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Assessment and management of connective tissue disease-associated interstitial lung disease

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Abstract. The intersection of the connective tissue diseases (CTD) and the interstitial lung diseases (ILD) is complex. Although often considered as a single entity, "CTD-ILD" actually reflects a heterogeneous spectrum of diverse CTDs and a variety of patterns of interstitial pneumonia. The evaluation of patients with CTD that develop ILD, or the assessment for underlying CTD in those presenting with presumed "idiopathic" ILD can be challenging and these evaluations can be optimized by effective multidisciplinary collaboration. When a diagnosis of CTD-ILD is confirmed, careful and thorough assessments to determine extra- versus intra-thoracic disease activity, and degrees of impairment are needed. Pharmacologic intervention with immunosuppression is the mainstay of therapy for all forms of CTD-ILD, but should be reserved only for those that demonstrate clinically significant and/or progressive disease. The management of CTD-ILD is not yet evidence based and there is a desperate need for controlled trials across the spectrum of CTD-ILD. Non-pharmacologic management strategies and addressing comorbidities or aggravating factors should be part of a comprehensive treatment plan for individuals with CTD-ILD. *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 2-21)*

Key words: Connective tissue disease, Collagen vascular disease, Interstitial lung disease, Interstitial pneumonia, Pulmonary fibrosis

Introduction

The connective-tissue diseases (CTDs) are a heterogeneous group of disorders characterized by systemic autoimmunity and varying degrees of inflammation and immune-mediated organ damage (Table 1). Lung involvement is common within the spectrum of CTDs (Table 2) (1), and interstitial lung disease (ILD) is a particularly challenging and potentially devastating manifestation (2, 3). Certain lung injury patterns of interstitial pneumonia (IP) are associated with specific CTDs (4), such as fibrotic non specific interstitial pneumonia (NSIP) in systemic sclerosis (SSc), usual interstitial pneumonia (UIP) in rheumatoid arthritis (RA), and lymphocytic interstitial pneumonia (LIP) in Sjögren's syndrome (SjS), but most of the IP lung injury patterns have been reported in each of the CTDs and a combination of patterns may co-exist in a given individual (Table 3) (5, 6).

The intersection of CTDs and ILD is often complex because of the variety of IP patterns encountered across the spectrum of CTDs, and in particular because the presentation of CTD-associated ILD (CTD-ILD) can vary by time of onset, order of or-

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Table 1. The connective-tissue diseases

Rheumatoid arthritis (RA)
Systemic sclerosis (SSc)
Systemic lupus erythematosus (SLE)
Idiopathic inflammatory myopathies (IIM)
Primary Sjögren's syndrome (SjS)
Mixed connective-tissue disease (MCTD)
Undifferentiated connective-tissue disease (UCTD)

gan manifestation, and degree of disease severity. ILD may be the initial manifestation of a CTD (with extra-thoracic features of a characterizable CTD developing months or years later) (7) or may be identified in well-established, long-standing CTD. Furthermore, ILD may be "subclinical" (radiographic or physiologic abnormalities without symptoms) in nature, chronically progressive, or may present in a fulminant, life-threatening manner (8).

It is important to keep in mind that although "CTD-ILD" is sometimes considered as a *homogeneous* entity (such as in this and many other reviews), the spectrum of "CTD-ILD" actually reflects a *heterogeneous* category of diseases comprised of the different CTDs along with the various IP patterns (Tables 1 and 3). It remains to be determined whether the approach to management of one type of CTD-ILD (e.g. SSc-NSIP) can be applied to other forms of CTD-ILD (e.g., RA-UIP or myositis-organizing pneumonia [OP]).

In this review, we initially discuss our approach to the clinical evaluation of individuals suspected of having CTD-ILD and how to determine their degree of respiratory impairment, and then turn our attention to the pharmacologic and non-pharmacologic therapeutic strategies for this group of diseases.

Table 2. Pulmonary manifestations of connective tissue diseases

Pleural disease
Pleuritis
Effusion
Thickening
Airways
Upper
Cricoarythenoid disease
Tracheal disease
Lower
Bronchiectasis
Bronchiolitis
Parenchyma
Interstitial lung disease
Diffuse alveolar hemorrhage
Acute pneumonitis
Nodules
Granulomatous diseases
Vascular
Pulmonary hypertension
Vasculitis
Thrombo-embolic disease

Modified from: (1)

General principles

1. Multi-disciplinary evaluation

ILD may be recognized within the context of a pre-existing, well-established CTD, or may be the initial manifestation of an underlying, oftentimes occult CTD (9). In those that develop ILD within the context of a pre-existing CTD, as with any patient that presents with interstitial infiltrates, a comprehensive evaluation is needed to explore all potential etiolo-

