

# Immunosuppressive Therapy for Autoimmune Lung Diseases

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## KEYWORDS

- Autoimmunity • Interstitial lung disease • Connective tissue disorder
- Immunosuppressive drug • Lung disease

## KEY POINTS

- Immunosuppressive drugs are typically administered when connective tissue disease (CTD)-interstitial lung disease (ILD) is diagnosed to try to prevent progressive loss of lung function by reducing inflammation and preventing pulmonary fibrosis or bronchiolitis obliterans.
- The lung is frequently involved and subject to inflammation and fibrosis in patients with CTD.
- Numerous drugs can be used for systemic autoimmune disorders, but none have US Food and Drug Administration labeling for treatment of CTD-ILD, and many have not been investigated for usefulness in treating autoimmune lung disease.
- Treatment with agents such as corticosteroids, azathioprine, cyclophosphamide, or mycophenolate may provide benefit to patients with CTD-ILD, and other therapies such as prevention of pathologic gastroesophageal reflux (GER) or treatment of bronchiolitis with macrolides may also prove beneficial.
- The therapeutic approach must be personalized to each individual patient and their specific disease process, clinical behavior of the disorder, and associated comorbidities.
- If lung disease relentlessly progresses despite medical therapy, lung transplantation is a therapeutic option, with acceptable outcomes if patients wish to pursue this option.

## INTRODUCTION

Pulmonary disorders that patients with various types of connective tissue disease (CTD) are at risk to develop range from airway-centered disorders (eg, cellular or follicular bronchiolitis, or bronchiectasis) to parenchymal disorders (eg, nonspecific interstitial

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pneumonia [NSIP], usual interstitial pneumonia [UIP] or organizing pneumonia [OP]), pulmonary hypertension (PH) (with or without the presence of interstitial lung disease [ILD]) or pleural disease.<sup>1-3</sup> Because CTD-associated ILD or CTD-associated bronchiolitis may lead to progressive lung function impairment, respiratory insufficiency, and death, immunosuppressive drugs are typically administered when CTD-ILD is diagnosed to try to prevent progressive loss of lung function by reducing inflammation and preventing pulmonary fibrosis or bronchiolitis obliterans. Newer drugs that may benefit patients with CTD are being evaluated in clinical trials or reaching approval for clinical use, but virtually none of the immunosuppressive drugs currently used to treat inflammatory disorders has been properly assessed for efficacy in treating CTD-associated lung disease in adequately powered, randomized, placebo-controlled clinical trials, although many have been validated as capable of inducing partial or complete remission for systemic aspects of some forms of CTD, such as disease-modifying antirheumatic drugs (DMARDs) for the treatment of rheumatoid arthritis (RA).

Rheumatologic disorders have long been recognized as systemic autoimmune diseases, and diagnosis is made via a combination of clinical presentation and types/patterns of autoantibodies that are usually present in the peripheral circulation.<sup>4</sup> However, recent studies suggest that autoantibodies and T cells associated with reactivity to self-antigens can be found in disorders such as idiopathic pulmonary fibrosis (IPF),<sup>5-8</sup> which raises the question whether ILDs such as NSIP or UIP that do not seem to be associated with the presence of a CTD are also autoimmune disorders (ie, lung-dominant CTD) that lack extrapulmonary involvement and often lack typical CTD-associated autoantibodies (as would be perceived for CTD-ILD when diagnostic autoantibodies are detected in the peripheral circulation).<sup>3</sup> In addition, Feghali-Bostwick and colleagues<sup>5</sup> have reported abnormal proliferation of CD4+ T-cell clones and identified IgG autoantibodies directed against several cellular antigens in most of a cohort of 48 patients with IPF. Extracts of IPF lung were found to be capable of stimulating autologous CD4 T-cell proliferation (but not preparations from normal lung or non-IPF lung disease), suggesting that these responses were driven by autoantigens in the IPF lung. Other investigations have also suggested that autoimmunity may play a role in idiopathic UIP (IPF),<sup>6,7,9,10</sup> and some patients diagnosed with idiopathic NSIP or UIP who seem to have no evidence of CTD at the time of diagnosis may have occult CTD and may eventually develop systemic CTD syndromes with the appearance of associated autoantibodies.<sup>11</sup> ILD associated with undifferentiated CTD<sup>12</sup> is frequently seen in referral clinics, and CTD serologies should be obtained when patients are evaluated for new-onset ILD or possible IPF.<sup>13</sup>

The demarcation between lung diseases that are considered classic autoimmune lung disorders versus disorders that do not involve autoimmunity (**Box 1**) has become even more blurred because evidence for sensitization to self-antigens has also been reported for obstructive lung disease. Rinaldi and colleagues<sup>14</sup> examined plasma from 320 patients with chronic obstructive pulmonary disease (COPD) and found a significant increase in T-cell sensitization to collagen V in both smokers and patients with COPD versus never smokers. Similarly, Liu and colleagues<sup>15</sup> found that patients with asthma had higher concentrations of anticollagen V antibodies versus controls, and higher antibody levels correlated with more severe asthma and with use of corticosteroids. Antibodies to other self-antigens were also detected; these included epidermal growth factor receptor, activin A type 1 receptors, and  $\alpha$ -catenin. In addition, Núñez and colleagues<sup>16</sup> detected circulating antitissue antibodies in 26% of 328 patients with COPD, suggesting a role of autoimmunity in its pathogenesis. Even sarcoidosis has been suggested to represent a form of autoimmune disease and is frequently associated with other autoimmune disorders,<sup>17</sup> but proof of this has been elusive.

**Box 1****Autoimmune disorders associated with lung disease**

- Classic rheumatologic disorders
  - RA
  - Juvenile RA
  - Systemic sclerosis
  - Inflammatory myopathies
    - Dermatomyositis
    - Antisynthetase syndrome
  - Systemic lupus erythematosus (SLE)
  - Sjögren syndrome
  - Mixed CTD
  - Vasculitis
    - Antineutrophil cytoplasmic antibody (ANCA)-associated
    - Other
  - Undifferentiated CTD
- Goodpasture syndrome
- IgG4-related disease
- Lung disease associated with autoimmune phenomena
  - IPF
  - Asthma
  - COPD
  - Posttransplant bronchiolitis obliterans

In light of evolving evidence that autoimmunity may play a role in many lung disorders in addition to CTD-associated ILD, a discussion that covers treatment of autoimmune lung disorders could be expansive if a broad definition of autoimmune lung disease was used. This article focuses on issues of safety and monitoring when immunosuppressive pharmacologic therapies are prescribed for the treatment of CTD-associated interstitial pneumonias, vasculitides, and bronchiolitis. All such therapies are off-label, and prospective, randomized placebo-controlled clinical trials have yet to be performed to evaluate the efficacy and safety of various immunosuppressive agents used to treat patients with CTD-ILD or idiopathic interstitial pneumonias (IIP) other than IPF (idiopathic UIP) that are not associated with the presence of CTD. All of these agents, both nonbiologic and biologic, can cause serious adverse reactions that can be life-threatening.<sup>18</sup> Knowledge of their potential toxicities and interactions with other drugs combined with the adoption of a systematic approach to monitoring therapy can minimize the likelihood that life-threatening reactions occur.

**CORTICOSTEROIDS**

Corticosteroids were recognized to have potent antiinflammatory properties in the early twentieth century from their ability to decrease formation of granulation tissue.<sup>19</sup> These agents rapidly became the mainstay of treatment of a variety of diffuse lung

disorders soon after the introduction of cortisone into clinical use in 1948, and steroids and other immunosuppressive therapies were also gradually introduced into treatment regimens for various rheumatic disorders. Consequently, clinicians who treated patients with various forms of ILD after the introduction of steroids into clinical medical practice perceived that treatment with corticosteroids could dampen the progression of ILD and prevent irreversible fibrosis, respiratory failure, and death.<sup>20</sup> Although nonsteroidal antiinflammatory drugs (NSAIDs) showed some benefit for systemic manifestations of RA, NSAIDs did not seem to have a significant impact on CTD-ILD.

Several reports in the 1970s and 1980s described beneficial clinical responses to methylprednisolone or prednisone for patients diagnosed with cryptogenic fibrosing alveolitis (CFA), which was considered to be essentially the same clinical entity as IPF as (IPF was perceived at that time).<sup>21</sup> Analysis of responders diagnosed as having CFA revealed that they were frequently younger, female, and had evidence of circulating autoantibodies or arthritis.<sup>22</sup> When bronchoalveolar lavage (BAL) was performed, the responders tended to have BAL lymphocytosis.<sup>23</sup> We now recognize that most of these responders likely had CTD-ILD, and the entities of CFA or IPF as recognized in the 1970s to the late 1990s encompassed and lumped together several entities that we now recognize as specific IIP entities, with IPF redefined as idiopathic UIP.<sup>13,24</sup> The entities of idiopathic cellular NSIP or OP can respond well to corticosteroid therapy,<sup>25–27</sup> and both of these forms of IIP are frequently present in patients with CTD-ILD. In addition, it is now recognized that NSIP or OP histopathologic patterns may be present in patients diagnosed with hypersensitivity pneumonitis.<sup>28</sup>

In pulmonary fibrosis associated with scleroderma, improvements in alveolitis and pulmonary function have been observed with steroid therapy.<sup>29,30</sup> Nearly half of patients with RA-associated ILD have been shown to have objective improvement with treatment, but complete remission is unlikely.<sup>31,32</sup> Patients with underlying SLE, mixed CTD, or undifferentiated CTD can have a good response to corticosteroids (which may be given with other pharmacologic immunosuppressive agents during acute inflammatory events), but a poorer response is observed for patients with established fibrosis.<sup>33–35</sup> For patients with Sjögren syndrome-associated ILD, corticosteroids are often recommended, but the effect on outcome remains unclear.<sup>36,37</sup> Despite the lack of clinical trial data, corticosteroids are usually used in conjunction with other immunosuppressive medications to treat CTD-ILD.

