Interstitial lung disease (ILD) is a frequent complication of patients with connective tissue disease (CTD) and significantly affects morbidity and mortality. Disease course may vary from stable or mildly progressive to more severe, with rapid loss of lung function. We conducted a search of PubMed (National Library of Medicine) and the Web of Science Core Collection using the key words lung, pulmonary, pneumonia, pneumonitis, and alveolar and subtypes of CTD. All clinical studies from January 1, 1980, through September 1, 2018, were reviewed for descriptions of specific therapies and their efficacy or safety and were categorized as controlled interventional trials, observational prospective or retrospective cohort studies, case series (>5 patients), and case reports (<5 patients). Low-quality reports (<5 patients) before 2000, reviews, editorials, popular science papers, and letters to the editor without complete descriptions of the therapies used or their outcomes were excluded. Directed therapy for CTD-ILD is dominated by empirical use of immunosuppressive agents, with the decision to treat, treatment choice, and treatment duration limited to cases and cohort observations. Only a few higher-level controlled studies were available specifically in scleroderma-related ILD. We summarize herein for the clinician the published treatment scope and experience, highlighted clinical response, and common adverse reactions for the management of CTD-ILD.
systemic toxicities from therapy if not indicated. Emphasis should be given to closely following reported and objectively measured outcomes, such as improvements in respiratory symptoms, pulmonary function test (PFT) results, and radiologic findings, after therapy has been started. Although no specific criteria are given for CTD-ILD, using parameters commonly pursued in other ILDs, such as forced vital capacity (FVC) and resolution of acute ground glass or reticular findings on chest computed tomography (CT), may be helpful. Careful monitoring for medication-related adverse effects and complications from immunosuppression, including bone marrow suppression and opportunistic infections, are also important for minimizing drug or treatment toxicities and reducing morbidity.15

There is currently little high-level evidence to guide the management of CTD-ILD. Prospective randomized controlled trials (RCTs) have been completed only in SSc-ILD.16-22 Review of the available literature suggests that immunosuppressive agents are the initial mainstay treatment of choice. A general overview of reported medical options with typical dosing and common adverse effects is provided in Table 1. Novel approaches, including biological agents, autologous hematopoietic stem cell transplant (HSCT), and antifibrotic drugs, have been reported to be successful in selected patients, with further investigations ongoing regarding their generalized efficacy and safety. Herein, we present for the clinician a summary of the available evidence for treatment of the CTD-ILDs and discuss the reported benefits and limitations of each approach. For this report, we did not include a review of undifferentiated CTD–ILD or the recently identified entity of interstitial pneumonia with autoimmune features23 given their varied definitions (narrow vs broad)24,25 and only recent description, respectively.