Table 3. Histologic and clinico-radio-pathologic patterns of the idiopathic interstitial pneumonias

Histologic patterns	Clinico-radio-pathologic diagnosis
Usual interstitial pneumonia (UIP)	Idiopathic pulmonary fibrosis (IPF)
Non specific interstitial pneumonia (NSIP	Non specific interstitial pneumonia †
Organizing pneumonia (OP)	Cryptogenic organizing pneumonia (COP) §
Diffuse alveolar damage (DAD)	Acute interstitial pneumonia (AIP)
Respiratory bronchiolitis (RB	Respiratory bronchiolitis interstitial lung disease (RBILD)
Desquamative interstitial pneumonia (DIP)	Desquamative interstitial pneumonia (DIP)
Lymphocytic interstitial pneumonia (LIP)	Lymphocytic interstitial pneumonia (LIP)

† This group represents a heterogeneous group with poorly characterized clinical and radiologic features.
§ COP is the preferred term, but it is synonymous with idiopathic bronchiolitis obliterans organizing pneumonia (BOOP).
Modified from: (5)

gies (e.g., infection, medication-toxicity, environmental and occupational exposures, familial disease, smoking-related lung disease, malignancy, etc.). The determination that the ILD is *associated* with the pre-existing CTD is through a process of elimination and requires a thorough and often multidisciplinary evaluation (9). In general, when considering the evaluation of ILD in patients with CTD, we consider the following steps.

a. Confirm the presence of a CTD. This may be simple, especially when the background CTD is well characterized and established, such as with rheumatoid factor (RF)/anti-cyclic citrullinated peptide (CCP) positive RA. Yet, quite often, the precise rheumatologic diagnosis is uncertain and the development of ILD may impact its classification. Take for instance the patient with an isolated positive SS-A autoantibody that may have been considered to have primary SjS. If the patient evolves to a presentation of fulminant NSIP with overlap of OP, along with radiographic features of a dilated esophagus, and the peripheral digital fissuring of "mechanic hands", one might consider the anti-synthetase syndrome; rather than what was initially suspected, in the absence of lung disease, to be more likely a case of primary SjS.

b. Determine whether the ILD pattern "fits". All of the well-characterized lung injury patterns as defined by thoracic high-resolution computerized tomographic (HRCT) are known to occur across the spectrum of CTD, with some patterns occurring more commonly with specific CTDs. However, the finding of atypical features – such as unilateral or upper lobe predominant or nodular parenchymal involvement – should prompt consideration for alternative etiologies rather than concluding the ILD is CTD-*associated*.

c. Exclude infection and medication-induced pneumonitis. A comprehensive and often multidisciplinary evaluation is needed in patients with CTD and ILD and rendering a diagnosis of CTD-*associated* ILD requires exclusion of other etiologies for the ILD (9). In particular, pulmonary infection and drug-induced lung disease almost always deserve thoughtful consideration.

d. Perform bronchoalveolar lavage when clinically indicated to exclude infection. In CTD-ILD patients, bronchoalveolar lavage (BAL) can be useful in sorting through the initial differential diagnosis, especially to exclude infection. Its usefulness as a baseline predictor of disease progression however is unclear (10, 11). Two recent well-designed prospective studies failed to demonstrate any prognostic significance obtained from BAL in patients with SSc-ILD, and therefore, the routine use of BAL to solely predict the likelihood of disease progression in CTD-ILD is not recommended (10, 11).

e. Biopsy the atypical ILD pattern. Because data have yet to show that determining a specific histopathologic pattern of lung injury impacts prognosis in CTD-ILD (12, 13), the role of surgical lung biopsy in patients with pre-existing CTD remains controversial. The relatively small study cohort sizes and the impact of selection and referral bias cannot be discounted and therefore the predictive power of different patterns of lung histopathology remains uncertain in CTD-ILD. Furthermore, CTD-ILD patients tend to be treated with immunosuppressive therapies, targeting both progressive ILD and extrathoracic inflammatory features, irrespective of specific ILD pattern. In this context, because the biopsy finding may not impact the use of immunosuppression, when the imaging pattern provides a strongly suggestive pattern that is consistent with the clinical scenario of CTD-ILD, clinicians often elect not to proceed with a surgical biopsy.