Although patients with autoimmune lung disease can show good (and sometimes dramatic) responses to corticosteroid therapy, systemic corticosteroid therapy, especially if high-dose and sustained, is associated with numerous, significant side effects (**Box 2**). If extensive fibrosis is present (eg, UIP or fibrotic NSIP associated with systemic sclerosis), corticosteroid therapy may not induce a significant response. As with treatment of systemic CTD, administration of nonsteroidal immunosuppressive agents can allow corticosteroid doses to be tapered to low levels that are better tolerated and less likely to induce unwanted side effects and complications such as diabetes, systemic hypertension, excessive weight gain, and osteoporosis.

## CYTOTOXIC AGENTS

Cytotoxic (or antiproliferative) agents that have been used to treat various forms of CTD include azathioprine, cyclophosphamide, leflunomide, methotrexate, and mycophenolic acid derivatives (**Table 1**). These agents are used for a wide spectrum of inflammatory/autoimmune disorders and can allow corticosteroid dosage to be reduced, thereby decreasing the risk of adverse effects of corticosteroid therapy, especially if treatment is long-term and relatively high doses of steroid as a single

**Box 2****Complications of chronic systemic corticosteroid therapy**

- Weight gain
- Obesity
- Impaired glucose metabolism
- Diabetes mellitus
- Systemic hypertension
- Myopathy
- Infection
- Decreased bone mineral density
- Osteoporosis
- Avascular necrosis of bone
- Dyslipidemia
- Accelerated atherosclerosis
- Nervous system perturbation
  - Adverse psychological effects
  - Sleep disturbance
- Eye/vision changes
  - Cataract formation
  - Glaucoma
- Growth retardation
- Cushingoid changes
- Dyspepsia

immunosuppressive agent are needed to suppress disease activity and maintain clinical stability. In addition, many of these agents have been evaluated for safety and efficacy in the treatment of several other disorders such as various vasculitides, inflammatory bowel disease (IBD), posttransplant solid-organ rejection, and various forms of ILD.

**Azathioprine**

Azathioprine is a prodrug that inhibits the activity of T cells and, to a lesser extent, B cells, by interfering in the early phase of lymphoid cell proliferation.<sup>38</sup> It is metabolized to 6-mercaptopurine (6-MP), which inhibits purine metabolism, likely inhibiting DNA and RNA synthesis, and, therefore, protein synthesis. The mechanisms of action remain unclear, but it seems that 6-MP interacts with Rac1, blocking upregulation of Bcl-xL messenger RNA and protein,<sup>39</sup> which leads to suppression of delayed hypersensitivity reactions and cell-mediated cytotoxicity. Controlled clinical trials in RA, SLE, and other forms of CTD have supported the efficacy of azathioprine as a steroid-sparing agent, and it is labeled by the US Food and Drug Administration (FDA) for adjunct therapy for renal transplant rejection and RA. Azathioprine was shown to stabilize scleroderma-associated ILD (which is usually fibrotic NSIP but may also be UIP on lung histopathology) when initiated after 6 months of monthly

<b>Table 1 Cytotoxic (antiproliferative) drugs</b>				
<b>Specific Agent</b>	<b>Mechanism of Action</b>	<b>Major Side Effects</b>	<b>Precautions</b>	<b>Suggested Monitoring</b>
Azathioprine	Purine metabolism antagonist May inhibit DNA, RNA, and protein synthesis Inhibits cellular mitosis	Leukopenia Pancreatitis Hepatitis Other bone marrow suppression	Check for thiopurine methyltransferase deficiency (avoid use if deficient) Avoid allopurinol Start with low dose (50 mg/d) and escalate gradually	Monthly CBC Monthly LFT
Cyclophosphamide	Alkylating agent Cross-links DNA and RNA (inhibits protein synthesis and cell function)	Bone marrow suppression Hemorrhagic cystitis Bladder cancer Pulmonary fibrosis	Maintain adequate fluid intake to avoid bladder toxicity	CBC with platelets every 2–4 wk Monthly urinalysis LFT
Methotrexate	Inhibits dihydrofolate reductase (reversible)	Pulmonary toxicity Hepatitis	Give prophylactic folic acid (1–2 mg/d)	Monthly CBC and LFT Periodic renal function laboratory tests
Mycophenolate	Blocks de novo guanosine nucleotide synthesis (inhibits nucleic acid synthesis, which impairs T-lymphocyte and B-lymphocyte proliferative responses)	Diarrhea Bone marrow suppression PML (black box warning)	Blood level can be assayed to assist assessment of GI toxicity (high value supports mycophenolate as cause)	Monthly CBC
Leflunomide	Dihydroorotate dehydrogenase inhibition May inhibit T-cell pyrimidine biosynthesis	GI (nausea, diarrhea) Systemic hypertension Hepatotoxicity Skin (alopecia, rash)	Obtain CBC, LFT, phosphate, and creatinine level tests before initiation of therapy	CBC, LFT, phosphate, creatinine level tests every 4–6 wk for first 6 mo; check every 6–12 wk beyond 6 mo

*Abbreviations:* CBC, complete blood count; GI, gastrointestinal; LFT, liver function testing; PML, progressive multifocal leukoencephalopathy.

intravenous (IV) cyclophosphamide infusions.<sup>40</sup> However, a National Institutes of Health-sponsored IPF Network study recently showed a significant mortality and hospitalization risk for patients with IPF receiving azathioprine plus *N*-acetylcysteine (NAC) versus patient groups receiving placebo or monotherapy with NAC.<sup>41</sup> This outcome led to early termination of the azathioprine/NAC study arm and raised concern for treatment of IPF with azathioprine. It is unknown whether azathioprine therapy may pose a similar risk for patients with CTD-ILD.

Azathioprine and 6-MP are both oxidized or methylated in erythrocytes and liver. Thiopurine methyltransferase (TPMT) converts mercaptopurine, via thiol methylation, to thiopurine analogues. Approximately 1 in 300 individuals lack this enzyme and can develop severe myelosuppression with the initiation of azathioprine.<sup>42</sup> Low levels of this enzyme have been associated with severe gastrointestinal (GI) distress and bone marrow suppression when azathioprine is taken.<sup>43</sup> It is now considered cost-effective to evaluate TPMT levels before initiating treatment with azathioprine; the number of patients needed to test to avoid 1 adverse event is estimated at 20.<sup>44,45</sup>

Azathioprine side effects include acne, GI distress, cholestasis, increased liver function tests, arthralgias, bone marrow suppression, alopecia, dizziness, allergy, opportunistic infections, and pancreatitis.<sup>46,47</sup> Adverse reactions occur in up to 19% of patients treated with azathioprine,<sup>47</sup> and azathioprine administration has been linked to an increased risk of malignancy, particularly lymphomas.<sup>18</sup> Monitoring for bone marrow suppression and liver toxicity needs to be performed when initiating therapy with azathioprine. Complete blood count (CBC) and liver function testing has been recommended every 2 weeks for the first 4 weeks, then every 4 weeks for the duration of treatment.<sup>48</sup>

### **Cyclophosphamide**

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Cyclophosphamide is a synthetic alkylating agent that is related to the nitrogen mustards. It has been FDA-labeled for the treatment of hematologic and nonhematologic malignancies,<sup>18</sup> but it is not FDA-labeled for treatment of CTD. High doses suppress T-helper 1 (TH1) and enhance TH2 lymphocyte activity and also affect CD4+CD25+ regulatory T cells, leading to marked immunosuppression.<sup>49</sup> Cyclophosphamide has also been used to treat various forms of ILD<sup>50</sup> as well as CTD-related lung disease,<sup>51</sup> and it has become the drug of choice for the treatment of ANCA-associated vasculitis.<sup>52</sup> Controlled trials have shown efficacy for lupus nephritis, systemic vasculitis, and ILD associated with scleroderma. It has been reported to benefit patients with progressive scleroderma-ILD, with improved quality of life and stabilization of pulmonary function and radiographic progression of fibrosis,<sup>40,51,53</sup> but these gains can be lost after 12 months if maintenance immunosuppressive therapy is not continued.<sup>53</sup> In addition, a recent, follow-up analysis of the Scleroderma Lung Study data reported that only a subset of patients received benefit from cyclophosphamide.<sup>54</sup>

Cyclophosphamide is converted to active metabolites (aldophosphamide and phosphoramidate mustard) by the liver, and the kidney excretes both cyclophosphamide and the active metabolites. The metabolites induce cell death by inhibiting DNA replication. Cyclophosphamide can be dosed orally or via intermittent IV pulse therapy. For both ANCA-related vasculitis<sup>52</sup> and scleroderma-related lung disease,<sup>51</sup> pulse therapy has been shown to be as effective and less toxic than daily dosing. IV pulse therapy allows for daily dosage adjustments based on the patient's white blood cell (WBC) count; however, that benefit must be weighed against the cost and support staff required for administration.