EVIDENCE FOR DISEASE-SPECIFIC MANAGEMENT OF THE CTD-ILDS BY DISEASE TYPE

We conducted a search on PubMed (National Library of Medicine) and Web of Science Core Collection using the key words lung, pulmonary, pneumonia, pneumonitis, and alveolar and subtypes of CTD (eg, (lung[Title] OR pulmonary[Title] OR pneumonia[Title] OR pneumonitis[Title] OR alveolar[Title]) AND rheumatoid arthritis [Title])). All available clinical studies from January 1, 1980, through September 1, 2018, were reviewed for descriptions of specific therapies and their efficacy or safety and were categorized as controlled interventional trials, observational prospective or retrospective cohort studies, case series (>5 patients), and case reports (<5 patients). Included publications were limited to English language and involved only adults (age >18 years), with no restrictions for race, ethnicity, or geographic location. Reviews, editorials, popular science papers, and letters to the editor without complete descriptions of the therapies used or their outcomes were excluded. Low-quality (case reports [<5 patients]) reports before 2000 were excluded, highlighting only controlled trials or larger case series or cohorts from before that year. An initial search found 7959 publications, and their abstracts were reviewed for the exclusion of topics unrelated to the specific treatment of CTD-ILDs. Excluded publications were general descriptions of...
<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Typical doses</th>
<th>Common adverse effects</th>
<th>Reported pulmonary adverse reactions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids (prednisone and methylprednisolone)</td>
<td>Anti-inflammatory and immunosuppressant</td>
<td>Acute phase: 0.5-1 g/d intravenously for 3 d, followed by 1 mg/kg per day PO Chronic phase: 0.5-1 mg/kg per day PO</td>
<td>Infection; decreased carbohydrate tolerance; weight gain; psychosis; insomnia; osteoporosis; osteonecrosis of femoral and humeral heads</td>
<td>None</td>
<td>Induction therapy mainstay in most CTD-ILD except for SSc-ILD. Long-term exposure should be avoided if possible. Pneumocystis prophylaxis where appropriate (20 mg/d for ≥30 d of exposure).</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>Inhibitor of the inosine monophosphatedehydrogenase; inhibits B- and T-lymphocyte proliferation</td>
<td>1.0-1.5 g bid</td>
<td>Infection; edema; bone marrow suppression; gastrointestinal toxicity; neoplasia</td>
<td>Pneumonia</td>
<td>Increasingly used as maintenance corticosteroid-sparing agent in CTD-ILDs. Demonstrated equal efficacy with cyclophosphamide but less toxic in the treatment of SSc-ILD; avoid antacids to maximize absorption. Complete blood cell monitoring weekly initially to monthly in the first year of therapy.</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Inhibitor of purine synthesis, depletes adenosine and guanosine in activated T cells</td>
<td>1-2 mg/kg PO daily</td>
<td>Infection; GI intolerance; leukopenia</td>
<td>Interstitial pneumonia; pulmonary nodulosis</td>
<td>Generally effective and well-tolerated as a maintenance corticosteroid-sparing agent in multiple CTD-ILDs. Assess thiopurine methyltransferase enzyme profile before use with initial weekly blood count monitoring then monthly while on therapy or with dose adjustment.</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Alkylating immunosuppressant</td>
<td>1-2 mg/kg per day PO or 500-1000 mg IV pulse induction (various induction intervals reported)</td>
<td>Infection; alopecia; bone marrow suppression; cardiac toxicity; GI intolerance; hemorrhagic cystitis</td>
<td>Pneumonia</td>
<td>A potent corticosteroid-sparing immunosuppressant, first-line therapy in most severe and refractory CTD, multiple toxicities and increased risk of neoplasm. Avoid long-term exposure. Complete blood cell count and urinalysis (assessing for hematuria) during therapy.</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Binds to immunophilins in lymphocytes, alters the activity of calcineurin</td>
<td>1 mg bid; 0.075 mg/kg bid</td>
<td>Infection; hypertension; hepatic dysfunction; renal dysfunction; electrolyte disturbances;</td>
<td>Interstitial pneumonia</td>
<td>Similar mechanism to cyclosporine A but with greater potency. Anecdotally reported in the</td>
</tr>
<tr>
<td>Medication</td>
<td>Mechanism</td>
<td>Typical doses</td>
<td>Common adverse effects</td>
<td>Reported pulmonary adverse reactions</td>
<td>Comments</td>
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<tr>
<td>Cyclosporine A</td>
<td>Leading to inhibition of T-cell activation</td>
<td>3-7.5 mg/kg per day up to 150 mg bid in resistant PM/DM-ILD cases</td>
<td>Diabetes mellitus; GI tract intolerance; leukopenia</td>
<td>Treatment of refractory DM/PM-ILD and ARS-ILD.</td>
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<tr>
<td>Pirfenidone</td>
<td>An antifibrotic agent with reported inhibition of proinflammatory cytokines and inhibition of inflammatory cell proliferation</td>
<td>Days 1-7: 267 mg PO TID (801 mg/d); Days 8-14: 534 mg PO TID (1602 mg/d); Day 15 and thereafter (maintenance): 801 mg PO TID; not to exceed 2403 mg/d</td>
<td>GI tract intolerance; skin reaction; hepatic dysfunction</td>
<td>None</td>
<td>Studied in SSc-ILD and DM-ILD, anecdotally reported in pSS-ILD and SLE-ILD.</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Tyrosine kinase inhibitor that binds to c-abl with resultant downregulation of TGF-β</td>
<td>100 mg/d and increased by 100 mg every 2 wk (up to 600 mg/d)</td>
<td>Infection; hematologic toxicity; hepatotoxicity; musculoskeletal disorders; GI tract intolerance</td>
<td>Interstitial pneumonia</td>
<td>Studied in SSc-ILD.</td>
</tr>
<tr>
<td>Rituximab</td>
<td>A chimeric monoclonal antibody that targets CD20 surface antigen leading to B-cell depletion</td>
<td>500-1000 mg IV infusion, repeat after 2 wk, repeat course every 24 wk or based on clinical evaluation (but no sooner than 16 wk)</td>
<td>Infection; serum sickness; cardiovascular complications; GI tract intolerance; blood and lymphatic disorders</td>
<td>Interstitial pneumonia</td>
<td>Approved for the treatment of RA and antineutrophil cytoplasmic antibody-associated vasculitis. Multiple cohort and series studies reported in several CTD-ILD subtypes. Complete blood cell count monitoring monthly to every 2-4 mo.</td>
</tr>
<tr>
<td>Abatacept</td>
<td>Antagonist of T-lymphocyte co-stimulation</td>
<td>Weight-based infusion (500, 750, or 1000 mg infused over 30 min) repeated at weeks 2 and 4 and every 4 wk thereafter; may transition to 125 mg/wk SC</td>
<td>Infection; headache; nasopharyngitis; GI tract intolerance</td>
<td>Interstitial pneumonia</td>
<td>Biological agent mostly studied in the treatment of RA-ILD. Hepatitis B and latent tuberculous screening before use.</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Tumor necrosis factor inhibitor</td>
<td>40 mg SC every 2 wk</td>
<td>Infection; increased creatine phosphokinase; headache; rash</td>
<td>Interstitial pneumonia</td>
<td>Anecdotal reporting in the treatment of RA-ILD and DM/PM-ILD, latent tuberculosis screening before use.</td>
</tr>
<tr>
<td>Etanercept</td>
<td></td>
<td>50 mg SC once weekly; 25 mg SC twice weekly</td>
<td>Infection; headache; rhinitis</td>
<td>Interstitial pneumonia, pulmonary nodulosis</td>
<td>Biological agent studied in the treatment of RA-ILD, latent tuberculosis screening before use.</td>
</tr>
</tbody>
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Continued on next page
multiple agents or multiple disease subtypes without a clear delineation of treatment effects, were unavailable, or were retracted. Two hundred sixty-nine reports were included describing specific treatments, related adverse effects, or outcomes in CTD-ILDs, including 8 controlled trials, 140 observational studies, and 121 case reports or case series (Figure).

RHEUMATOID ARTHRITIS ILD

Lung involvement is frequent and significantly implicates poor survival, contributing up to 20% of the overall mortality in patients with RA. In general, the predominant radiologic patterns of RA-ILD are nonspecific interstitial pneumonia (NSIP) and usual interstitial pneumonia (UIP), followed less commonly by lymphocytic interstitial pneumonia (LIP) and organizing pneumonia (OP). Histologic and/or radiologic patterns are associated with prognosis, as patients with RA-ILD with UIP-like findings have a poorer prognosis than those without.

Published evidence for the treatment of RA-ILD includes 8 case reports involving abatacept (n=1), etanercept (n=1), tacrolimus (n=1), infliximab (n=2), mycophenolate mofetil (n=1), and rituximab (n=2); 27 observational cohort studies involving abatacept (n=3), cyclophosphamide (n=1), mycophenolate mofetil (n=1), methotrexate (n=6), rituximab (n=12), and tocilizumab (n=2); and no controlled trials (see Supplemental Figure 1, available online at http://www.mayoclinicproceedings.org, and Table 2 for additional summarized outcomes, adverse events, and study-specific total number of patients reported).

Corticosteroids remain a first-choice empirical treatment directed at RA-ILD. Long-term exposure should be avoided even in modest doses, considering its known adverse effects. A recent report involving 181 patients with RA-ILD from a single center with median follow-up of 3.1 years found a higher risk of serious infection (need for antimicrobial agents or hospitalization) in patients taking prednisone, greater than 10 mg/d.
have been combined with other immunosuppressive agents, such as mycophenolate and cyclophosphamide, with limited observational data. Rojas-Serrano et al34 retrospectively studied 40 patients treated with corticosteroids and disease-modifying antirheumatic drugs followed for a minimum of 4 months, noting improvement in baseline FVC (P < .004). Intensive immunosuppressive therapy with cyclophosphamide seemed to improve outcomes in severe cases by stabilizing pulmonary function decline and improving ground glass opacities and consolidation on CT.35 Mycophenolate mofetil was cited in a case report as having similar efficacy to that described in other types of CTD-ILD.36