f. Detecting occult CTD. It can be challenging to distinguish "idiopathic" ILD from occult forms of CTDs. Many centers have found that a multi-disciplinary evaluation that includes pulmonologists, rheumatologists, radiologists, and pathologists can help in distinguishing idiopathic ILD from "forme fruste" CTD-ILD (9). Mittoo and colleagues retrospectively evaluated a cohort of 114 consecutive patients referred to a tertiary referral center for ILD evaluation (14). Thirty-four subjects (30%) were found to have CTD-ILD and, of these, only half had presented with established, pre-existing CTD. Younger age, high-titer ANA, and elevated muscle enzymes were associated with underlying CTD. Castelino and colleagues also described a cohort of 50 patients with ILD evaluated over a one-year period at a tertiary referral center (15). Of the 25 patients with a final diagnosis of CTD-ILD, 28% had

been initially referred with a diagnosis of idiopathic pulmonary fibrosis (IPF). Among those referred with CTD-ILD, 36% had their diagnosis changed to an alternate CTD. In total, the diagnosis was changed in 54% of the cohort. One small series from a multidisciplinary ILD program that incorporated rheumatologic evaluation described 6 patients evaluated within a 12-month span for presumed idiopathic IP (16). All were found to have a positive nucleolar-pattern ANA, along with either an anti-Th/To or anti-Scl-70 antibody, and all had subtle extra-thoracic features of SSc that included telangiectasia, Raynaud's phenomenon, digital edema, or esophageal hypomotility. This small series reinforced the concept that ILD may be the presenting manifestation of SSc, that engaging rheumatology for ILD evaluation can be helpful, and that suspicions for SSc are warranted in patients with a nucleolar-pattern ANA and NSIP or UIP. Another recent study highlights the importance of maintaining a heightened suspicion for occult CTD in cases of NSIP, even when the ANA and RF are negative (17). Nine patients evaluated over a 2-year period with idiopathic NSIP were ANA and RF negative but found to have the antisynthetase syndrome based on the presence of a tRNA-synthetase antibody (PL-7, or PL-12), NSIP, and subtle extra-thoracic features that included "mechanic hands", Raynaud's phenomenon, inflammatory arthritis, myositis, or esophageal hypomotility.

However, because it is both unrealistic and impractical to have rheumatologic specialty evaluation for all cases of idiopathic IP, and in the absence of evidence-based guidelines to help determine when to seek rheumatologic expertise, some have proposed that rheumatologic consultation could have more utility in certain clinical scenarios because of a higher index of suspicion for the presence of underlying CTD (Table 4) (18).

2. Determining impairment

A diagnosis of CTD-ILD does not necessarily mean that the patient will require treatment. Indeed, a fundamental principle pertinent to CTD-ILD is that many patients *will not* actually require immunosuppressive therapy targeting the ILD. In many cases, immunosuppressive treatment may be needed for the extra-thoracic inflammatory disease features (e.g., synovitis or myositis) but not the ILD. And, in many cases, neither intra- nor extra-thoracic disease requires immunosuppression. Given the high prevalence of subclinical ILD in RA and other CTDs, and the fact that most patients with SSc-ILD do not have progressive, clinically significant disease, it is

Table 4. Suggested categories of interstitial lung disease patients that require further rheumatologic evaluation

1. Women, particularly those < 50 years old
2. Any patient with extra-thoracic manifestations highly suggestive of CTD: a. Raynaud's phenomenon b. Esophageal hypomotility c. Inflammatory arthritis of the metacarpal-phalangeal joints or wrists d. Digital edema c. Symptomatic keratoconjuctivitis sicca
3. All cases of NSIP, LIP, or any ILD pattern with secondary histopathology features that might suggest CTD: a. Extensive pleuritis b. Dense perivascular collagen c. Lymphoid aggregates with germinal center formation d. Prominent plasmacytic infiltration
4. Patients with a positive ANA or RF in high titer (generally considered to be ANA > 1:320 or RF > 60 IU/mL), a nucleolar-staining ANA at any titer, or any positive autoantibody specific as to a particular CTD: a. Anti-CCP b. Anti-Scl-70 c. Anti-SSA, anti-SSB d. Anti-dsDNA, anti-Smith, anti-RNP e. Anti-tRNA synthetase

CTD: Connective tissue disease; NSIP: Non specific interstitial pneumonia; LIP: Lymphocytic interstitial pneumonia; ILD: Interstitial lung disease; Modified from: (18)

crucial to determine the degree of respiratory impairment in all patients with CTD-ILD.
The decision to treat CTD-ILD is often based upon whether the patient is clinically impaired by the ILD, whether the ILD is progressive by symptoms, physiology, or imaging, and what extra-thoracic features require therapy. Furthermore, the clinician must also consider potential contraindications, comorbid conditions or other mitigating factors that may exist. In the following sections, we discuss specific tools that are useful for determining respiratory impairment and disease monitoring.