Both IV and oral dosing can cause hematuria, fibrosis of the urinary bladder, bladder cancer, and hemorrhagic cystitis, which can be a life-threatening complication. Both

cyclophosphamide and its active metabolites have been implicated in the development of hemorrhagic cystitis; 1 step toward prevention of this complication is ensuring a daily intake of at least 3 L of fluid. Hematuria seems to be time-dependent and dose-dependent.<sup>55</sup> Up to 15% of patients treated with cyclophosphamide for a year develop hematuria.<sup>55</sup> Bladder cancer risk is increased in patients who smoke cigarettes and also in those who developed hemorrhagic cystitis during therapy with cyclophosphamide.<sup>55</sup> Like hemorrhagic cystitis, bladder cancer also seems to be time-dependent and dose-dependent. Every 10 g of cumulative exposure to cyclophosphamide leads to a 2-fold increased risk of bladder cancer.<sup>56</sup> Cancers may occur many years after cyclophosphamide has been stopped. Screening with urinalysis and appropriate evaluation of hematuria, if noted, seems to be sufficient.<sup>55</sup>

Cyclophosphamide can also cause bone marrow suppression. Leukopenia is a dose-related complication and leads to alteration in the dosing regimen in many patients.<sup>57</sup> Cyclophosphamide administration can also lead to lymphomas, leukemias, skin cancers, and likely solid-organ tumors.<sup>58</sup> Many of the disease states that cyclophosphamide is used to treat predispose patients to higher rates of various malignancies. One prospective 15-year study of 726 patients with lung cancer that had previously been treated with busulfan, cyclophosphamide, or placebo, found no difference in rate of malignancies between the placebo and the cyclophosphamide arms.<sup>59</sup>

Cyclophosphamide has been associated with congestive heart failure (CHF), hemorrhagic pericarditis, and hemopericardium after particularly high doses. These conditions typically reverse after cessation of the drug. Skin rashes and even toxic epidermal necrolysis have been reported. Alopecia is a common side effect, which often reverses with cessation of the drug. However, the new hair that returns may be a new texture or color. Bacterial, viral, fungal, and protozoan infections are increased with cyclophosphamide use, although no consensus on preventive prophylactic medications exists.

Lung pneumonitis/fibrosis has been described extensively in animals exposed to cyclophosphamide<sup>60</sup> and in patients exposed to the drug,<sup>61</sup> but this relationship has been difficult to clearly show in human studies because of confounding variables. If fibrosis is suspected, cessation of the drug is recommended; typically these manifestations resolve with or without the use of corticosteroids.

Patients who are receiving cyclophosphamide should have a CBC with platelet count performed every 2 weeks. Because of infection risk, WBC count should be maintained greater than 4000 and absolute neutrophil count greater than 2000 cells/mm<sup>3</sup>, and dosing adjustments may be necessary to maintain this level. Urinalysis should be performed before the initiation of therapy and then at least every 3 months. If the patient has received greater than 10 g cumulative dose or developed hemorrhagic cystitis during treatment, urinalysis with cytology should be performed yearly after cessation of therapy.<sup>18</sup>

### **Leflunomide**

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Leflunomide inhibits de novo pyrimidine synthesis, thereby inhibiting T-lymphocyte and B-lymphocyte activation and proliferation.<sup>62</sup> It is metabolized in the bowel wall and liver to an active metabolite, which is then excreted primarily by the biliary system. Little renal excretion occurs,<sup>63</sup> and its half-life is approximately 2 weeks. Clinical trials have supported the use of leflunomide for polyangiitis with granulomatosis, ankylosing spondylitis, SLE, Sjögren syndrome, psoriatic arthritis, and psoriasis,<sup>64–66</sup> and it is FDA-labeled for the treatment of RA.<sup>67</sup>

There are multiple side effects, which seem to be dose-related and typically resolve with dose reduction of leflunomide. These side effects include rash, nausea,



hypertension, increased liver enzymes, alopecia, and diarrhea. Reports of serious infection, angioedema, cytopenias, interstitial pneumonitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, and fulminant hepatitis have been published; however, these data are difficult to interpret because of the presence of often severe, underlying disease and the simultaneous use of other immunosuppressive medications.

Hepatic toxicity was found in 2% to 4% of patients treated with leflunomide for RA<sup>68</sup> and typically occurred within 6 months of initiating therapy. Hepatic toxicity was more prevalent in patients also treated with methotrexate or who had preexisting liver dysfunction,<sup>69</sup> and decreased dosing or cessation of therapy typically resulted in laboratory value normalization. Folic acid supplementation can help to prevent hepatic toxicity in patients treated with both leflunomide and methotrexate. Hepatocellular necrosis has been reported, but is less common than increased transaminase levels.<sup>70</sup>

Perineural vasculitis associated with leflunomide administration seems to lead to peripheral neuropathy as early as 3 days after initiation of therapy.<sup>71</sup> The best outcomes have been reported when leflunomide is stopped as soon as symptoms of neuropathy arise. Up to 54% of patients with RA who are treated with leflunomide have neuropathic symptoms compared with 8% treated with other agents.<sup>72</sup> Oral cholestyramine administration may be a useful adjunct to leflunomide cessation in cases of severe neuropathy.<sup>72</sup> Fatal cases of interstitial pneumonitis associated with leflunomide administration have been reported.<sup>73</sup>

Before initiating treatment with leflunomide, baseline CBC, phosphate, creatinine, and liver function tests are recommended.<sup>18</sup> Once treatment has begun, these laboratory tests should be repeated every 4 to 6 weeks for the first 6 months, and if stable can then be checked every 6 to 12 weeks. If leflunomide is given with methotrexate, these tests should be repeated every 4 weeks until the treatment is stopped. Serious side effects require the cessation of leflunomide and the administration of cholestyramine. Leflunomide undergoes enterohepatic recirculation, resulting in a prolonged half-life. Cholestyramine binds and eliminates the active metabolite, and activated charcoal can also be used if cholestyramine is not tolerated.

### **Methotrexate**

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Methotrexate interrupts nucleic acid and protein metabolism by inhibiting dihydrofolate reductase, and it is metabolized in the liver, where it is converted to polyglutamates, which have an immunosuppressive effect via inhibition of extracellular adenosine metabolism.<sup>74</sup> Evidence of the immunosuppressive activity of methotrexate has been found in blood cells for up to 1 week, although the half-life is only 8 to 15 hours. Caffeine, theophylline, and other adenosine receptor antagonists have been shown to inhibit the antiinflammatory properties of methotrexate in animal models.<sup>75</sup> Methotrexate is FDA-labeled for juvenile RA (JRA), psoriasis, and RA.

Methotrexate is known to have multiple toxicities as well as many side effects. Major toxicities documented in association with methotrexate include cytopenias, liver damage, and pneumonitis. Common side effects include nausea, diarrhea, rash, fatigue, cognitive impairment, alopecia, and headaches. In trials for RA and psoriasis, side effects led to drug cessation in up to 30% of patients, most commonly for abnormal liver function tests, GI symptoms, and peripheral blood cytopenias.<sup>76</sup> Risk factors for toxicity from methotrexate include impaired renal function or advanced age.<sup>77</sup> Pulmonary toxicity most commonly presents as hypersensitivity pneumonitis.<sup>78</sup> It may also present as bronchitis with airway hyperreactivity, pneumonitis, OP, pulmonary fibrosis, or diffuse alveolar damage (DAD). Monitoring with

pulmonary function testing or high-resolution computed tomography (HRCT) does not seem to be useful in this population.<sup>79</sup>

Up to 5% of patients must stop methotrexate because of hepatic toxicity. Most cases of hepatic toxicity present as increased transaminase levels, which typically reverse with cessation of the medication; however, as many as 1 in 1000 patients develop severe liver failure and cirrhosis.<sup>76</sup> Risk factors for severe hepatic toxicity include heavy alcohol use, large cumulative dose of methotrexate, and history of psoriasis. Based on data from a large meta-analysis, liver biopsy was suggested for patients with psoriasis after each 1-g to 1.5-g cumulative dose of methotrexate.<sup>80</sup> However, patients with RA are considered to be at lower risk for the development of severe liver toxicity associated with methotrexate, and liver function tests obtained on a regular basis are considered sufficient for monitoring.<sup>81</sup> Current American College of Rheumatology recommendations regarding monitoring for liver toxicity include checking transaminase levels every 4 to 12 weeks, and if the levels show sustained increases more than normal, then liver biopsy is recommended.

