J Rheum Dis 2020;23:1009–18.
27. Gunnarsson R, Aaløkken TM, Molberg Ø, Lund MB, Mynarek GK, Lexberg AS, et al. Prevalence and severity of interstitial lung disease in mixed connective tissue disease: a nationwide, cross-sectional study. Ann Rheum Dis 2012;71:1966–72.
28. Ungprasert P, Crowson CS, Chowdhary VR, Ernste FC, Moder KG, Matteson EL. Epidemiology of mixed connective tissue disease, 1985–2014: a population-based study. Arthritis Care Res (Hoboken) 2016;68:1843–8.
29. Narváez J, Borrell H, Sánchez-Alonso F, Rúa-Figueroa I, López-Longo FJ, Galindo-Izquierdo M, et al. Primary respiratory disease in patients with systemic lupus erythematosus: data from the Spanish rheumatology society lupus registry (RELESSER) cohort. Arthritis Res Ther 2018;20:280.
30. Vij R, Noth I, Strek ME. Autoimmune-featured interstitial lung disease: a distinct entity. Chest 2011;140:1292–9.
31. Fischer A, Antoniou KM, Brown KK, Cadranel J, Corte TJ, du Bois RM, et al. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. Eur Respir J 2015;46:976–87.
32. Collins BF, Spiekerman CF, Shaw MA, Ho LA, Hayes J, Spada CA, et al. Idiopathic interstitial pneumonia associated with autoantibodies: a large case series followed over 1 year. Chest 2017;152: 103–12.
33. Sambataro G, Sambataro D, Torrisi SE, Vancheri A, Pavone M, Rosso R, et al. State of the art in interstitial pneumonia with autoimmune features: a systematic review on retrospective studies and suggestions for further advances. Eur Respir Rev 2018; 27:170139.
34. Gochuico BR, Avila NA, Chow CK, Novero LJ, Wu HP, Ren P, et al. Progressive preclinical interstitial lung disease in rheumatoid arthritis. Arch Intern Med 2008;168:159–66.
35. Doyle TJ, Dellaripa PF, Batra K, Frits ML, Iannaccone CK, Hatabu H, et al. Functional impact of a spectrum of interstitial lung abnormalities in rheumatoid arthritis. Chest 2014;146:41–50.
36. Suliman YA, Dobrota R, Huscher D, Nguyen-Kim TD, Maurer B, Jordan S, et al. Brief report: pulmonary function tests: high rate of false-negative results in the early detection and screening of scleroderma-related interstitial lung disease. Arthritis Rheumatol 2015;67:3256–61.
37. Showalter K, Hoffmann A, Rouleau G, Aaby D, Lee J, Richardson C, et al. Performance of forced vital capacity and lung diffusion cutpoints for associated radiographic interstitial lung disease in systemic sclerosis. J Rheumatol 2018;45:1572–6.
38. Ross L, Stevens W, Wilson M, Strickland G, Walker J, Sahhar J, et al. Can patient-reported symptoms be used to measure disease activity in systemic sclerosis? A multi-center study. Arthritis Care Res (Hoboken) 2020;72:1459–65.
39. Rahaghi FF, Strek ME, Southern BD, Saggar R, Hsu R, Mayes MD, et al. Expert consensus on the screening, treatment, and management of patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD), and the potential future role of anti-fibrotics in a treatment paradigm for SSc-ILD: a Delphi consensus study. Am J Respir Crit Care Med 2019;199:A7445.
40. Hoffmann-Vold AM, Maher TM, Philpot EE, Ashrafzadeh A, Barake R, Barsotti S, et al. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. Lancet Rheumatol 2020;2:E71–83.
41. Bocchino M, Bruzzese D, D'Alto M, Argiento P, Borgia A, Capaccio A, et al. Performance of a new quantitative computed tomography index for interstitial lung disease assessment in systemic sclerosis. Sci Rep 2019;9:9468.
42. Zamora-Legoff JA, Krause ML, Crowson CS, Ryu JH, Matteson EL. Patterns of interstitial lung disease and mortality in rheumatoid arthritis. Rheumatology (Oxford) 2017;56:344–50.