Biological agents have significantly improved joint symptoms for patients with RA but have also been reported in the directed treatment of RA-ILD, particularly in more severe or refractory cases. Data from 2 large recent observational studies involving patients with RA-ILD treated with rituximab suggested a protective and therapeutic effect.37,38 In a report of a single-center retrospective study involving 56 patients, relative median FVC% changes during the 6 to 12 months before and after rituximab treatment were −2.4% and 1.2% (P = .025), respectively. The diffusion capacity for carbon monoxide (DLCO) decline was −4.4% and −1.3% (P = .045). Of the 14 available HRCT comparisons in that study performed in patients who exhibited respiratory deterioration or decline in PFT parameters, 1 (7%) experienced improvement, 6 (43%) were stable, and 7 (50%) had worsening radiologic findings. Overall, the authors concluded that 52% of the patients remained stable and 16% improved.38 Fernandez-Diaz et al39 conducted a multicenter uncontrolled observational study of 63 patients with RA-ILD treated with abatacept, a T-cell signaling inhibitor. During mean ± SD follow-up of 9.4 ± 3.2 months, relative to baseline, two-thirds of the patients remained stable and one-quarter reported improvement in dyspnea based on the modified Medical Research Council dyspnea scale (P < .01). FVC% remained stable in nearly two-thirds of the patients, with improvement observed in one-fifth (P < .05); DLCO remained stable in two-thirds and improved in one-quarter as assessed at 6 months (P < .05) and 12 months (P < .01).39 Nakashita et al40 reviewed the records of 16 patients with RA-ILD treated with abatacept for more than a year. After drug initiation, no patients experienced further deterioration of ILD as defined by stabilization of CT findings and decreased levels of the serum markers KL-6 and MMP-3.40 Other tumor necrosis factor inhibitors (infliximab and etanercept) and a humanized anti–interleukin 6 receptor monoclonal antibody (tocilizumab) have been reported in the treatment of RA in general, with little reported on its effect on related ILD, as limited to case reports or case series.41-43

In summary, lacking high-level evidence to guide the use of additional immunosuppressive therapies, corticosteroids are an initial choice for the directed treatment of RA-ILD. However, prolonged courses should
be avoided due to related adverse effects. Corticosteroids in conjunction with corticosteroid-sparing agents, such as azathioprine and mycophenolate mofetil, are a consideration. As preferred long-term therapy or with extrapulmonary disease, biological agents may be an effective approach for ILD, with rituximab having the most reported evidence, followed by infliximab, etanercept, and tocilizumab. In general, clinicians should be cautious of infectious complications or direct pulmonary toxicity, with chest radiography and PFT performed at baseline as comparisons should respiratory symptoms continue to worsen. A summary of drug-related study target outcomes and adverse effects is reported in Table 2.

### SYSTEMIC SCLEROSIS ILD

Interstitial lung disease is the most significant factor contributing to mortality in patients with SSc, with a high but divergent reported incidence ranging from 40% to 91%. Radiologically and pathologically, NSIP is the predominant pattern, being present in more than half of all patients with SSc-ILD, followed by UIP.

Published evidence for the treatment of SSc-ILD includes 24 case reports involving azathioprine (n=3), cyclosporin A (n=3), cyclosporin A + azathioprine (n=1), cyclophosphamide (n=2), infliximab (n=1), cyclophosphamide + imatinib (n=1), mycophenolate mofetil (n=2), pirfenidone (n=3), rituximab (n=9), intravenous immunoglobulin G (IVIG) (n=1), and tocilizumab (n=1); 74 observational cohort studies involving azathioprine (n=6), corticosteroids alone (n=1), cyclophosphamide (n=38), tacrolimus (n=1), imatinib (n=2), mycophenolate mofetil (n=22), pirfenidone (n=2), rituximab (n=15), and stem cell transplant (n=2); and 8 controlled trials involving cyclophosphamide followed by azathioprine (n=1), cyclophosphamide (n=2), cyclophosphamide vs azathioprine (n=1), cyclophosphamide vs mycophenolate mofetil (n=1), cyclophosphamide vs rituximab (n=1), mycophenolate mofetil (n=1), tocilizumab (n=1), or cyclophosphamide vs HSCT (n=1) (see Supplemental Figure 2, available online at http://www.mayoclinicproceedings.org, and Table 3 for additional summarized outcomes, adverse events, and study-specific total number of patients reported).
Cyclophosphamide remains a cornerstone treatment for SSc-ILD based on more robust evidence from previous multiple observational studies and RCTs. The most substantial evidence supporting cyclophosphamide comes from the Scleroderma Lung Study I, a multicenter double-blinded RCT of oral cyclophosphamide therapy in 158 patients with SSc-ILD. Treatment with 1 year of oral cyclophosphamide, at least 2 mg/kg per day, was compared with placebo use, with change in FVC as the primary outcome. Patients treated with cyclophosphamide exhibited slowing of FVC decline (mean absolute difference in adjusted 12-month FVC, 2.53%; \( P < .03 \)), with improved dyspnea, total lung capacity, and modified Rodnan skin scores (mRSSs) compared with controls at 1 year. However, such benefits seemed diminished at 2 years. Hoyles et al \(^{17} \) conducted an RCT comparing monthly intravenous (IV) cyclophosphamide for 6 months plus prednisolone and azathioprine compared with placebo in patients with SSc-ILD; however, the suggested FVC improvement in the treatment group was not statistically significant.

Mycophenolate mofetil seems to be an equally effective and safer alternative to cyclophosphamide for the treatment of SSc-ILD. Although Naidu et al \(^ {21} \) recently reported in a small RCT that mycophenolate seemed to be more effective at controlling skin manifestations than stabilizing ILD progression, \(^ {21} \) mycophenolate has gained recent support as preferred first-line therapy based on data from the Scleroderma Lung Study II. This multicenter, double-blinded RCT randomized 142 patients to receive 2 years of mycophenolate vs 1 year of oral cyclophosphamide followed by 1 year of placebo. The primary outcome was change in FVC% during the 2-year period. Adjusted FVC% change from baseline to 24 months was 2.17 (95% CI, 0.53-3.84) and 2.86 (95% CI, 1.19-4.58) in the mycophenolate and cyclophosphamide group, respectively. There was no relative difference between