a. Subjective assessment of impairment. The use of reproducible, subjective measures of the degree of breathlessness, exercise capacity, and quality of life with standardized clinical tools can help assess respiratory disease progression and functionality over time. However, given the significant extra-thoracic features associated with the CTDs, determining degree of impairment related to the ILD specifically can be a challenge. For example, in a patient with idiopathic inflammatory myositis (IIM), active myositis and associated diaphragmatic weakness may be a more potent driver of dyspnea than actual parenchymal disease. Similarly, pleural involvement in patients with systemic lupus erythematosus (SLE) or the diffusely thickened chest skin in a patient with SSc can also lend to severe dyspnea out of proportion to parenchymal involvement. In addition, because many CTD patients are sedentary and deconditioned due to chronic musculoskeletal involvement, depression and disability, reliably determining causes of respiratory impairment can be a challenge. A number of dyspnea indices have been validated in ILD. We find that the choice of which index to use is less important than their consistent implementation to reliably quantify subjective dyspnea. In one study, the self-reported measures of the Multi-Dimensional Health Assessment Questionnaire, University of California San Diego Dyspnea Questionnaire and Dypsnea-12 Questionnaire were found to be useful in the assessment of patients with a broad spectrum of CTD-ILD (19). Questionnaires take into account the patient perspective of the impairment are often self-administered and provide the clinician a reliable and reproducible longitudinal assessment of the subjective degree of respiratory impairment associated with CTD-ILD.

b. 6-minute-walk test. The 6-minute-walk test (6MWT) has been shown to correlate with the severity and the prognosis of IPF (20, 21), but the usefulness of 6MWT in CTD-ILD is not well defined. Because of concomittant extra-pulmonary manifestations in CTD, particularly joint and muscle disease, this test may not always be realistic to perform in CTD populations. In one study of patients with SSc-ILD, the 6MWT was found to be reproducible in the same patient over time, but it correlated poorly with the forced vital capacity (FVC) (22). In practice, unless musculoskeletal disease precludes its use, we find the 6MWT to be a relatively easy, inexpensive and reliable tool to gauge exercise capacity longitudinally in patients with CTD-ILD.

c. Pulmonary function testing. Pulmonary function testing (PFT) is a relatively easy, inexpensive, non-invasive and reliable method used to objectively and longitudinally assess the status of ILD. In particular, the longitudinal assessment of FVC and diffusing capacity for carbon monoxide (DLco) helps determine degree of respiratory impairment, response to therapy, and prognostication: longitudinal declines in FVC and DLco are associated with shortened survival (12, 13) in IPF and CTD-ILD. A recent study of 215 subjects with SSc-ILD demonstrated that the HRCT extent of fibrosis and degree of FVC reduction provides discriminatory prognostic information (23). In another study of RA-ILD, prospective follow-up over two years with PFT and thoracic HRCT showed that a DLco <54% of predicted had a 80% sensitivity and 93% specificity in predicting progression of the ILD (24).

d. Thoracic high-resolution computed tomography. Thoracic HRCT yields valuable information about ILD including the lung injury pattern and extent of disease, an assessment of disease progression, and the evaluation of extra-parenchymal abnormalities. In many cases of CTD-ILD, a specific radiologic pattern (e.g. UIP) can be determined with a high-degree of confidence (25). This pattern recognition within specific clinical scenarios may obviate the need for surgical lung biopsy and provide prognostic information. In SSc-ILD, Goh et al. showed that determining ILD extent by thoracic HRCT has prognostic value (23). A similar study in RA-ILD

Table 5. Suggested immunization schedule for individuals with connective tissue disease-associated interstitial lung disease

Vaccines	Schedule and particularities
Influenza vaccine (intramuscular)	Annually unless contraindicated
Pneumococcal vaccine -Pneumococcal 13-valent conjugate (PCV13) vaccine -Pneumococcal polysaccharide (PPSV23) vaccine	If first vaccinated with PPSV23 †: -PCV13 first followed by PPSV23 8 weeks later -PPSV23 each 5 years after If never vaccinated †: -PCV13 should be administered no sooner than 1 year after PPSV23 -PPSV23 each 5 years after (and at least 8 weeks after PCV13 if recent)
Other inactivated vaccines (e.g. diphtheria-tetanus-acellular pertussis (TDaP), human papilloma virus (HPV), hepatitis B)	Usual recommended schedule -Ideally before starting immunosuppressive therapy -But acceptable under DMARDs and biologics, except for RTX, where should be given 4 weeks before and 6 months after infusion ¶
Live attenuated vaccines (e.g. Bacillus Calmette-Guérin (BCG), nasal/oral influenza, measles-mumps-rubella (MMR))	-Consult specialist -Ideally 4 weeks before immunosuppression and at least five half-life after therapy discontinuation ¶
Herpes Zoster vaccine (live vaccine)	-Independen of age and prior episode status † -Ideally before starting immunosuppressive therapy; can be given with CS at <20 mg/day of prednisone equivalent or ≥20 mg/day if used for <2 weeks and AZA <3 mg/kg/day § ¶ -Other immunosuppressive agents (like MMF) or higher doses of the above mentioned agents should be stopped for 4 weeks before Herpes Zoster vaccine administration §