43. Hyldgaard C, Ellingsen T, Hilberg O, Bendstrup E. Rheumatoid arthritis-associated interstitial lung disease: clinical characteristics and predictors of mortality. Respiration 2019;98:455–60.
44. Alsumrain M, De Giacomi F, Mirza S, Moua T. Utility of autoimmune serology testing in the assessment of uncharacterized interstitial lung disease: a large retrospective cohort review. Respir Res 2017;18:161.
45. De Sadeleer LJ, Meert C, Yserbyt J, Slabbynck H, Verschakelen JA, Verbeken EK, et al. Diagnostic ability of a dynamic multidisciplinary discussion in interstitial lung diseases: a retrospective observational study of 938 cases. Chest 2018;153:1416–23.
46. Castelino FV, Goldberg H, Dellaripa PF. The impact of rheumatological evaluation in the management of patients with interstitial lung disease. Rheumatology (Oxford) 2011;50:489–93.
47. Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. Am J Respir Crit Care Med 2008;177:1248–54.
48. Goh NS, Hoyles RK, Denton CP, Hansell DM, Renzoni EA, Maher TM, et al. Short-term pulmonary function trends are predictive of mortality in interstitial lung disease associated with systemic sclerosis. Arthritis Rheumatol 2017;69:1670–8.
49. Raimundo K, Solomon JJ, Olson AL, Kong AM, Cole AL, Fischer A, et al. Rheumatoid arthritis-interstitial lung disease in the United States: prevalence, incidence, and healthcare costs and mortality. J Rheumatol 2019;46:360–9.
50. Solomon JJ, Chung JH, Cosgrove GP, Demoruelle MK, Fernandez-Perez ER, Fischer A, et al. Predictors of mortality in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J 2016;47:588–96.
51. Singh N, Varghese J, England BR, Solomon JJ, Michaud K, Mikuls TR, et al. Impact of the pattern of interstitial lung disease on mortality in rheumatoid arthritis: a systematic literature review and meta-analysis. Semin Arthritis Rheum 2019;49:358–65.
52. Kim EJ, Elicker BM, Maldonado F, Webb WR, Ryu JH, van Uden JH, et al. Usual interstitial pneumonia in rheumatoid arthritis-associated interstitial lung disease. Eur Respir J 2010;35:1322–8.
53. Moua T, Zamora Martinez AC, Baqir M, Vassallo R, Limper AH, Ryu JH. Predictors of diagnosis and survival in idiopathic pulmonary fibrosis and connective tissue disease-related usual interstitial pneumonia. Respir Res 2014;15:154.

54. Wijsenbeek M, Kreuter M, Olson A, Fischer A, Bendstrup E, Wells CD, et al. Progressive fibrosing interstitial lung diseases: current practice in diagnosis and management. Curr Med Res Opin 2019;35:2015–24.
55. Hansell DM, Goldin JG, King TE, Lynch DA, Richeldi L, Wells AU. CT staging and monitoring of fibrotic interstitial lung diseases in clinical practice and treatment trials: a position paper from the Fleischner Society. Lancet Respir Med 2015;3:483–96.
56. Meyer KC, Decker C, Baughman R. Toxicity and monitoring of immunosuppressive therapy used in systemic autoimmune diseases. Clin Chest Med 2010;31:565–88.
57. Duru N, van der Goes MC, Jacobs JW, Andrews T, Boers M, Buttgereit F, et al. EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis 2013;72:1905–13.
58. Roofeh D, Khanna D. Management of systemic sclerosis: the first five years. Curr Opin Rheumatol 2020;32:228–37.
59. Hoyles RK, Ellis RW, Wellsbury J, Lees B, Newlands P, Goh NS, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. Arthritis Rheum 2006;54:3962–70.
60. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006;354:2655–66.