| TABLE 3. Studies (2000-2018) Reporting Treatment and Adverse Effects of Medical Therapy for Systemic Sclerosis ILD* |
|-------------|-----------------|-----------------|-----------------|
| Treatment   | Case reports/case series | Observational studies | RCTs |
|             | Studies/patients (No.) | Outcome measurements | Studies/patients (No.) | Outcome measurements | Studies/patients (No.) | Outcome measurements | Adverse events |
| AZA         | 3/3              | 1.2,6            | 6/194           | 1.2,4,5            | 2/105           | 1.2,4,6            | 1,3,5,8,13 |
| CS          | 0/0              | ND              | 1/71            | I                | 0/0             | ND              | ND              |
| CsA         | 3/3              | 1.2,6            | 0/0             | ND              | 0/0             | ND              | ND              |
| CsA+AZA     | 1/1              | 1.2,6            | 0/0             | ND              | 0/0             | ND              | ND              |
| CYC         | 2/2              | 1.2,6            | 38/2248         | 1.2,4,5,6         | 6/474           | 1.2,4,5,6         | 1,3,9,13,14,15 |
| CYC+IMT     | 1/5              | 1.2,6            | 0/0             | ND              | 0/0             | ND              | ND              |
| FK506       | 0/0              | ND              | 1/20            | 1.2              | 0/0             | ND              | ND              |
| IXF         | 1/1              | 1.2,6            | 0/0             | ND              | 0/0             | ND              | ND              |
| IMT         | 0/0              | ND              | 2/47            | 1.2,4,6          | 0/0             | ND              | 1,3,7,9 |
| MMF         | 2/6              | 1.2,6            | 22/1213         | 1.2,4,5,6,8       | 2/183           | 1.2,4,5,6         | 1,3,7,8,9,15 |
| RTX         | 9/19             | 1.2,6            | 15/389          | 1.2,4,5,6         | 1/60            | 1.2,5             | 1,2,3,9 |
| PFd         | 3/7              | 1.2,6            | 2/88            | 1.2,4             | 0/0             | ND              | 1.3,5,9,11 |
| TCZ         | 1/9              | 1.2,6            | 0/0             | ND              | 1/87            | 1.2             | 1,2,3,4,5,6,7,9,13 |

*ILD = interstitial lung disease; ND = no data or data not accessible; RCT = randomized controlled trial.

AZA = azathioprine; CS = corticosteroid; CsA = cyclosporine A; CYC = cyclophosphamide; FK506 = tacrolimus; IXF = infliximab; IMT = imatinib; MMF = mycophenolate mofetil; PFD = pirfenidone; RTX = rituximab; TCZ = tocilizumab.

1 Absolute difference in adjusted 12-month FVC, 2.53%; \( P < .03 \).

2 Pulmonary function test parameters; 2 = radiographic findings; 4 = respiratory questionnaires (eg, modified Medical Research Council dyspnea scale, 36-item Short Form Health Survey); 5 = 6-minute walk test; 6 = respiratory syndrome; 8 = doses of prednisolone.

3 Infections and infestations; 2 = cardiac disorders; 3 = gastrointestinal disorders; 4 = musculoskeletal, osteal, or connective tissue disorders; 5 = skin and subcutaneous tissue disorders; 6 = vascular disorders; 7 = blood and lymphatic system disorders; 8 = renal and urinary disorders; 9 = general disorders; 11 = nervous system disorders; 12 = endocrine disorders; 13 = psychiatric disorders; 14 = reproductive system and breast disorders; 15 = respiratory, thoracic, and mediastinal disorders.
the 2 treatments (P=.24). However, adverse events such as weight loss and leukopenia/thrombocytopenia occurred more frequently in those treated with cyclophosphamide, with fewer patients discontinuing treatment on mycophenolate mofetil. Shenoy et al reported similar findings from a single-center retrospective study. After follow-up at 6 months in cyclophosphamide- (n=23) and mycophenolate- (n=34) treated patients, FVC improvement from baseline was statistically significant in both groups (P<.01) and comparable between the two (P=.373). There were no major adverse events reported except in 4 patients with lower respiratory tract infection in the cyclophosphamide-treated group. Owen et al followed treated patients up to 36 months and reviewed PFT data from 18 with mycophenolate mofetil and 29 with azathioprine, noting fewer adverse events for mycophenolate and a protective effect for FVC decline. Azathioprine is often used as an alternative to mycophenolate mofetil for maintenance therapy. Several observational studies found azathioprine to have an effect on stabilization or improvement in FVC and dyspnea scores. Unfortunately, it seemed to be less effective than cyclophosphamide, with greater adverse reactions compared with mycophenolate mofetil.

Corticosteroids are often used concomitantly with other immunosuppressant agents at the time of treatment initiation or in acute progression or exacerbation but are not preferred as long-term maintenance therapy. Although Ando et al observed improved annual change in FVC without SSc renal crisis in their retrospective review of corticosteroid-treated patients, long-term benefit of corticosteroid monotherapy may be limited by adverse effects and is usually avoided.

Current novel therapies include biological agents, antifibrotic drugs, and autologous stem cell transplant. Sircar et al randomly assigned 60 patients with diffuse cutaneous SSc-ILD to compare the efficacy and safety of rituximab with cyclophosphamide. There was a significant improvement in mean ± SD FVC% in the rituximab group from 61.3±11.28 at baseline to 67.52±13.59 at the end of the study (6 months, P=.002). The FVC (in liters), mRSS, and Medsger severity score improved significantly in the rituximab group (all P<.001). A significantly higher percentage of patients experienced improvement in FVC% in the rituximab group vs the cyclophosphamide group (26.7% [8 of 30] vs 6.7% [2 of 30], respectively; P=.038). A case-control study of 63 patients treated with rituximab and 25 matched controls found that rituximab significantly slowed FVC decline. Lepri et al conducted a retrospective assessment of rituximab efficacy in the treatment of CTD-ILD, including 23 patients with SSc. The PFT decline seemed to stabilize by the second year of follow-up (P=.07, compared with P=.1 at 1 year). In a phase 2 RCT of tocilizumab in SSc, investigators concluded that tocilizumab may potentially attenuate FVC decline after noting that significantly fewer patients experienced a drop in FVC% compared with placebo at 48 weeks (P=.0373). Autologous HSCT has recently been explored as a possible option for severe cases refractory to typical treatments. In the ASSIST (Autologous Stem Cell Systemic Sclerosis Immune Suppression Trial), 10 patients with diffuse cutaneous SSc (mRSS >14 with internal organ involvement or mRSS <14 with pulmonary involvement, both younger than 60 years) were treated with HSCT and had improvement in mRSS (P<.0001) and FVC (P<.03) at 12 months compared with those treated with IV cyclophosphamide for 6 months. Pirfenidone and nintedanib, 2 recently approved antifibrotic agents, have demonstrated efficacy in slowing FVC decline in idiopathic pulmonary fibrosis. Clinical trials are ongoing regarding their use in SSc-ILD and other nonidiopathic pulmonary fibrosis fibrotic lung diseases. Stabilized percent-predicted FVC and DLCO were observed for patients with SSc treated with pirfenidone, although the study’s primary focus was safety and tolerability involving follow-up of only 16 weeks.