Folic acid supplementation (1–2 mg/d) may be used to prevent many side effects associated with methotrexate but does not seem to affect the efficacy of the drug.<sup>82,83</sup> Folic acid is able to bypass the blockade of nucleic acid synthesis by methotrexate. In 1 study, folic acid supplementation decreased the methotrexate cessation because of toxicity from 38% in the control group to 17% in the group that received folic acid.<sup>83</sup> Folic acid may be added or increased if patients report symptoms of stomatitis, diarrhea, and nausea.<sup>82</sup>

Monitoring for methotrexate toxicities requires routine measures of renal function and CBCs.<sup>84</sup> If leukopenia is noted, the dose of methotrexate should be adjusted. Up to 26% of patients studied showed hematologic abnormalities while taking methotrexate, resulting in cessation of the medication. Greater than 95% of these patients were found to have symptoms of viral infection, and the hematologic abnormality returned to normal after a 1-month holiday from methotrexate, and the abnormality did not return when methotrexate was resumed.<sup>85</sup>

### ***Mycophenolic Acid***

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Mycophenolic acid inhibits the de novo purine pathway, causing potent inhibition of T lymphocytes and B lymphocytes.<sup>86</sup> It has FDA approval for use in solid-organ transplant (heart, kidney, and liver) for rejection prophylaxis. However, it has been used to treat a myriad of diseases, including SLE,<sup>87</sup> lupus nephritis,<sup>88</sup> RA,<sup>89</sup> polyangiitis with granulomatosis,<sup>90</sup> and CTD-ILD.<sup>91</sup> A retrospective review of patients with CTD-ILD showed that the drug was well tolerated, allowed a reduction in corticosteroid dose, and was associated with stabilization of lung function.<sup>91</sup> In addition, other small studies suggest benefit for patients with scleroderma-ILD or other CTD-ILD.<sup>92–95</sup>

Mycophenolate is available as mycophenolate mofetil, which is orally administered and rapidly hydrolyzed to mycophenolic acid, and mycophenolate sodium, which is an extended release enteric formulation. Mycophenolic acid is metabolized by binding to glucuronide, and this complex is then cleared via the kidneys; it may accumulate in renal failure, requiring dosage adjustments or dialysis. Mycophenolic acid has been linked to respiratory, cardiovascular, genitourinary, dermatologic, endocrinologic, ocular, neurologic, metabolic, musculoskeletal, infectious, GI, and hematologic adverse events but is generally well tolerated. Neutropenia may occur but typically responds to reduced mycophenolate dosing.<sup>96</sup>

Mycophenolate interacts with many drugs. Azathioprine and mycophenolate should not be coadministered because both inhibit purine metabolism. The absorption of mycophenolate can be inhibited by colessevalam, colestipol, activated charcoal,

cholestyramine, iron, aluminum, or magnesium salts.<sup>97</sup> Plasma concentrations of acyclovir and ganciclovir may be increased when coadministered with mycophenolate, and renal failure can exacerbate this effect. Mycophenolate may diminish the immunologic response to vaccination,<sup>98</sup> and patients on mycophenolate should not receive live attenuated virus vaccines.

Monitoring for mycophenolate toxicities include weekly CBCs for the first month, then every 2 weeks for the next 2 months, then monthly. It has not been shown that monitoring mycophenolate blood levels detects toxicity reliably enough to decrease its incidence, and blood levels have not been shown to be useful for predicting rejection prophylaxis efficacy in solid-organ transplantation.<sup>99</sup> However, following blood levels may be useful in patients with renal dysfunction.<sup>100</sup>

## BIOLOGIC AGENTS

An expanding number of anticytokine agents (antibodies that inhibit and/or bind cytokines or inhibit cytokine cell surface receptors) and anti-immune cell antibodies (eg, antilymphocyte agents that can mediate cytotoxicity or inhibit cytokine production) are being developed and coming into clinical use (**Tables 2** and **3**). Some of these agents have FDA approval for use as DMARDs for RA, and others have received approval for use in transplantation or hematologic malignancies. The clinical use of many of these agents is likely to expand in the coming years, but significant and potentially life-threatening adverse reactions can occur with these agents, and clinicians should be aware of these untoward reactions when these drugs are administered to patients. This section provides an overview of these drugs.

### *Tumor Necrosis Factor Antagonists*

Tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) plays a central role in tissue inflammation including granuloma formation, and various anti-TNF agents have been developed and approved for treatment of RA, psoriasis, ankylosing spondylitis, and IBD (see **Table 2**). The first 2 anti-TNF agents approved for clinical use were etanercept, which acts by binding TNF and preventing its interaction with the p75 TNF receptor on cell membranes, and infliximab, a monoclonal antibody that binds both endogenous-soluble and membrane-bound TNF and renders it biologically inactive.<sup>101</sup> Three additional monoclonal antibody preparations (adalimumab, certolizumab, golimumab) are now available for clinical use. These biologic agents have allowed targeted therapy that has essentially revolutionized treatment of rheumatoid disorders,<sup>102</sup> but the effect of these agents on CTD-ILD remains unknown. A recently published meta-analysis systematically examined results of clinical trials for treatment of RA with each of the 5 anti-TNF agents, and there was no clear difference in efficacy among the agents.<sup>103</sup> The data suggested that etanercept might have the best safety profile, and efficacy could not be stated to be better with any TNF agent compared with methotrexate, which is a substantially less expensive treatment option.

Significant risks associated with anti-TNF agents are numerous and include infection, lymphomas and other malignancies, and nervous system disorders, including demyelination syndromes (data are extracted from Micromedex). The risk of tuberculosis has been suggested to be greater with infliximab versus other agents, and infliximab therapy has been associated with risk of worsened cardiac dysfunction. Rare or unusual adverse events associated with anti-TNF therapy include lupus-like syndromes, bone marrow suppression, hepatotoxicity, and reactivation of viral hepatitis. In addition to taking a detailed baseline history and obtaining routine blood chemistries, patients should be evaluated for latent or active tuberculosis infection with skin

Table 2

FDA-approved cytokine antagonists used in transplant prophylaxis or for treatment of autoimmune disorders<sup>a</sup>

Specific Agent	Mechanism of Action	FDA-Approved Indications	Common Adverse Effects (>5%)	Serious Adverse Effects Reported
Etanercept	Soluble fusion protein form of p75 TNF receptor (binds TNF- $\alpha$ and TNF- $\beta$ , which inhibits binding of TNF- $\alpha$ and TNF- $\beta$ to p75 receptors)	RA, psoriasis, AS, JRA	Injection site reaction; respiratory (rhinitis, URI)	CHF; dermatologic (erythema multiforme, fasciitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, malignancy); anemia; leukopenia; neutropenia; pancytopenia; thrombocytopenia; malignancy (lymphoma, leukemia); autoimmune hepatitis; hypersensitivity reaction; neurologic (demyelinating CNS disease, Guillain-Barré syndrome, seizure, acute transverse myelitis, seizure); optic neuritis; infection (TB, <i>Legionella pneumonia</i> )
Infliximab	Monoclonal antibody (high-affinity binding to free and membrane TNF- $\alpha$ that neutralizes TNF- $\alpha$ activity)	RA, AS, psoriasis, IBD	Rash; abdominal pain; nausea; headache; pharyngitis or respiratory infection (children); fatigue	Cardiovascular (acute coronary syndrome, heart failure); dermatologic (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis); pancytopenia; leukopenia; neutropenia; thrombocytopenia; hepatotoxicity; hypersensitivity reaction; infusion reaction; drug-induced lupus erythematosus; malignancy (lymphoma); neurologic

				(demyelinating CNS disease, Guillain-Barré syndrome); infection (TB, <i>Legionella</i> , histoplasmosis, listeriosis)
Adalimumab	Monoclonal antibody (binds TNF- $\alpha$ , blocking interaction with p55 and p75 cell surface receptors)	RA, JRA, AS, psoriasis, IBD	Injection site reaction or pain; rash; headache; sinusitis; URI; antiadalimumab antibody development; positive ANA	CHF; dermatologic (erythema multiforme, Stevens-Johnson syndrome); agranulocytosis; aplastic anemia; erythrocytosis; leukopenia; pancytopenia; thrombocytopenia; acute hepatic failure; anaphylaxis; hypersensitivity reaction; malignancy (lymphoma); demyelinating CNS disease; infection ( <i>Legionella</i> pneumonia, TB, listeriosis)
Certolizumab	Humanized Fab fragment conjugated to polyethylene glycol (binds TNF- $\alpha$ but not TNF- $\beta$ )	RA, IBD	Arthralgia; UTI; URI	Cardiovascular (CHF; cardiac rhythm disturbance, MI, pericardial effusion, pericarditis); skin (erythema multiforme, erythema nodosum, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticarial); bone marrow suppression; bowel obstruction; hypersensitivity reaction; lupus erythematosus; demyelinating CNS disease; seizure; suicide risk; nephrotic syndrome; renal failure; infection (TB, listeriosis); malignancy