61. Tashkin DP, Roth MD, Clements PJ, Furst DE, Khanna D, Kleerup EC, et al. Mycophenolate mofetil versus oral cyclophosphamide in scleroderma-related interstitial lung disease (SLS II): a randomised controlled, double-blind, parallel group trial. Lancet Respir Med 2016;4:708–19.
62. Tashkin DP, Elashoff R, Clements PJ, Roth MD, Furst DE, Silver RM, et al. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. Am J Respir Crit Care Med 2007;176:1026–34.
63. Naidu GS, Sharma SK, Adarsh MB, Dhir V, Sinha A, Dhooria S, et al. Effect of mycophenolate mofetil (MMF) on systemic sclerosis-related interstitial lung disease with mildly impaired lung function: a double-blind, placebo-controlled, randomized trial. Rheumatol Int 2020;40:207–16.
64. Khanna D, Denton CP, Jahreis A, van Laar JM, Frech TM, Anderson ME, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. Lancet 2016;387:2630–40.
65. Khanna D, Lin CJ, Furst DE, Goldin J, Kim G, Kuwana M, et al. Tocilizumab in systemic sclerosis: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med 2020;8:963–74.
66. Daoussis D, Liossis SN, Tsamandas AC, Kalogeropoulou C, Kazantzi A, Sirinian C, et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. Rheumatology (Oxford) 2010;49:271–80.
67. Daoussis D, Liossis SN, Tsamandas AC, Kalogeropoulou C, Paliogianni F, Sirinian C, et al. Effect of long-term treatment with rituximab on pulmonary function and skin fibrosis in patients with diffuse systemic sclerosis. Clin Exp Rheumatol 2012;30:S17–22.
68. Daoussis D, Melissaropoulos K, Sakellaropoulos G, Antonopoulos I, Markatseli TE, Simopoulou T, et al. A multicenter, open-label, comparative study of B-cell depletion therapy with rituximab for systemic sclerosis-associated interstitial lung disease. Semin Arthritis Rheum 2017;46:625–31.
69. Jordan S, Distler JH, Maurer B, Huscher D, van Laar JM, Allanore Y, et al. Effects and safety of rituximab in systemic sclerosis: an analysis from the European Scleroderma Trial and Research (EUSTAR) group. Ann Rheum Dis 2015;74:1188–94.
70. Trang G, Steele R, Baron M, Hudson M. Corticosteroids and the risk of scleroderma renal crisis: a systematic review. Rheumatol Int 2012;32:645–53.
71. Kowal-Bielecka O, Fransen J, Avouac J, Becker M, Kulak A, Allanore Y, et al. Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis 2017;76:1327–39.
72. Burt RK, Shah SJ, Dill K, Grant T, Gheorghiade M, Schroeder J, et al. Autologous non-myeloablative haemopoietic stem-cell transplantation compared with pulse cyclophosphamide once per month for systemic sclerosis (ASSIST): an open-label, randomised phase 2 trial. Lancet 2011;378:498–506.
73. Van Laar JM, Farge D, Sont JK, Naraghi K, Marjanovic Z, Larghero J, et al. Autologous hematopoietic stem cell transplantation vs intravenous pulse cyclophosphamide in diffuse cutaneous systemic sclerosis: a randomized clinical trial. JAMA 2014;311:2490–8.
74. Sullivan KM, Goldmuntz EA, Keyes-Elstein L, McSweeney PA, Pinckney A, Welch B, et al. Myeloablative autologous stem-cell transplantation for severe scleroderma. N Engl J Med 2018;378:35–47.
75. Singh JA, Saag KG, Bridges SL, Akl EA, Bannuru RR, Sullivan MC, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2016;68:1–25.
76. Md Yusof MY, Kabia A, Darby M, Lettieri G, Beirne P, Vital EM, et al. Effect of rituximab on the progression of rheumatoid arthritis-related interstitial lung disease: 10 years' experience at a single centre. Rheumatology (Oxford) 2017;56:1348–57.
77. Vadillo C, Nieto MA, Romero-Bueno F, Leon L, Sanchez-Pernaute O, Rodriguez-Nieto MJ, et al. Efficacy of rituximab in slowing down progression of rheumatoid arthritis-related interstitial lung disease: data from the NEREA Registry. Rheumatology (Oxford) 2020;59:2099–108.