In summary, ILD is common and contributes significantly to the morbidity and
mortality of SSc. Cyclophosphamide and mycophenolate mofetil have been more rigorously studied and should be considered first-line therapy based on controlled data. The effect of corticosteroids has not been as well defined; monotherapy or longer-term high-dose regimens are discouraged. Rituximab and tocilizumab have had more robust comparison studies, whereas autologous HSCT and antifibrotic agents remain novel choices, with more rigorous and larger-scale investigations still needed to clarify efficacy and safety. A summary of published treatment end points and drug-related adverse effects is presented in Table 2.

DM/PM- AND AS-ILD

Both NSIP and OP are typical patterns of ILD in patients with DM/PM and AS, with UIP being less common. Radiologic findings may vary depending on disease severity and acuity.\textsuperscript{58} Reticular and ground glass opacities are often associated with more rapid and acute ILD courses, whereas consolidative findings tend to be more prevalent in patients with long-term and slower progression.\textsuperscript{7} Compared with other CTD-ILDs, rapidly progressive ILD is more frequent in idiopathic inflammatory myositis, particularly clinically amyopathic or hypomyopathic DM with positive anti–melanoma differentiation associated protein-5 autoantibodies.\textsuperscript{59,61}

Published evidence for the treatment of DM/PM-ILD includes 34 case reports involving adalimumab (n=1), azathioprine (n=1), cyclosporine A (n=1), cyclophosphamide (n=3), cyclophosphamide + cyclosporine A (n=6), tacrolimus (n=4), tacrolimus + azathioprine (n=1), tacrolimus + cyclophosphamide (n=1), tacrolimus + cyclophosphamide + rituximab (n=1), mycophenolate mofetil (n=5), mycophenolate + rituximab (n=1), rituximab (n=8), IVIG (n=3), and stem cell transplant (n=2); 19 observational cohort studies involving cyclosporine A (n=4), corticosteroids (alone) (n=1), cyclophosphamide (n=2), cyclophosphamide + cyclosporine A (n=1), tacrolimus (n=6), infliximab (n=2), mycophenolate mofetil (n=1), pirfenidone (n=1), and rituximab (n=1); and no controlled trials (see Supplemental Figure 3, available online at http://www.mayoclinicproceedings.org, and Table 3 for additional summarized outcomes, adverse events, and study-specific total number of patients reported).

Published evidence for the treatment of AS-ILD includes 14 case reports involving azathioprine (n=2), corticosteroids (alone) (n=1), cyclosporine A (n=1), cyclophosphamide (n=3), tacrolimus (n=1), rituximab (n=4), leflunomide (n=1), and mycophenolate mofetil (n=2); 12 observational cohort studies involving azathioprine (n=1), cyclosporine A (n=3), tacrolimus (n=3), and rituximab (n=6); and no controlled trials (see Supplemental Figure 4, available online at http://www.mayoclinicproceedings.org, and Table 4 for additional summarized outcomes, adverse events, and study-specific total number of patients reported).

Corticosteroid are considered first-line treatment of initially diagnosed DM- or PM-associated ILD.\textsuperscript{62} However, data regarding long-term monotherapy for ILD associated with DM/PM are limited. Oral regimens typically consist of prednisone at a dose of 0.75 to 1 mg/kg for 6 to 8 weeks, tapered afterward. In severe cases, pulse therapy with IV methylprednisolone at 1000 mg/d administered for 1 to 3 days may be given.\textsuperscript{63} Patients with chronic ILD seemed to have a better response to corticosteroid therapy compared with those with more rapidly progressive disease, which often required combination therapy with corticosteroid-sparing immunosuppressive agents.\textsuperscript{64} Patients with ILD with anti–aminocyl-tRNA synthetase antibodies often exhibited a better response to corticosteroid therapy, whereas those with positive anti–melanoma differentiation associated protein-5 autoantibodies were more often treatment resistant.\textsuperscript{65} Differences in corticosteroid effect for PM-ILD vs DM-ILD was observed by Fujisawa et al\textsuperscript{66} in 28 treated patients with ILD (16 PM and 12 DM). Six patients with PM-ILD (37.5%) seemed responsive to corticosteroid monotherapy compared with only 1 (8.3%) with DM-ILD.\textsuperscript{66}
Combination therapy with corticosteroid and corticosteroid-sparing immunosuppressive agents is commonly used in DM/PM, particularly in patients with symptomatic or progressive ILD. Lacking high-quality evidence, choice and regimen of immunosuppressive agents seem to be based on clinician familiarity and experience. To date, commonly reported agents include cyclophosphamide, cyclosporine A, and azathioprine.  

Although controlled trials for the treatment of extrapulmonary manifestations in PM suggested overall benefit with azathioprine, evidence of response or efficacy for related ILD is limited. Azathioprine is often used as a corticosteroid-sparing maintenance agent after IV cyclophosphamide but may not be effective in those with rapidly progressive ILD because it may take several months to