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**Table 2**  
(continued)

Specific Agent	Mechanism of Action	FDA-Approved Indications	Common Adverse Effects (>5%)	Serious Adverse Effects Reported
Golimumab	Monoclonal antibody (binds soluble and cell surface membrane TNF- $\alpha$ )	RA, AS, psoriasis	Injection site reaction; URI	CHF; HBV reactivation; hypersensitivity reaction; lupus erythematosus and erythema multiformelike syndrome; neurologic (demyelinating CNS disease, Guillain-Barré syndrome, peripheral demyelinating neuropathy); optic neuritis; infection (TB, invasive mycosis, <i>Legionella</i> pneumonia; listeriosis); malignancy
Basiliximab	IL-2 receptor antagonist	Renal transplant prophylaxis	Vomiting; abdominal pain; asthenia; dizziness; insomnia	Infusion reaction (hypersensitivity); HTN; edema; anemia; dysuria; cough; dyspnea
Tocilizumab	IL-6 receptor antagonist	RA, JRA	HTN, rash, diarrhea, LFT increase, dizziness, headache, nasopharyngitis	Infection site reaction; GI perforation; thrombocytopenia, neutropenia; anaphylaxis or hypersensitivity reactions; URI; malignancy
Anakinra	IL-1 receptor antagonist	RA	Injection site reaction	Cardiorespiratory arrest; hypersensitivity reaction; malignancy

*Abbreviations:* ANA, antinuclear antibody; AS, ankylosing spondylitis; CNS, central nervous system; HBV, hepatitis B virus; HTN, systemic hypertension; LFT, liver function testing; MI, myocardial infarction; TB, tuberculosis; URI, upper respiratory infection; UTI, urinary tract infection.

<sup>a</sup> All agents are associated with increased risk of infection.

testing (or via peripheral blood testing for evidence of reactivity) and appropriate imaging to rule out active pulmonary infection before initiation of anti-TNF therapy.

### **Other Biologic Agents**

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Various antilymphocyte and nonanti-TNF anticytokine agents have been approved for clinical use for the treatment of malignancies, transplantation, and various forms of CTD. Some of these agents may prove useful for the treatment of autoimmune lung disorders, but none has been evaluated in clinical trials that specifically target CTD-ILD that could lead to FDA approval for such use. Currently available anticytokine agents include baxiliximab (interleukin 2 [IL-2] signaling inhibition, FDA-labeled for kidney transplantation), tocilizumab (IL-6 receptor antagonist, FDA-labeled for RA), and anakinra (IL-1 receptor antagonist, FDA-labeled for RA).

Antilymphocyte agents currently available for clinical use include rituximab, abatacept, belatacept, belimumab, bortezomib, alemtuzumab, anti-CD3, and antithymocyte globulin (see **Table 3**). Rituximab has received FDA approval for treatment of RA and vasculitis, and it is also under investigation as a treatment of other autoimmune disorders, acute exacerbations of IPF, refractory sarcoidosis, and pulmonary alveolar proteinosis. However, it has been associated with a considerable number of potential adverse events including fatal infusion reactions and pulmonary toxicity.<sup>18,104</sup> However, recent systematic analyses have found rituximab therapy for RA to be safe and relatively free of adverse events.<sup>105–107</sup> Frequent monitoring of vital signs during infusions is recommended, and clinicians must also be vigilant for the appearance of other complications such as infection including reactivation of latent viral infections, cardiac complications, and bowel perforation.

### **CHLOROQUINES**

These synthetic 4-aminoquinolone antimalarial drugs (**Table 4**) have antiinflammatory properties via mechanisms that remain unclear. Chloroquine is rapidly absorbed from the GI tract and sequestered in many tissues, including the lung, kidney, liver, spleen, and nervous tissue, and its half-life is estimated to range from 30 to 60 days, with the drug remaining in tissues for years after therapy is discontinued. Prolonged therapy is associated with several adverse events, and some can be serious and life-threatening, but the drug is generally well tolerated. Hydroxychloroquine sulfate is FDA-labeled for SLE and RA and is commonly used in initial therapeutic regimens as an agent for mild CTD that is symptomatic; it may be useful in pediatric ILD<sup>108</sup> and may induce a clinical response in some patients with sarcoidosis.<sup>109</sup>

### **CALCINEURIN INHIBITORS**

The calcineurin inhibitors, cyclosporine A and tacrolimus, are the key immunosuppressive agents in posttransplant immunosuppressive regimens and are usually administered along with an antiproliferative agent (mycophenolate or azathioprine) and prednisone, although mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus) may also be used to allow calcineurin dose reduction (or occasionally in place of a calcineurin inhibitor).<sup>110</sup> Calcineurin inhibitors have been administered to patients with refractory inflammatory myopathy or RA when other therapies have been ineffective,<sup>111,112</sup> but randomized, controlled clinical trials to evaluate such therapy have not been reported. Major concerns with these agents include opportunistic infections and nephrotoxicity, and many other adverse effects may occur. In addition, numerous drug-drug interactions can occur when other drugs that affect CYP 3A4 (cytochrome P450), the hepatic enzyme that degrades both the calcineurin inhibitors and mTOR inhibitors, are simultaneously

**Table 3**  
**Antilymphocyte antibodies available for clinical use<sup>a</sup>**

<b>Specific Agent</b>	<b>Mechanism of Action</b>	<b>FDA-Approved Indications</b>	<b>Common Adverse Effects (&gt;5%)</b>	<b>Serious Adverse Effects</b>
Rituximab	Anti-CD20 (monoclonal antibody (mediates B-cell cytotoxicity via binding of cell surface CD20	RA, microscopic PAN, ANCA-associated vasculitis, CLL, lymphoma	Fever; cardiovascular (hypotension, edema); dermatologic (rash, night sweats, pruritus); GI (abdominal pain, nausea, diarrhea); anemia; arthralgia; myalgia; neurologic (headache, dizziness, asthenia, sensory neuropathy); cough	Cardiac (shock, CHF, dysrhythmia, MI); GI (obstruction, perforation, ileocolitis); PML; dermatitis/rash; angioedema; anemia (aplastic, hemolytic); neutropenia; lymphocytopenia; thrombocytopenia; HBV; infusion reaction; nephrotoxicity; respiratory (dyspnea, OB, pneumonitis/fibrosis)
Abatacept	CTLA-4 costimulation antagonist (suppresses T-cell proliferation, cytokine release)	RA, JRA	Nausea; UTI; headache; respiratory (acute exacerbation of COPD, nasopharyngitis, URI)	Sepsis; cellulitis; acute pyelonephritis; pneumonia; malignancy
Belatacept	Binds B7 ligand (CD80, CD86) (suppresses T-cell proliferation and cytokine release)	Renal transplant rejection or prophylaxis	Hypotension; peripheral edema; GI (nausea, vomiting, diarrhea, constipation); anemia; leukopenia; UTI; hyperkalemia or hypokalemia; cough; fever; headache	Severe infections; Guillain-Barré syndrome; PML; nephropathy (transplanted kidney)
Bortezomib	Anti-CD19 (inhibits plasma cells)	MM, lymphoma	Rash; hypotension; GI (nausea, vomiting, diarrhea, constipation, suppressed appetite; anemia; fever; musculoskeletal (arthralgia, myalgia, cramp, bone pain); neurologic (asthenia, dizziness, dysesthesia, headache, insomnia, paresthesia,	CHF; toxic epidermal necrolysis; neutropenia; thrombocytopenia; acute hepatic failure; angioedema; postherpetic neuralgia, TIA; respiratory (ARDS, interstitial pneumonitis)



peripheral neuropathy);  
psychiatric disorder; cough;  
dyspnea; pneumonia

Belimumab	Inhibits B cells (anti-B-lymphocyte stimulator-BLyS)	SLE	Diarrhea; nausea; fever; limb pain; insomnia; nasopharyngitis	Anaphylaxis; hypersensitivity reaction; infusion reaction; bronchitis; pneumonia
Ofatumumab	Anti-CD20 (B-cell lysis)	CLL	Respiratory (bronchitis, dyspnea, cough, pneumonia, URI); rash; nausea; diarrhea; anemia; fever; fatigue	Neutropenia; PML; HBV (fulminant, relapse); bowel obstruction; infusion reaction
Alemtuzumab	Binds CD52 (antibody-dependent cellular-mediated lysis of T and B lymphocytes, monocytes, macrophages, natural killer cells and some granulocytes)	CLL	Systemic hypotension; rash, urticarial; GI (nausea, vomiting, diarrhea); anemia; neutropenia; thrombocytopenia; musculoskeletal pain; insomnia; anxiety; bronchospasm; dyspnea; fever; fatigue; shivering; CMV infection	Cardiovascular (dysrhythmia, CHF, cardiomyopathy); anemia (aplastic or autoimmune hemolytic); thrombocytopenia (may be autoimmune); neutropenia; lymphocytopenia; PTLD; GVHD; neurologic (demyelinating CNS disease, Guillain-Barré syndrome); optic neuropathy; Goodpasture syndrome; severe infection; CMV or EBV infection
Muromonab	Murine monoclonal anti-CD3 antibody that inhibits T-cell proliferation and response to antigen challenge	Renal, liver, and heart transplant rejection	Fever; systemic hypotension; tachycardia; edema; rash; diarrhea; nausea; vomiting; headache; tremor; dyspnea; shivering	Cardiac dysrhythmia; hypertension; Stevens-Johnson syndrome; thrombosis; hepatitis; anaphylaxis; neurologic (cerebral edema, encephalopathy, seizure); pulmonary edema; respiratory failure and arrest