78. Fernandez-Diaz C, Loricera J, Castaneda S, Lopez-Mejias R, Ojeda-Garcia C, Olive A, et al. Abatacept in patients with rheumatoid arthritis and interstitial lung disease: A national multicenter study of 63 patients. Semin Arthritis Rheum 2018;48:22–7.
79. Cassone G, Manfredi A, Atzeni F, Venerito V, Vacchi C, Picerno V, et al. Safety of abatacept in Italian patients with rheumatoid arthritis and interstitial lung disease: a multicenter retrospective study. J Clin Med 2020;9:277.
80. Yamasaki Y, Yamada H, Yamasaki M, Ohkubo M, Azuma K, Matsuoka S, et al. Intravenous cyclophosphamide therapy for progressive interstitial pneumonia in patients with polymyositis/dermatomyositis. Rheumatology (Oxford) 2007;46:124–30.
81. Mira-Avendano IC, Parambil JG, Yadav R, Arrossi V, Xu M, Chapman JT, et al. A retrospective review of clinical features and treatment outcomes in steroid-resistant interstitial lung disease from polymyositis/dermatomyositis. Respir Med 2013;107:890–6.
82. Miyake S, Ohtani Y, Sawada M, Inase N, Miyazaki Y, Takano S. Usefulness of cyclosporine A on rapidly progressive interstitial pneumonia in dermatomyositis. Sarcoidosis Vasc Diffuse Lung Dis 2002;19:128–33.
83. Nagasaka K, Harigai M, Tateishi M, Hara M, Yoshizawa Y, Koike T, et al. Efficacy of combined treatment with cyclosporine A and corticosteroids for acute interstitial pneumonitis associated with dermatomyositis. Mod Rheumatol 2003;13:231–8.
84. Go DJ, Park JK, Kang EH, Kwon HM, Lee YJ, Song YW, et al. Survival benefit associated with early cyclosporine treatment for dermatomyositis-associated interstitial lung disease. Rheumatol Int 2016;36:125–31.
85. Suzuka T, Kotani T, Takeuchi T, Fujiki Y, Hata K, Yoshida S, et al. Efficacy and safety of oral high-trough level tacrolimus in acute/

subacute interstitial pneumonia with dermatomyositis. Int J Rheum Dis 2019;22:303–13.
86. Kurita T, Yasuda S, Oba K, Odani T, Kono M, Otomo K, et al. The efficacy of tacrolimus in patients with interstitial lung diseases complicated with polymyositis or dermatomyositis. Rheumatology (Oxford) 2015;54:39–44.
87. Chen D, Wang XB, Zhou Y, Zhu XC. Efficacy of infliximab in the treatment for dermatomyositis with acute interstitial pneumonia: a study of fourteen cases and literature review. Rheumatol Int 2013;33:2455–8.
88. Andersson H, Sem M, Lund MB, Aalokken TM, Gunther A, Walle-Hansen R, et al. Long-term experience with rituximab in anti-synthetase syndrome-related interstitial lung disease. Rheumatology (Oxford) 2015;54:1420–8.
89. Doyle TJ, Dhillon N, Madan R, Cabral F, Fletcher EA, Koontz DC, et al. Rituximab in the treatment of interstitial lung disease associated with antisynthetase syndrome: a multicenter retrospective case review. J Rheumatol 2018;45:841–50.
90. Marie I, Dominique S, Janvresse A, Levesque H, Menard JF. Rituximab therapy for refractory interstitial lung disease related to antisynthetase syndrome. Respir Med 2012;106:581–7.
91. Labirua-Iturburu A, Selva-O'Callaghan A, Martinez-Gomez X, Trallero-Araguas E, Labrador-Horrillo M, Vilardell-Tarres M. Calcineurin inhibitors in a cohort of patients with antisynthetase-associated interstitial lung disease. Clin Exp Rheumatol 2013; 31:436–9.