| TABLE 4. Studies (2000-2018) Reporting Treatment and Adverse Effects of Medical Therapy for DM/PM-ILD and AS-ILD<sup>a</sup> |
|---------------------------------------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Treatment<sup>b</sup>                                          | Case report/case series | Observational studies | RCTs | Adverse events<sup>c</sup> |
|                                                               | (No.) | Outcome measurements<sup>d</sup> | (No.) | Outcome measurements<sup>d</sup> | (No.) | Outcome measurements<sup>d</sup> | (No.) | Outcome measurements<sup>d</sup> |
| ADA                                                          | 1/1   | 1.2,6           | 0/0   | ND                           | 0/0   | ND                           | ND    |
| AZA                                                          | 1/1   | 1.2,6           | 0/0   | ND                           | 0/0   | ND                           | ND    |
| CsA                                                         | 1/1   | 1.2,6           | 4/87  | 1.2,7                        | 0/0   | ND                           | 1,5,8,13 |
| CS (alone)                                                   | 0/0   | ND              | 1/28  | 1.2                          | 0/0   | ND                           | ND    |
| CYC                                                          | 3/3   | 1.2,6           | 2/29  | 1.2,6                        | 0/0   | ND                           | 1,7,8,14 |
| CYC+CsA                                                     | 6/13  | 1.2,6           | 1/22  | 1.2,6                        | 0/0   | ND                           | 1,5,6 |
| FK506                                                       | 4/12  | 1.2,6           | 6/13  | 1.2,3,6,7,8                  | 0/0   | ND                           | 1.8   |
| FK506+AZA                                                   | 1/1   | 1.2,6           | 0/0   | ND                           | 0/0   | ND                           | ND    |
| FK506+CYC                                                   | 1/1   | 1.2,6           | 0/0   | ND                           | 0/0   | ND                           | ND    |
| FK506+CYC+RTX                                               | 1/1   | 1.2,6           | 0/0   | ND                           | 0/0   | ND                           | ND    |
| IFX                                                          | 0/0   | ND              | 2/48  | 1.2,3,6                      | 0/0   | ND                           | ND    |
| MMF                                                         | 5/12  | 1.2,6,8         | 1/125 | 1.2,6,8                      | 0/0   | ND                           | 1,3,7,8,15 |
| MMF+RTX                                                     | 1/1   | 1.2,6           | 0/0   | ND                           | 0/0   | ND                           | ND    |
| PFD                                                          | 0/0   | ND              | 1/30  | 1.2,6                        | 0/0   | ND                           | 3,5,15 |
| RTX                                                         | 8/13  | 1.2,6,8         | 1/18  | 1.2,6,8                      | 0/0   | ND                           | 1,5,7 |
| AS-ILD                                                      |       |                 |       |                              |       |                              |       |
| AZA                                                         | 2/2   | 1.2,6           | 1/18  | 1.8                          | 0/0   | ND                           | 1,3,7 |
| CS (alone)                                                  | 1/1   | 1.2,6           | 0/0   | ND                           | 0/0   | ND                           | ND    |
| CsA                                                         | 1/1   | ND              | 1/68  | 7                            | 0/0   | ND                           | ND    |
| CYC                                                         | 3/12  | 1.2,6,8         | 0/0   | ND                           | 0/0   | ND                           | 8,14  |
| FK506                                                       | 1/2   | 1.2,6           | 2/78  | 1.3,6,8                      | 0/0   | ND                           | 2,7,8,11,12 |
| LEF                                                         | 1/2   | 1.2,6           | 0/0   | ND                           | 0/0   | ND                           | ND    |
| MMF                                                         | 2/3   | 1.2,6           | 0/0   | ND                           | 0/0   | ND                           | ND    |
| RTX                                                         | 4/17  | 1.2,6,8         | 6/150 | 1.2,3,6,8                    | 0/0   | ND                           | 1      |

<sup>a</sup>AS = antisynthetase syndrome; DM = dermatomyositis; ILD = interstitial lung disease; ND = no data or data not accessible; PM = polymyositis; RCT = randomized controlled trial.

<sup>b</sup>ADA = adalimumab; AZA = azathioprine; Cs = corticosteroids; CsA = cyclosporine A; CYC = cyclophosphamide; FK506 = tacrolimus; IFX = infliximab; LEF = leflunomide; MMF = mycophenolate mofetil; PFD = pirfenidone; RTX = rituximab; TCZ = tocilizumab.

<sup>c</sup>1 = pulmonary function test parameters; 2 = Radiographic findings; 3 = ILD-related laboratory test (eg, KL6); 6 = respiratory syndrome; 7 = survival; 8 = mean doses of prednisolone.

<sup>d</sup>1 = infections and infestations; 2 = cardiac disorders; 3 = gastrointestinal disorders; 5 = skin and subcutaneous tissue disorders; 6 = vascular disorders; 7 = blood and lymphatic system disorders; 8 = renal and urinary disorders; 11 = nervous system disorders; 12 = endocrine disorders; 13 = psychiatric disorders; 14 = reproductive system and breast disorders; 15 = respiratory, thoracic, and mediastinal disorders.
achieve effect.\textsuperscript{67,71,72} Cyclophosphamide is generally used in more rapidly progressive or refractory ILD. Yamasaki et al\textsuperscript{73} observed improvement in FVC or HRCT score in 70% of patients (12 of 17) with DM/PM-related progressive interstitial pneumonia treated with IV cyclophosphamide. Early cyclosporine A treatment seemed to be associated with lower mortality and stable CT findings.\textsuperscript{74} Kotani et al\textsuperscript{75} also reported that combination therapy with corticosteroids and cyclosporin improved PFT parameters (total lung capacity $\%$, $P=.027$; vital capacity $\%$, $P=.003$; FVC$\%$, $P=.002$; forced expiratory volume in 1 second $\%$, $P=.002$; and CT scores, $P=.001$). Earlier intervention was emphasized based on findings that improvements in CT score were correlated with time from ILD diagnosis to cyclosporin initiation ($P=.014$).\textsuperscript{75} Mycophenolate mofetil has been reported to significantly improve FVC$\%$ and DLCO$\%$ in patients with DM/PM-ILD over follow-up of 104 weeks.\textsuperscript{76} As a relatively less toxic alternative, mycophenolate is increasingly being used in patients with DM/PM-ILD. Tacrolimus has been investigated and used commonly in Japan, given its greater potency and more stable blood concentrations compared with cyclosporine A.\textsuperscript{77-82} Kurita et al\textsuperscript{81} retrospectively investigated tacrolimus efficacy by comparing its addition to conventional therapy (n=25) and conventional therapy alone (n=24, prednisolone, IV cyclophosphamide, and/or cyclosporine A). The tacrolimus group exhibited significantly longer event-free survival by comparison ($P=.008$).\textsuperscript{81} Intravenous immunoglobulin has been used for the treatment of numerous autoimmune diseases, including refractory myositis. It also seems to be effective in treating refractory DM/PM-ILD, as reported in several Japanese studies.\textsuperscript{83-85} Suzuki et al\textsuperscript{85} retrospectively studied 5 fatal myopathy-ILD cases composed of 1 acute PM-ILD and 4 acute amyopathic DM–ILD refractory to immunosuppressive therapy. One patient with PM-ILD and 1 with amyopathic DM–ILD survived. No adverse reactions were observed due to IVIG treatment.\textsuperscript{83} Plasma exchange has been used in 1 reported case refractory to corticosteroid and conventional immunosuppressive therapy.\textsuperscript{86} Novel therapies for DM/PM-ILD comprise the biological and antifibrotic agents. Among these, rituximab has been more extensively studied. Efficacy has been reported in several recent retrospective studies. Unger et al\textsuperscript{87} reviewed the effect of rituximab in 19 patients with DM/PM-ILD and noted significant total lung capacity improvement in 7 of 8 patients at 7 months ($P<.05$). Complications included severe infections and hypogammaglobulinemia in 1 patient, and 2 had mild infusion reactions.\textsuperscript{87} Infliximab and adalimumab have also been reported in acute or refractory cases in a small case series and a case report.\textsuperscript{88,89} Pirfenidone seems to improve prognosis in patients with subacute ILD (disease duration, 3-6 months) related to clinically amyopathic DM. Thirty patients with clinically amyopathic DM–ILD with pirfenidone added to conventional therapy (corticosteroids and/or corticosteroid-sparing immunosuppressants) were compared with 27 matched retrospective controls. Patients with subacute ILD (n=10) in the pirfenidone add-on group had significantly higher survival (n=9) (90% vs 44.4%; $P=.045$).\textsuperscript{90} Antisynthetase syndrome seems to have a higher prevalence of ILD compared with DM/PM, with similar treatment options. Corticosteroids (1 mg/kg) are often considered initial treatment to assess for clinical responsiveness to immunosuppressant or anti-inflammatory therapy. Monotherapy often exhibits good initial response for extrapulmonary manifestations, although recurrence frequently occurs during tapering.\textsuperscript{91} No consensus has been reached on the most effective corticosteroid-sparing regimen. Evidence for treatment is similar and to some extent overlaps with that used in DM/PM. Calcineurin inhibitors (cyclosporine and tacrolimus) have been studied as conventional oral immunosuppressive agents. Cyclosporine A can be used as first- or second-line therapy in refractory cases.\textsuperscript{92} Tacrolimus has also demonstrated efficacy and a relatively safe profile for refractory ILD and myositis in AS.\textsuperscript{93}
Azathioprine has been reported as a corticosteroid-sparing agent or as maintenance therapy after remission in AS-ILD.94 Cyclophosphamide is an effective alternative agent in severe cases.95,96 Rituximab is the most widely reported biological agent used in the treatment of AS-ILD, particularly as rescue therapy in severe or refractory cases. Recently, 25 patients with AS-ILD (84% were recurrent or refractory cases) treated with rituximab from 2 medical centers in the United States were retrospectively reviewed by Doyle et al.97 The CT score and FVC were stable or improved at 12 months compared with baseline in 88% and 79% of participants, respectively. Rituximab was well tolerated in most patients; only 3 had adverse events (1 with anaphylaxis and 2 with gastrointestinal intolerance).97