DMARDs: Disease-Modifying Anti-Rheumatic Drugs; RTX: Rituximab; CS: Corticosteroids; AZA: Azathioprine; MMF: Mycophenolate mofetil
Sources: (107-109)

also showed that initial extent and distribution of the ILD on thoracic HRCT were predictive of increased mortality (24). The presence of a fibrotic radiographic pattern as evidenced by reticular opacities, traction bronchiectasis and honeycombing are predictive of poor outcomes in both idiopathic IP and RA-ILD (26-28).

3. Treating the extra-thoracic manifestations in the context of CTD-ILD

Over the past 20 years, the armamentarium of pharmacologic therapies for rheumatologic conditions has greatly expanded. Traditional and biologic disease modifying anti-rheumatic drugs (DMARDs) have changed the face of modern rheumatology and are commonly used to treat the extra-thoracic manifestations of the CTD, particularly synovitis and myositis. Essentially all of these agents are immunosuppressive by design, and as such, all patients on DMARDs are at increased risk for respiratory and other infections with both typical and atypical pathogens. Furthermore, there is also some evidence that some of these therapies, methotrexate in particular (29), have the potential for causing pneumonitis and as such, their use in patients with CTD-ILD can pose challenges.

Methotrexate is one of the most popular traditional DMARDs in rheumatology and is considered first-line therapy for RA (30-32). Methotrexate is also a cause of acute pneumonitis in RA patients, with the incidence ranging from less than 1% (33) to as high as 11.3% (34). It appears that those with prior lung involvement are possibly more susceptible to the development of methotrexate pneumonitis (35, 36). Because methotrexate is such an effective DMARD in controlling the synovitis of RA, there are instances when we find the need to continue this agent in patients with RA-ILD to optimize their articular disease control. However, in general, because of its potential for causing pneumonitis, and the fact that it is difficult to distinguish methotrexate pneumonitis from a flare of underlying ILD, we tend to avoid methotrexate in our patients with CTD-ILD.

The biologic DMARDs, such as the anti-TNF agents, have become a mainstay in rheumatology practice over the past 15-20 years (37, 38). These agents have demonstrated high degree of efficacy for synovitis, myositis, ocular, and cutaneous aspects of RA and other CTDs and in some ways have revolu-

tionized the approach to managing CTD (37, 38). However, these agents are highly immunosuppressive in nature and patients on these agents are at particularly high risk for a wide variety of respiratory and other infections, including tuberculosis reactivation, non-tuberculous mycobacterial infections, and fungal infections, in addition to the usual pathogens (39-41). As such, the development of interstitial infiltrates or other parenchymal abnormalities in patients being treated with these agents mandates a heightened suspicion for typical or atypical infection. Furthermore, there has been some evidence based on case reports and post-marketing surveillance that a number of these biologic DMARDs can be associated with pneumonitis and as such they should be used with caution in patients with CTD-ILD (42, 43).

In our experience, we frequently use all of the classes of biologic DMARDs in our patients with CTD-ILD. Most often we use these agents to manage the extra-thoracic manifestations (e.g., synovitis or myositis) and find that these agents have no impact on the ILD. Interestingly, and as discussed below, there is some evidence that rituximab (RTX) may be an agent to consider for treating the ILD in refractory cases of CTD-ILD (44). Finally, when both ILD and extra-thoracic manifestations require immunosuppressive treatment, we often find it useful to combine one agent to target the ILD (e.g., azathioprine [AZA] or mycophenolate mofetil [MMF]) along with a biologic DMARD (e.g. etanercept or RTX) to target the synovitis or myositis.

Pharmacologic therapy for CTD-ILD (figure 1)

For those individuals with CTD-ILD in whom the ILD has been deemed to be clinically significant and progressive in nature, pharmacologic treatment with immunosuppression is often judged an appropriate step in management. An important qualifier when discussing therapy for CTD-ILD is that there are few data to adequately inform the discussion on management strategies for CTD-ILD. In fact, the only form of CTD-ILD for which any controlled data exist is limited to very modest results from two clinical trials in SSc-ILD. As such, much of the management of the spectrum of CTD-ILD is left to "experience-based" practice rather than "evidence-based" practice.