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**Table 3**  
**(continued)**

<b>Specific Agent</b>	<b>Mechanism of Action</b>	<b>FDA-Approved Indications</b>	<b>Common Adverse Effects (&gt;5%)</b>	<b>Serious Adverse Effects</b>
ATG	Polyclonal immunoglobulin mixture (raised in rabbits or horses immunized with human thymus lymphocytes)	Aplastic anemia; renal transplant (rejection or prophylaxis)	Fever; shivering; chest or back pain; arthralgia; myalgia; hypertension; peripheral edema; tachycardia; rash; hyperkalemia; GI (nausea, vomiting, diarrhea, abdominal pain); leukopenia, thrombocytopenia; hemolysis; serum sickness; anti-ATG antibody development; asthenia; headache; nephrotoxicity; dyspnea	Anaphylaxis; ARDS; PTLD, hyperkalemia

*Abbreviations:* ARDS, acute respiratory distress syndrome; ATG, antithymocyte globulin; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; CTLA-4, cytotoxic T-lymphocyte antigen 4; EBV, Epstein-Barr virus; GVHD, graft-versus-host disease; HBV, hepatitis B virus infection/reactivation; MI, myocardial infarction; MM, multiple myeloma; OB, obliterative bronchiolitis; PAN, polyarteritis nodosa; PML, progressive multifocal leukoencephalopathy; PTLD, posttransplant lymphoproliferative disease; TIA, transient ischemic attack; URI, upper respiratory infection; UTI, urinary tract infection.

<sup>a</sup> All agents are associated with increased risk of infection.

administered because of either enhanced degradation (CYP 3A4 stimulation) or competition (drug is metabolized by CYP 3A4). It is essential that treating physicians understand these interactions and carefully monitor drug blood levels, CBCs, and kidney function, with appropriate intervals between testing.

### MISCELLANEOUS ADDITIONAL PHARMACOLOGIC THERAPIES

Several other agents (not necessarily immunosuppressive agents) may have a role in treating autoimmune lung disease, but relatively little clinical information is available to support their use. The mTOR inhibitors, sirolimus and everolimus, have potent immunosuppressive and antiproliferative effects.<sup>18,110</sup> Sirolimus binds to intracellular FK-binding protein, and this complex subsequently binds to the mTOR and suppresses the function of this serine/threonine kinase, which plays a key role in the cell cycle and T-cell proliferation. mTOR signaling has been shown to play a crucial role in joint destruction in animal models of experimental inflammatory arthritis,<sup>113</sup> and inhibition of mTOR by sirolimus has been shown to suppress activities of synovial fibroblasts in a rat model of RA.<sup>114</sup> In addition, everolimus coadministered with methotrexate produced a significantly greater response compared with patients receiving methotrexate alone in a 3-month prospective, double-blind, placebo-controlled proof of concept clinical trial.<sup>115</sup> However, one of the adverse events associated with sirolimus administration is pulmonary toxicity.<sup>116</sup>

Thalidomide has FDA approval for the treatment of multiple myeloma and has been studied in sarcoidosis, Langerhans cell histiocytosis, and RA. It has been shown to suppress TNF- $\alpha$  production and has antiangiogenic properties, although its mechanism of action remains unclear. It may benefit some patients with Langerhans cell histiocytosis,<sup>117</sup> but it did not clearly benefit patients with sarcoidosis,<sup>118</sup> although its maximal dosing was limited by side effects. Small studies have suggested potential benefit in JRA,<sup>119–121</sup> but thalidomide and its analogues, pomalidomide and lenalidomide, have been linked to acute pulmonary toxicity and interstitial pneumonitis as adverse events.<sup>122,123</sup>

Tetracyclines have antiinflammatory as well as antibacterial properties and have been used to treat several inflammatory disorders.<sup>124</sup> They can suppress matrix metalloproteinases, collagenase, and phospholipase A2 activity, suppress production of IL-1 $\beta$  and TNF- $\alpha$ , and may suppress neutrophil and T-cell function. Several placebo-controlled, randomized studies have been performed in RA with minocycline, and 1 large study showed significant improvement in joint disease and markers of inflammation over a 48-week treatment period.<sup>125</sup> Another trial reported superiority of minocycline over hydroxychloroquine for symptom control and prednisone-sparing over a 2-year study period.<sup>126</sup>

Macrolides (eg, erythromycin), neomacrolides (eg, clarithromycin), and azalides (eg, azithromycin) also have both antiinflammatory and antimicrobial properties,<sup>127</sup> and they have been shown to have clinical benefit or promise in treating bronchiolitis (eg, diffuse pan-bronchiolitis, bronchiolitis obliterans syndrome [BOS]) cystic fibrosis (CF) bronchiectasis, non-CF bronchiectasis, COPD, and asthma.<sup>122–129</sup> These agents can inhibit the respiratory burst of neutrophils, and they can also suppress cytokine production (eg, IL-8, IL-6, TNF- $\alpha$ ). Azithromycin is highly concentrated in lung tissue and alveolar macrophages, and it can be safely used in patients with liver disease because it is not metabolized by the cytochrome P450 system. Several studies support their potential usefulness for the treatment of bronchial disorders (ie, bronchiolitis, bronchiectasis) associated with autoimmune disorders. Erythromycin has been shown to significantly improve symptoms of patients with RA-associated

**Table 4**  
**Miscellaneous drugs with potential benefit for autoimmune disorders**

<b>Drug Class</b>	<b>Specific Agent</b>	<b>Mechanism of Action</b>	<b>Potential Toxicities</b>	<b>Precautions and Monitoring</b>
Chloroquines	Hydroxychloroquine sulfate	Antiinflammatory effects (FDA-labeled for SLE and RA)	Cardiac (cardiomyopathy, dysrhythmia); peripheral neuropathy; myopathy; CNS (headache, confusion, seizure, coma); GI upset; hepatic failure; visual disturbance; urticaria; pruritis; bone marrow suppression	Periodic ocular screening Avoid prolonged, high-dose therapy (associated with risk of irreversible retinopathy and ototoxicity)
Calcineurin inhibitor <sup>a</sup>	Cyclosporine A	Inhibits T-cell function by disrupting IL-2 signaling	Nephrotoxicity; hypertension; tremor; hyperkalemia; hypomagnesemia; hepatotoxicity; CNS (headache, tremor, seizure, coma, encephalopathy, leukoencephalopathy); hirsutism, gingival hyperplasia, burning sensation in eye	Frequent (as appropriate) monitoring of peripheral blood (drug level, renal function, serum K and Mg, and LFT)
	Tacrolimus	Inhibits T-cell function by disrupting IL-2 signaling via formation of FK 506-binding proteins	Cardiac (prolonged QT interval, hypertension, cardiomegaly); diabetes mellitus; nephrotoxicity; hypomagnesemia; hyperkalemia; neurologic (headache, tremor, insomnia, paresthesia, coma); leukoencephalopathy; skin (alopecia, pruritus, rash); GI upset; anemia; thrombocytopenia	Frequent (as appropriate) monitoring of peripheral blood (drug level, renal function, serum K and Mg, LFT, and glucose)

mTOR inhibitors <sup>a</sup>	Sirolimus	Inhibits mTOR, which suppresses T cells, antibody production, and cytokine production	Fever; infection; pain; hypertension; edema; acne; rash; GI upset; anemia; thrombocytopenia; arthralgia; headache; PML; increased serum creatinine level; UTI; HUS; nephrotic syndrome; epistaxis; coronary artery stent thrombosis; dyslipidemia; DVT; PE; TTP; pancytopenia; hepatotoxicity; ILD; pulmonary hemorrhage; malignancy	Avoid use in early postoperative period Monitor CBC, renal function, serum cholesterol and triglycerides Monitor whole blood levels
	Everolimus	Everolimus-FK506 binding protein complex binds and inhibits mTOR	Fever; infection; fatigue; asthenia; cough; dyspnea; URI; otitis; impaired wound healing; LFT increase; creatinine increase; HUS; anemia; leukopenia; thrombocytopenia; GI upset (stomatitis; nausea, vomiting, diarrhea, constipation); dyslipidemia; hyperlipidemia; thrombosis; thrombotic microangiopathy; TTP; PE; hyperglycemia; acne; rash	Avoid use in early postoperative period Monitor CBC, renal function, serum cholesterol, and triglycerides Monitor whole blood levels
Miscellaneous	Macrolides and azalides	Various antiinflammatory and immunomodulatory effects	Prolonged QT interval; torsades de pointes or other ventricular dysrhythmia; GI upset; headache; allergic reaction; increased LFT; hepatitis; pancreatitis; rash; Stevens-Johnson syndrome; ototoxicity; seizure	Monitor LFTs with chronic therapy if P450-metabolized Consider pretherapy ECG and early on-therapy ECG to check QT interval