In summary, ILD is associated with poorer prognosis and is a leading cause of morbidity in DM/PM and AS. Combination therapy with corticosteroid and immunosuppressive agents perhaps initiated earlier in those with suspected rapidly progressive ILD are highlighted treatment points. Calci-neurin inhibitors, IV cyclophosphamide,
and rituximab have been reported and studied options showing efficacy in stabilizing progression for more severe or refractory cases.

**PRIMARY SJÖGREN SYNDROME ILD**
The reported frequency of pulmonary involvement in pSS varies widely from 9% to 26% as reported in several studies.\(^98-100\) Interlobular septal thickening and ground glass are the most common radiographic abnormalities on HRCT, followed by reticulation and cysts.\(^99,100\) Notably, the formation of multiple cysts on HRCT, although recognized in Sjögren-ILD as possibly consistent with LIP, may also be associated with pulmonary amyloidosis.\(^99\) The predominant histologic pattern is still NSIP, accounting for 28% to 61% of cases, although LIP (17%) is thought to be more characteristic of SS. Varied histologic findings associated with SS include OP, UIP, lymphoma, and amyloid.\(^98,99,101\)

Published evidence for the treatment of pSS includes 8 case reports involving azathioprine + hydroxychloroquine (n=1), rituximab (n=2), corticosteroids (n=2), tocilizumab (n=1), tacrolimus + abatacept (n=1), and pirfenidone (n=1); 4 observational cohort studies involving azathioprine (n=1), mycophenolate mofetil (n=1), and rituximab (n=3), and no controlled trials (see Supplemental Figure 5, available online at http://www.mayoclinicproceedings.org, and Table 5 for additional summarized outcomes, adverse events, and study-specific total number of patients reported).

Often, ILD associated with pSS is slower to progress and may be initially observed for progression. Reevaluation at 6-month intervals has been suggested for patients with identified abnormalities affecting less than 10% of the lung tissue and DLCO greater than 65% in the absence of respiratory symptoms.\(^102\) In most progressive cases, corticosteroids and corticosteroid-sparing immunosuppressive agents usually offer a favorable response. Current published evidence regarding treatment of pSS-ILD is limited to case reports and case series. Corticosteroids are considered first-line agents in those with symptoms or evidence of ILD progression. A typical regimen is prednisone dosed at 0.5 to 1.0 mg/kg per day tapered over several weeks to months. Azathioprine, hydroxychloroquine, and cyclophosphamide have been found to stabilize or halt progression in reported cases.\(^103-105\) Hydroxychloroquine treatment was also reported to reduce extraglandular manifestations.\(^106\) Cyclophosphamide is often reserved for more severe or rapidly progressive cases unresponsive initially to corticosteroid therapy.\(^107\) In a retrospective study, significant improvement in pulmonary function and visual analog scale scores for cough were noted, along with stabilized HRCT findings at 6 months in patients treated with rituximab.\(^108\) In another case series, 6 of 8 patients with pSS-ILD treated with rituximab had improvement in their pulmonary symptoms and PFT parameters.\(^109\) Tacrolimus combined with abatacept was reported in 1 patient as an acceptable alternative to rituximab.\(^110\)

In summary, ILD in pSS is often less severe, with better response to corticosteroids and initial first-line corticosteroid-sparing immunosuppressive agents. Regular monitoring and evaluation may often be pursued before directed therapy. For severe cases, cyclophosphamide and rituximab are potential agents taking into account the general increased risks of infectious and malignant complications.

**MIXED CONNECTIVE TISSUE DISEASE ILD**
The reported incidence of ILD in MCTD ranges from 47% to 90% based on HRCT and PFT findings, contributing to 20.8% mortality during mean observation of 4 years.\(^111-114\) Still, NSIP is the most common histologic pattern, presenting as ground glass attenuation and linear opacities with a peripheral and lower-lobe predominance.\(^115\)

Published evidence for the treatment of MCTD includes 7 case reports involving corticosteroids (alone) (n=1), cyclophosphamide (n=1), cyclosporine A (n=1), azathioprine (n=1), methotrexate + azathioprine (n=1), tocilizumab (n=1), and imatinib (n=1); 1 observational cohort study involving rituximab (n=1); and no controlled...
trials (see Supplemental Figure 6, available online at http://www.mayoclinicproceedings.org, and Table 4 for additional summarized outcomes, adverse events, and study-specific total number of patients reported).