In the following sections we offer our approach to the pharmacologic and non-pharmacologic management strategies in CTD-ILD (Figure 1). We re-emphasize that "CTD-ILD" is not a homogeneous single disorder and that it is doubtful that one approach to management can be applied to the entire spectrum of CTD-ILD.

1. Corticosteroids

Therapy with corticosteroids (CS) remains the cornerstone of induction treatment in most forms of CTD-ILD in which immunosuppressive therapy is deemed to be necessary. CS have broad anti-inflammatory and immunosuppressive effects and, due to their rapid onset of action and efficacy in the treatment of CTD, CS have served as an initial and mainstay of therapy for CTD-ILD. There are some small case series supporting the use of CS for CTD-ILD (45, 46) but no controlled studies. In general, we would not advocate for CS as monotherapy for CTD-ILD. Rather, our approach is to initiate treatment with CS and either concomitantly or shortly thereafter initiate a secondary agent (e.g. AZA, MMF, or cyclophosphamide [CYC]) to serve as a steroid-sparing therapy. We tend to initiate CS at a dose of 0.5-1.0 mg/kg/day of prednisone equivalent. Depending on the clinical response and tolerability of the CS and the secondary agent, we attempt to slowly taper the CS to attain a daily dose of approximately 10 mg of prednisone equivalent between the 4th and 6th month of therapy, and hope for tapering off altogether as soon as clinically feasible. No tapering regimen has been studied or proven to be more effective. A notable exception is in SSc-ILD, in which moderate to high doses of CS is traditionally considered a risk for SSc renal crisis (47). In this scenario, we are reluctant to use prednisone in general, or when indicated, we aim to keep the prednisone dose ≤15 mg/day.

In our experience, there are clinical scenarios in which much more intense use of CS should be considered. Presentations of acute interstitial pneumonia (AIP) or the cellular form of NSIP or OP may be more "reversible" with more intense up-front dosing of CS followed by a prolonged taper. Another scenario is the NSIP encountered in those with anti-synthetase syndrome. In these cases, we often administer much higher doses of CS such as with a