92. Distler O, Highland KB, Gahlemann M, Azuma A, Fischer A, Mayes MD, et al. Nintedanib for systemic sclerosis-associated interstitial lung disease. N Engl J Med 2019;380:2518–28.
93. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. Nintedanib in progressive fibrosing interstitial lung diseases. N Engl J Med 2019;381:1718–27.
94. Brown KK, Martinez FJ, Walsh SL, Thannickal VJ, Prasse A, Schlenker-Herceg R, et al. The natural history of progressive fibrosing interstitial lung diseases. Eur Respir J 2020;55:2000085.
95. Wells AU, Flaherty KR, Brown KK, Inoue Y, Devaraj A, Richeldi L, et al. Nintedanib in patients with progressive fibrosing interstitial lung diseases-subgroup analyses by interstitial lung disease diagnosis in the INBUILD trial: a randomised, double-blind, placebo-controlled, parallel-group trial. Lancet Respir Med 2020;8:453–60.
96. Seibold JR, Maher TM, Highland KB, Assassi S, Azuma A, Hummers LK, et al. Safety and tolerability of nintedanib in patients with systemic sclerosis-associated interstitial lung disease: data from the SENSCIS trial. Ann Rheum Dis 2020;79:1478–84.
97. Saunders P, Tsipouri V, Keir GJ, Ashby D, Flather MD, Parfrey H, et al. Rituximab versus cyclophosphamide for the treatment of connective tissue disease-associated interstitial lung disease (RECITAL): study protocol for a randomised controlled trial. Trials 2017;18:275.
98. Solomon JJ, Danoff SK, Goldberg HJ, Woodhead F, Kolb M, Chambers DC, et al. The design and rationale of the TRAIL trial: a randomized double-blind phase 2 clinical trial of pirfenidone in rheumatoid arthritis-associated interstitial lung disease. Adv Ther 2019;36:3279–87.
99. Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, et al. A consensus document for the selection of lung transplant candidates: 2014—an update from the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2015;34:1–15.
100. Yazdani A, Singer LG, Strand V, Gelber AC, Williams L, Mittoo S. Survival and quality of life in rheumatoid arthritis-associated interstitial lung disease after lung transplantation. J Heart Lung Transplant 2014;33:514–20.
101. Park JE, Kim SY, Song JH, Kim YS, Chang J, Lee JG, et al. Comparison of short-term outcomes for connective tissue disease-related interstitial lung disease and idiopathic pulmonary fibrosis after lung transplantation. J Thorac Dis 2018;10:1538–47.
102. Lim RK, Humphreys C, Morisset J, Holland AE, Johannson KA, O2 Delphi Collaborators. Oxygen in patients with fibrotic interstitial lung disease: an international Delphi survey. Eur Respir J 2019;54:1900421.
103. Ryerson CJ, Cayou C, Topp F, Hilling L, Camp PG, Wilcox PG, et al. Pulmonary rehabilitation improves long-term outcomes in interstitial lung disease: a prospective cohort study. Respir Med 2014;108:203–10.
104. Dowman LM, McDonald CF, Hill CJ, Lee AL, Barker K, Boote C, et al. The evidence of benefits of exercise training in interstitial lung disease: a randomised controlled trial. Thorax 2017;72:610–9.
105. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015;46:903–75.
106. Loza E, Lajas C, Andreu JL, Balsa A, González-Álvaro I, Illera O, et al. Consensus statement on a framework for the management of comorbidity and extra-articular manifestations in rheumatoid arthritis. Rheumatol Int 2015;35:445–58.
107. Meier FM, Frommer KW, Dinser R, Walker UA, Czirjak L, Denton CP, et al. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. Ann Rheum Dis 2012;71:1355–60.
108. Lanken PN, Terry PB, Delisser HM, Fahy BF, Hansen-Flaschen J, Heffner JE, et al. An official American Thoracic Society clinical policy statement: palliative care for patients with respiratory diseases and critical illnesses. Am J Respir Crit Care Med 2008;177:912–27.