Similarly, there are no specific guidelines or protocols for the treatment of ILD associated with MCTD, whose options are extrapolated from experience with the empirical management of other CTDs. Corticosteroids are the initial mainstay, followed by corticosteroid-sparing agents, which have been reported to include cyclosporine A, azathioprine, and mycophenolate mofetil.116,117 Severe ILD is often treated with oral or IV cyclophosphamide.118,119 Novel biological agents have been reported in the literature, but evidence is limited in quality and quantity. Imatinib was described as being effective in a 64-year-old woman with MCTD and rapidly progressive pulmonary fibrosis. Significant improvements in PFT parameters, HRCT findings, and exercise tolerance were observed after 20 weeks of treatment dosed at 400 mg/d.120 Six patients with MCTD (of 44 total with CTD) were assessed for efficacy of rituximab in CTD-ILD. The FVC% remained stable at 1 year (63 [range, 59-71]) compared with baseline (64.5 [range, 63.0-68.0]).55

Although ILD is notably prevalent in MCTD and significantly affects prognosis and outcome, evidence for directed therapy is the least reported among the CTD-ILDs. Screening in this population with earlier detection and monitoring may affect disease course and prognostication, with initial therapy seeming to consist of corticosteroids plus or minus corticosteroid-sparing agents such as azathioprine or mycophenolate, followed by cyclophosphamide or rituximab in more refractory cases.

**SYSTEMIC LUPUS ERYTHEMATOSUS ILD**

The incidence of ILD in SLE is relatively low, ranging from 1% to 15%.121 The most common histopathologic pattern is NSIP, with other patterns, including OP, LIP, UIP, and diffuse alveolar damage, occurring less often.122-125 Diffuse alveolar damage may be found in severe cases associated with diffuse alveolar hemorrhage (DAH) or acute lupus pneumonitis (ALP), a rare but life-threatening condition characterized by abrupt onset of fever, pleuritic chest pain, and hypoxemia, with mortality as high as 50%.126 Bronchoscopy with bronchoalveolar lavage may be helpful in diagnosing associated DAH, which contributes significantly to mortality. Approximately 50% of patients with DAH require mechanical ventilation, an indicator and perhaps source of significant morbidity associated with the condition.127

Published evidence for the treatment of SLE-ILD includes 26 case reports involving cyclophosphamide (n=4), mycophenolate mofetil (n=3), rituximab (n=16), pirfenidone (n=1), IVIG (n=2), and stem cell transplant (n=4); 3 observational cohort studies involving corticosteroids (n=1), azathioprine (n=1), and recombinant activated factor 7 (n=1); and no controlled trials (see Supplemental Figure 7, available online at http://www.mayoclinicproceedings.org, and Table 4 for additional summarized outcomes, adverse events, and study-specific total number of patients reported).

Treatment for SLE-ILD is based generally on clinical experience and case observations. In acute or severe cases, due to the high risk of infection, broad spectrum antibiotic agents are often instituted early. Once infection is excluded, aggressive immunosuppression with pulsed high-dose IV methylprednisolone (1 g daily for 1-3 days) followed by oral corticosteroids or possibly cyclophosphamide is often pursued.128 Plasmapheresis has been reported in refractory cases combined with pulsed methylprednisolone or cyclophosphamide with an apparent 20% reduction in mortality.129 Rituximab has also been reported as an effective alternative in DAH and ALP, with observed reduction in recurrences.130-136 There are additional reported cases of successful therapy with IVIG, stem cell transplant, extracorporeal membrane oxygenation as rescue in acute respiratory failure, and recombinant activated factor 7.137-142

Regarding chronic ILD in SLE, oral corticosteroids are a reasonable first-line approach. The regimen is derived from an open-label trial published involving 14 patients treated...
with prednisone at 60 mg/d for at least 4 weeks reporting improvements in DLCO and respiratory symptoms in 11 survivors with mean follow-up of 7.3 years.143

In summary, chronic ILD in SLE is relatively rare. Acute presentations with ALP or DAH as life-threatening hypoxemic respiratory failure are more common, with aggressive high-dose immunosuppressive therapy and empirical antibiotics highlighted as important first-line therapies improving outcomes.

CONCLUSION
Interstitial lung disease is a common manifestation of CTD and significantly affects morbidity and mortality. A multidisciplinary approach to diagnosis and management is recommended because of heterogeneity of clinical presentation and varied time of pulmonary disease onset. Immunosuppression remains a mainstay of treatment and should be used in progressive cases or those with multorgan involvement. More aggressive immunosuppressive agents, such as cyclophosphamide and rituximab, are reserved for patients with initially refractory, severe, or rapidly progressive disease. Response to therapy and duration of treatment are also approached on a case-by-case basis.

Unfortunately, high-quality RCTs remain lacking for most treated CTD-ILD. To date, current treatment options are still based on reported experiences and observational studies, as well as extrapolated from more robust clinical trial data as studied in SSc-ILD. Novel approaches involving the biological agents, antifibrotic drugs, and even stem cell transplant have been introduced for CTD-ILD treatment, although specific pulmonary benefit has not been conclusive. Importantly, risk of publication bias should be noted in any review of observational or case-based therapeutic reports because failed or unresponsive cases are less likely to be published, and, therefore, firm conclusions on generalizability or extent of efficacy or adverse effects remain unclear. Ongoing research is needed to better understand the pathogenesis of CTD-ILD and to determine which patients may most benefit from which agents, and for what duration, so that therapy-related adverse effects may be minimized.

SUPPLEMENTAL ONLINE MATERIAL
Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: ABT = abatacept; ADA = adalimumab; ALP = acute lupus pneumonitis; ARS = anti–aminocylic-tRNA synthetase; AS = antisynthetase syndrome; AZA = azathioprine; CS = corticosteroid; CsA = cyclosporine A; CT = computed tomography; CTD = connective tissue disease; CYC = cyclophosphamide; DAH = diffuse alveolar hemorrhage; DLCO = diffusion capacity for carbon monoxide; DM = dermatomyositis; ENC = etanercept; FK506 = tacrolimus; FVC = forced vital capacity; GI = gastrointestinal; HCQ = hydroxychloroquine; HRCT = high-resolution computed tomography; HSCT = hematopoietic stem cell transplant; IFX = infliximab; ILD = interstitial lung disease; IMT = imatinib; IV = intravenous; IVIG = intravenous immunoglobulin; Lf = leflunomide; LIP = lymphocytic interstitial pneumonia; MCTD = mixed connective tissue disease; MMF = mycophenolate mofetil; mRSS = modified Rodnan skin score; MTX = methotrexate; NSIP = nonspecific interstitial pneumonia; OP = organizing pneumonia; PFT = pulmonary function test; PM = polymyositis; PO = per os (orally); pSS = primary Sjögren syndrome; RA = rheumatoid arthritis; RCT = randomized controlled trial; RTX = rituximab; SC = subcortaneous; SLE = systemic lupus erythematosus; SSc = systemic sclerosis; TCZ = tocilizumab; TGF-β = transforming growth factor β; UIP = usual interstitial pneumonia

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TREATMENT OF CTD-ILD