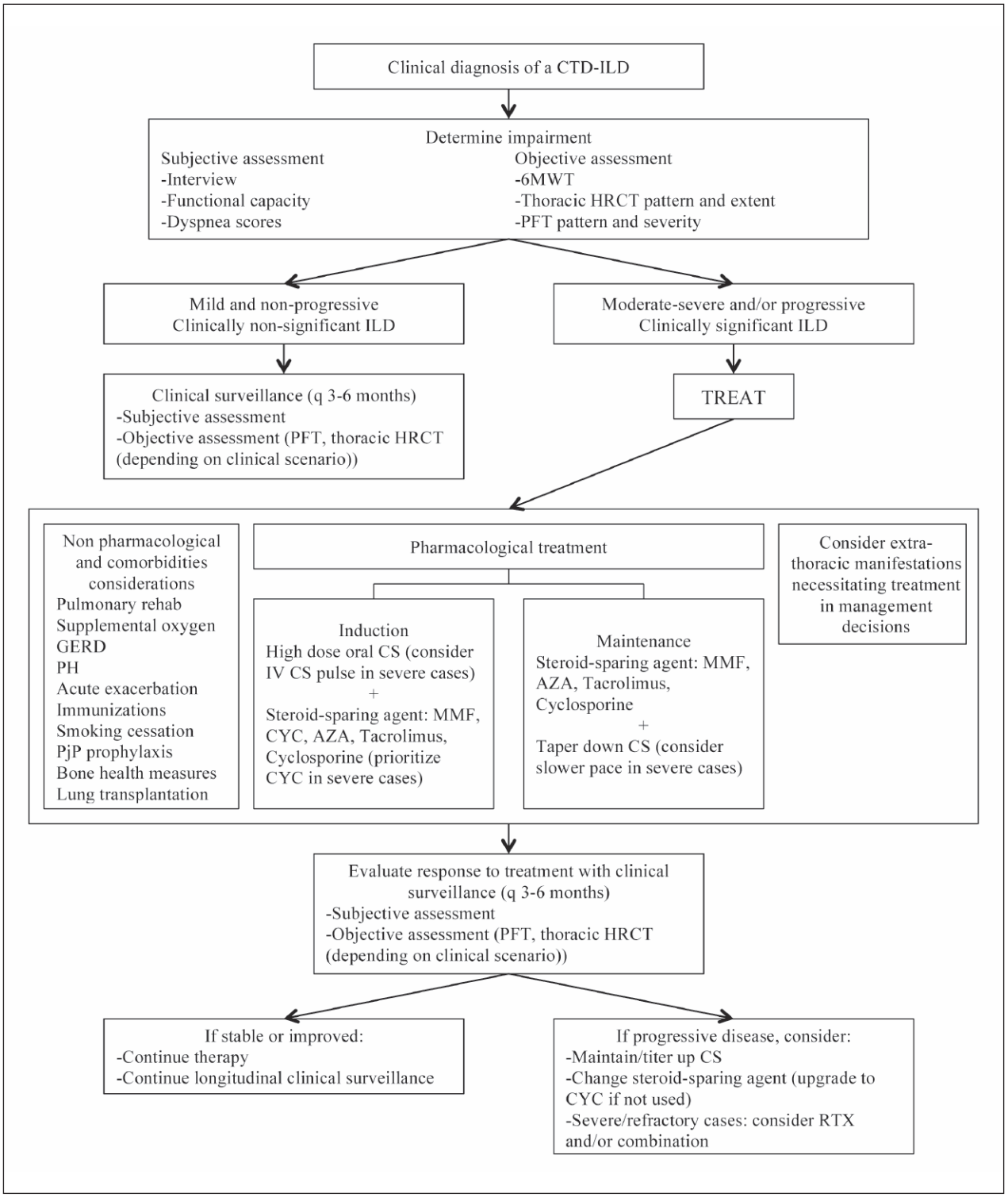

Fig. 1. Management algorithm for connective tissue disease-associated interstitial lung disease (CTD-ILD)
Legend: CTD: Connective tissue disease; ILD: Interstitial lung disease; 6MWT: 6-minute walk test; HRCT: High-resolution computed tomography; PFT: Pulmonary function testing; GERD: Gastroesophageal reflux disease; PH: Pulmonary hypertension; PjP: Pneumocystic jirovecii; CS: Corticosteroids; IV: Intravenous; MMF: Mycophenolate mofetil; CYC: Cyclophosphamide; AZA: Azathioprine; RTX: Rituximab

pulse course of intravenous (IV) methylprednisolone (500-1000 mg IV for 3 days followed by weekly pulses between 250-1000 mg for several weeks) concomitantly with daily CS at 1mg/kg of prednisone equivalent.
Further, given the significant short and long term adverse effects of CS, careful attention to a given individual's comorbid conditions factors in to how CS are utilized. Along with implementation of CS therapy, and as will be discussed in later sections, the clinician should be sure to give proper attention to bone health preservation and *Pneumocystis* prophylaxis.

2. Cyclophosphamide

CYC is one of the most potent steroid-sparing immunosuppressive medications and it is often used to treat a variety of organ-threatening manifestations of CTD. Small prospective (48-50) and retrospective studies (51, 52) have suggested that the use of CYC in CTD-ILD, and SSc-ILD in particular, may lead to stabilization or improvement in lung function. In practice, CYC is often considered the first line of therapy for the more severe forms of CTD-ILD. CYC is the only agent for which we have controlled clinical trial data in support of its use for CTD-ILD but those data are limited to SSc-ILD and, as will discussed below, their findings only lend modest support for this agent. Furthermore, it remains to be determined to what extent data from SSc-ILD can be applied to other forms of CTD-ILD.
The Scleroderma Lung Study (SLS) has provided some insights into the treatment of SSc-ILD (53). In SLS, 158 subjects were randomized to either oral CYC ≤2 mg/kg/day or placebo for a 12-month period. The primary endpoint was change in FVC. The study cohort was comprised of SSc subjects with evidence of active ILD by BAL or via thoracic HRCT, "early disease" (first non-Raynaud's symptom within 7 years), an FVC between 45-85% and at least moderate exertional dyspnea on the Mahler Dyspnea Index. The study excluded those with a DLco <30%, tobacco use in the previous six months, and any other significant pulmonary issue including pulmonary hypertension (PH) necessitating treatment. A majority of the subjects were women (70.3%) with a mean-age of 47.9±1.0 years and 59.5% had diffuse cutaneous SSc. The baseline mean FVC was 68.1±1.0% of predicted and DLco was 47.2±1.1% of predicted. The FVC difference at 12 months was +2.53% of predicted ($p<0.03$) in favor of the CYC group. The difference remained significant at eighteen months from study onset (six months after CYC had been discontinued) but was lost by twenty-four months (54), thus reinforcing the notion that longer-term immunosuppression is needed in SSc-ILD. Secondary endpoints achieved with CYC treatment included less radiographic progression of fibrosis (55), improved quality of life, and improvements in degree of skin thickening. Subjects with more restrictive disease (FVC <70%) (54), or higher fibrosis scores on thoracic HRCT, or more skin thickening had a more robust response to CYC, with improvement of their FVC instead of deterioration (FVC at 18 months from baseline: +5.10% of predicted with CYC versus -4.71% of predicted with placebo; average treatment effect of 9.81% [$p < 0.001$]) (56). Importantly, and as expected, treatment with oral CYC was associated with significant toxicities. There were statistically significant increases in the incidence of leukopenia and neutropenia and trends towards significantly higher prevalence rates of hematuria, pneumonia, and anemia, among those treated with CYC. Most of these adverse effects occurred during the first year (during CYC treatment) but similar trends were observed during the second year (after CYC discontinuation).
The only other controlled trial in CTD-ILD also involved SSc-ILD and the use of CYC. The Fibrosing Alveolitis in Scleroderma Trial (FAST) (57) randomized 45 subjects to active treatment (n=22) with IV CYC 600 mg/m^2 monthly for the first six months followed by AZA 2.5 mg/kg/day as maintenance therapy with background oral prednisolone 20 mg on alternate days compared with placebo (n=23). The majority of the subjects were women and most had limited cutaneous SSc. The difference in the change in FVC in the active treatment group (FVC_0 80.1±10.3% of predicted and FVC_{12} 82.5±11.3% of predicted) versus the placebo group (FVC_0 81.0±18.8% of predicted and FVC_{12} 78.0±21.6% of predicted) showed a trend toward statistical significance (FVC, after adjustment for baseline FVC, was 4.19% [$p=0.08$]). In fact, the FVC was more favorable in FAST than in SLS (+4.2% versus +2.5% respectively) but the smaller number of subjects in FAST (n=45) compared with SLS (n=158) impacted the ability to achieve statistical significance. Con-