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**Table 4**  
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Drug Class	Specific Agent	Mechanism of Action	Potential Toxicities	Precautions and Monitoring
	Minocycline	Antiinflammatory effects	Dizziness; vertigo; tooth discoloration; anaphylaxis; drug hypersensitivity reaction; SLE; pseudotumor cerebri	
	NAC (oral)	Antioxidant effects (replenishes oxidized glutathione)	Rash; urticaria; angioedema; GI upset (nausea, vomiting, diarrhea) IV NAC has been associated with several additional (and potentially severe) adverse events	Bronchospasm has occurred in patients given IV drug
	Pirfenidone	Inhibits fibroblast growth and collagen production via TGF- $\beta_1$ and PDGF inhibition	GI (anorexia, nausea, abdominal discomfort/bloating, diarrhea, vomiting, constipation); skin (photosensitivity, rash); fatigue; weakness; increased LFT	Avoid sun exposure Take with food
	Thalidomide	Suppresses TNF- $\alpha$ production; antiangiogenic; modulates T-cell subsets	Edema; atrial fibrillation; other cardiac dysrhythmia; hypocalcemia; pneumonia; leukopenia; GI upset or perforation; rash; Stevens-Johnson syndrome; asthenia; confusion; drowsiness, somnolence; tremor; peripheral neuropathy; PE; teratogenesis	Watch for peripheral neuropathy Periodic CBC

*Abbreviations:* CNS, central nervous system; DVT, deep venous thrombosis; ECG, electrocardiogram; HUS, hemolytic uremic syndrome; LFT, liver function testing; Mg, magnesium; PDGF, platelet-derived growth factor; PE, pulmonary embolus; PML, progressive multifocal leukoencephalopathy; mTOR, mammalian target of rapamycin; TTP, thrombotic thrombocytopenic purpura; URI, upper respiratory infection; UTI, urinary tract infection.

<sup>a</sup> CYP 3A4 (P450)-metabolized drugs (monitor closely for drug-drug interactions if other drugs that affect P450 function or are metabolized by P450 are coadministered).

follicular bronchiolitis or bronchiolitis obliterans.<sup>130,131</sup> In addition, OP may be the cause of ILD in patients with CTD-ILD, and bronchiolar inflammation with variable alveolar involvement is typically present. Several studies have reported treatment responses to macrolide therapy for OP,<sup>132–135</sup> including OP refractory to corticosteroids.<sup>134,135</sup> Azithromycin can stabilize or improve BOS in lung transplant recipients, and 1 mechanism may be its ability to diminish acid reflux.<sup>136–138</sup>

## GASTROESOPHAGEAL DYSMOTILITY AND REFLUX

An abnormal degree of GER has been increasingly recognized as playing a potential role in ILD.<sup>139</sup> Many patients with IPF or CTD-ILD have been shown to have significant (pathologic) GER, and patients with CTD-ILD frequently have esophageal dysmotility or GER.<sup>140</sup> Extent of pulmonary fibrosis has been correlated with the extent of GER in patients with scleroderma,<sup>141</sup> and extreme esophageal dysmotility (aperistalsis) is frequently detected in patients with scleroderma. Patients with IPF and abnormal GER can have disease stabilization when GER is adequately suppressed<sup>142</sup> or after antireflux surgery.<sup>143</sup> In addition, patients with IPF who receive proton pump inhibitor (PPI) therapy or undergo Nissen fundoplication have been shown to be associated with improved survival,<sup>144</sup> and GER may be linked to acute exacerbations of IPF.<sup>145</sup> Suppression of abnormal GER may benefit patients with CTD-ILD, but additional research is needed in this area, and chronic acid suppression may have significant adverse effects if sustained over long periods.

## ANTIFIBROTIC AGENTS

Although predominantly inflammatory idiopathic pneumonia (eg, cellular NSIP) can remain stable over time, the appearance of progressive fibrosis is what usually leads to progressive loss of function and death in patients with CTD-ILD, and antiinflammatory/immunosuppressive therapies may be ineffectual in preventing lung function decline despite having an effect on systemic disease. Antifibrotic agents (eg, pirfenidone or BIBF-1120) have been shown to have a potential impact on disease progression in patients with IPF,<sup>146,147</sup> and antifibrotic therapies may hold benefit for patients with CTD associated with progressive pulmonary fibrosis. Another agent, NAC, which has putative antifibrotic activity via its antioxidant activity (replenishing glutathione) has been studied for treatment of IPF in a fairly well-powered study<sup>148</sup> that suggested possible benefit. However, this trial was flawed by lack of a true placebo group; a National Institutes of Health-sponsored trial of oral NAC versus placebo for IPF that is in progress showed that a third treatment arm with azathioprine plus NAC had significantly increased mortality risk versus NAC alone or placebo.<sup>41</sup> Clinical investigations with adequately powered clinical trials of antifibrotic therapies for treatment of CTD-ILD have yet to be performed.

## LUNG TRANSPLANTATION

Lung transplantation is a well-accepted therapy for patients with advanced lung disease that is progressive and refractory to other therapies, and it can significantly prolong survival and improve quality of life for patients with IPF.<sup>149</sup> However, because patients with CTD-ILD may not only have debilitating systemic disease but also may have significant esophageal dysmotility and GER,<sup>150</sup> many centers may refuse to consider them for lung transplantation evaluation and wait-listing, although relatively good results have been reported in scleroderma.<sup>151</sup> A major consideration that can have a significant impact on posttransplant outcome is poorly controlled pathologic

GER, and posttransplant GER considerably increases the risk of allograft dysfunction, especially triggering of BOS, which can lead to graft loss.<sup>152</sup> Nonetheless, a substantial number of patients with CTD-ILD (scleroderma, inflammatory myositis, RA, SLE) have undergone successful lung transplantation and been reported to lung transplant databases, and we have had successful outcomes with many patients with CTD-ILD at our center. However, patients must be carefully evaluated for the presence of complications or comorbidities that predict a substantially increased risk of poor outcome.

### A SUGGESTED APPROACH TO TREATMENT AND TO MONITORING RESPONSE TO THERAPY

A treatment plan must consider the specific type of lung disease, systemic manifestations (when present) of a specific systemic CTD or other autoimmune disorder, degree of respiratory impairment, and the temporal behavior of the disease. Aggressive immunosuppressive therapy is indicated with rapidly advancing or clearly progressive disease. However, some patients may be clinically stable without receiving immunosuppressive therapy for prolonged periods, and exposing them to the risk of significant (and occasionally severe) adverse events associated with immunosuppressive therapies is generally not warranted for stable patients. In addition, individual patients can have their lung disease complicated by the presence of secondary PH, venous thromboembolism, or several comorbidities (eg, cardiac disease, anemia, osteoporosis) that may have a significant impact on behavior of the disease or symptoms and quality of life. Patients may have a complex combination of disease processes such as pulmonary fibrosis combined with secondary PH, ILD accompanied by significant bronchiectasis, pathologic GER (which may be asymptomatic and not necessarily controlled by acid-suppressing therapies), or significant extrapulmonary end-organ dysfunction. Interventions must be tailored/personalized to match a given patient with their specific pulmonary disease manifestations and comorbidities. A multidisciplinary approach to disease management across specialties with pulmonologist, rheumatologist, and primary physicians communicating and comanaging patients (especially those with severe or aggressive disease) is desirable and in the best interest of the patient.

A suggested approach to management is summarized in **Box 3**. Patients should understand the nature of their disease as well as the risks and benefits associated with various therapies. If pharmacologic therapies are chosen, patients should be aware of the risks associated with the specific drugs to which they are to be exposed and be educated as to what symptoms or signs may indicate that an adverse, therapy-related event is occurring. Similarly, care providers should be aware of potential side effects of pharmacologic therapies and appropriate precautions to be taken before and during therapy, including appropriate laboratory monitoring with surveillance of bone marrow, liver, or kidney function. Drug levels need to be monitored if calcineurin or mTOR inhibitors are administered, and drug-drug interactions must be avoided. If an agent is metabolized by the P450 cytochrome system, care must be taken to carefully monitor and adjust therapy if other drugs that affect or are metabolized by P450 are administered. If medications such as rituximab are administered IV, patients must be carefully monitored for infusion reactions. In addition, some drugs (methotrexate, mTOR inhibitors) are more likely than others to cause pneumotoxic reactions, and worsened pulmonary function may be caused by drug-associated pneumotoxicity rather than disease progression. If intense immunosuppression is used, infection prophylaxis should be considered to prevent infectious complications such as *Pneumocystis jiroveci* pneumonia or reactivation of tuberculosis.



**Box 3****Treating the patient with autoimmune lung disease: a suggested approach**

- Establish patient-provider partnership for disease and symptom management
- Provide patient education
  - Information concerning disease characteristics and prognosis
  - Knowledge of potential side effects and toxicity of pharmacologic agents if prescribed
  - Smoking cessation
- Obtain adequate baseline testing
  - Imaging (HRCT or CXR as appropriate)
  - Pulmonary function testing (spirometry, DLCO, 6-MWT, dyspnea assessment)
- Thoughtful discussion of treatment options
  - Observation
  - Pharmacologic therapy (if appropriate) to induce remission or stabilize disease
    - Evidence-based (eg, DMARDs)
    - Off-label use (eg, cytotoxic drugs, corticosteroids, therapies for PH)
  - Therapies to relieve symptoms and improve quality of life (eg, cough, dyspnea, fatigue)
  - Enrollment in clinical trials if available and appropriate
  - Lung transplantation for advanced disease refractory to other therapies
  - Best supportive care
- Vaccinations
  - Pneumococcal and influenza
  - Other if appropriate and not contraindicated (hepatitis, *Herpes zoster*, papillomavirus)
- Pulmonary rehabilitation if appropriate
- Supplemental oxygen as indicated for:
  - Resting hypoxemia
  - Nocturnal desaturation during sleep
  - Significant exertional oxyhemoglobin desaturation ( $\leq 88\%$ )
- Screen for GER (may be asymptomatic) or esophageal dysmotility as appropriate
  - Associated with presence of hiatal hernia (can be seen on HRCT)
  - Consider other testing (impedance/pH esophageal probe, esophagram, endoscopy) to detect, quantitate, and characterize (eg, acid vs nonacid)
- Screen and treat comorbidities and disease complications:
  - PH
  - Coronary artery disease
  - Thromboembolism
  - Infectious complications
  - Obstructive sleep apnea
  - Airway obstruction (eg, bronchiectasis, ILD superimposed on emphysema)
  - Diabetes mellitus
  - Osteopenia, osteoporosis

- Obesity (encourage weight-reduction)
- Cachexia/malnutrition (nutritional supplements)
- Anxiety and depression (refer for psychosocial support as needed)
- Adverse drug reactions
- Monitor disease activity at appropriate intervals
  - Pulmonary function testing
  - Intermittent thoracic imaging
    - CXR (frequency as needed for the specific disease process)
    - HRCT of the thorax if routine CXR imaging not adequate
- Prompt evaluation and treatment of disease exacerbations
- Discuss advance care planning as appropriate
  - End-of-life issues (resuscitation, ventilator support)
  - Directives (living will, durable power of attorney)
- Palliative care for end-stage disease (relief of suffering)

*Abbreviations:* CXR, chest radiograph; DLCO, diffusion capacity of the lung for CO; 6-MWT, 6-minute walk test.

Treatment that adequately treats/stabilizes systemic CTD may control associated pulmonary disease, and we have occasionally had patients at our center whose ILD stabilizes or even improves when they have undergone kidney transplant and been placed on posttransplant immunosuppression with a calcineurin inhibitor plus an anti-proliferative agent and low-dose prednisone. Rapid-onset pneumonitis/fibrosis with rapid progression may require intense therapy (eg, high-dose pulse IV methylprednisolone or IV cyclophosphamide combined with high-dose steroid) to attempt to stabilize the disease and prevent progression. In addition, similarly to patients with IPF,<sup>153</sup> patients with CTD-ILD can have acute pulmonary exacerbations with rapid deterioration.<sup>154,155</sup> Infection must be sought and treated if present, but these exacerbations may be caused by acute worsening with superimposed OP, DAD, or pulmonary hemorrhage as the cause of acute deterioration. BAL may prove useful in evaluating an acute deterioration in lung function,<sup>156</sup> and the presence of significant BAL lymphocytosis suggests the presence of a hypersensitivity drug reaction or other complication that is likely to respond to augmented immunosuppression if other causes (eg, infection, alveolar hemorrhage) are not identified.

If airway disease (eg, bronchiolitis) is the primary manifestation of lung involvement, adequate control of a systemic disorder may control and stabilize the lung disease. In addition, treatment with a macrolide or azalide may provide benefit for treatment of bronchiolitis or OP, and we have had several individuals with progressive bronchiolitis associated with RA achieve remission with substantial improvement in lung function with macrolide therapy. Macrolides may also benefit patients with bronchiectasis (which is usually associated with the presence of ILD) if used as an adjunctive therapy. When CTD is complicated by PH, either primary or secondary to CTD-ILD, it is unclear whether therapies used for treating precapillary pulmonary arterial hypertension (PAH),<sup>157</sup> such as prostanoids, phosphodiesterase inhibitors, or endothelin antagonists, are beneficial, because existing evidence is only anecdotal. A recent retrospective study of 70 patients with scleroderma from 2 large referral centers could not find clear benefit associated with PAH pharmacologic therapies.<sup>158</sup>

When patients have pathologic GER, measures to prevent GER should be considered. Lifestyle changes and positional changes (eg, elevation of the head of bed when recumbent) may help prevent reflux. Although PPI therapy may suppress acid secretion and alleviate symptoms of acid reflux if patients have associated symptoms (many do not), reflux may still occur despite PPI therapy. Antireflux surgery can be considered, although the presence of esophageal dysmotility, especially aperistalsis, greatly increases the challenge of surgical approaches that are intended to prevent GER, and antireflux surgery should be performed only by surgeons who are skilled at the procedure and can modify their approach appropriately if foregut dysmotility is present.<sup>140,159</sup> We have observed several patients with undifferentiated CTD-ILD and associated pathologic reflux to have lung disease stabilization or improvement after successful antireflux surgery.

To monitor established lung disease behavior over time or evaluate response to therapies, dyspnea assessment and intermittent pulmonary function testing along with a 6-minute walk test can usually provide an adequate gauging of disease status. Change in forced vital capacity over time correlates well with stability versus significant decline (>10% decline) in IPF, and similar observations have been made for diffusion capacity of the lung for CO ( $\geq 15\%$  decline) and 6-minute walk test (distance and desaturation).<sup>160</sup> Although HRCT is useful for diagnosis and fibrosis score severity is predictive of disease severity and prognosis in IPF, obtaining serial HRCTs to gauge disease progression is generally not useful and substantially increases radiation exposure. However, HRCT imaging can be useful to evaluate disease exacerbations, and it may be useful to gauge response to therapies if routine chest radiography is likely to be insensitive to parenchymal changes that suggest therapeutic benefit. Useful biomarkers that can predict prognosis and correlate with disease activity are much needed; with acute onset of CTD-ILD, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) may be considerably increased, and a significant decline or normalization of CRP and ESR generally correlates with response to therapy.

We need to know more about the natural history of autoimmune lung disorders, especially CTD-ILD. Autoimmune disorders occur because of loss of immune tolerance as the ability of regulatory mechanisms to maintain tolerance by suppressing autoreactive lymphocytes wanes,<sup>161</sup> which may correlate to some degree with advancing age.<sup>162</sup> A better understanding of regulatory mechanisms that depend on intact function of CD4+CD25+FoxP3+ regulatory T cells and the acquisition of knowledge that allows the manipulation or augmentation of this cell population such that immune tolerance can be reestablished may lead to a vastly improved ability to treat, control, or prevent various autoimmune disorders and avoid the many potential adverse side effects of currently used pharmacotherapeutic agents. Efforts to attain multidisciplinary consensus on criteria that can be used to measure disease activity and therapeutic response in CTD-ILD<sup>163,164</sup> are a step in the right direction and may lead to clinical trials that can establish therapies to improve our management of patients with autoimmune lung disease.

## SUMMARY

The lung is frequently involved and subject to inflammation and fibrosis in patients with CTD. Other autoimmune disorders such as Goodpasture syndrome can also involve the lung, and evolving research has identified autoimmune phenomena associated with non-CTD lung disease such as IPF and COPD. There are numerous drugs that can be used for systemic autoimmune disorders, but none have FDA labeling for treatment of CTD-ILD, and many have not been investigated for usefulness in treating

autoimmune lung disease. Nonetheless, treatment with agents such as corticosteroids, azathioprine, cyclophosphamide, or mycophenolate may provide benefit to patients with CTD-ILD, and other therapies such as prevention of pathologic GER or treatment of bronchiolitis with macrolides may also prove beneficial. The therapeutic approach must be personalized to each individual patient and their specific disease process, clinical behavior of the disorder, and associated comorbidities. Patients need to be educated concerning risks, benefits, and signs/symptoms of adverse reactions if immunosuppressive medications are prescribed, and treating medical personnel must be aware of potential adverse reactions and appropriate precautions and monitoring protocols for specific drugs when prescribed. If lung disease relentlessly progresses despite medical therapy, lung transplantation is a therapeutic option, with acceptable outcomes if patients wish to pursue this option. The natural history of CTD-ILD remains obscure, and clinical trials to evaluate efficacy of immunosuppressive therapies, especially promising new biologic or antifibrotic agents, are greatly needed.

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