trary to SLS, adverse events were few, without any bone marrow toxicity and fewer cases of hematuria. Respiratory tract infections occurred more frequently in the placebo group than with the actively treated group (17.4% versus 13.6%).
Taken together, in our opinion, the results from SLS and FAST have dampened enthusiasm for the use of CYC. Although improvements were noted in FVC, they were quite modest in nature. This, along with the substantial toxicity (bone marrow suppression, infection risk, and malignancy risk) associated with CYC has continued to temper its short- and long-term use in SSc-ILD and in all forms of CTD-ILD. Although CYC continues to be used in severe forms of CTD-ILD, there remains a desperate need to identify less toxic and more effective therapies for CTD-ILD.
The role of CYC in other forms of CTD-ILD is based on retrospective studies. A retrospective study of 46 IIM-ILD patients resistant to CS were treated with a subsequent immunosuppressive therapy (58). Twenty-four subjects were treated with oral CYC. At six months, the median change in FVC was +5.0% and the DLco increased by 2.93%. For the 33 subjects that remained on therapy for twelve months, the median change in FVC was +4.7% and the DLCO had increased from baseline by 2.3%. The prednisone dose was reduced from 40 mg/day to 10 mg/day at six months and at 7.5 mg/day at twelve months. In another report by Yamasaki et al. (59), 11 of 17 IIM-ILD patients showed improvement in their dyspnea, 8 of 17 had >10% improvement of vital capacity (VC) and 9 of 17 had >10 point reduction in their thoracic HRCT score after six months of treatment with CYC.
We tend to use CYC for the spectrum of CTD-ILD when the disease is severe or rapidly progressive in nature. Due to a better safety profile, we tend to use CYC in its IV form and infuse it monthly. We rarely use CYC for greater than twelve months and, in general, we try to switch to a less toxic agent (e.g., AZA or MMF) as soon as the clinical scenario allows.

3. Azathioprine

AZA is a commonly used medication in the treatment of CTD-ILD. However, other than as used in FAST, the data for AZA is limited to small and retrospective series. Studies (57, 60) using AZA as a maintenance therapy following 6 months of IV CYC in SSc-ILD report contradictory data, with one showing stabilized FVC and the other deteriorating FVC after eighteen months of AZA use. Less well studied as an induction agent, AZA in SSc-ILD has been retrospectively assessed in 14 patients (61). Three patients in this study failed prior use of CYC and its use for the other patients was felt to be inappropriate. Three patients had to stop the treatment due to adverse effects. Eight patients received treatment for at least twelve months and seven for eighteen months. With a baseline FVC of 54.3±3.5%, five patients had an increase of >10% of their FVC at twelve months and three stayed within 10% of there baseline FVC at twelve months.
There are numerous other case series or small retrospective reports demonstrating variable degrees of efficacy of AZA in CTD-ILD (58) and it is a commonly employed therapy without controlled data to guide its use. In general, we find AZA to be a well-tolerated therapy and one that can be an effective steroid-sparing agent suitable for the long-term treatment often needed for CTD-ILD. In our experience, we also find AZA to be particularly useful in RA-ILD as it can be effective in helping control both the synovitic and ILD components and for those with more severe synovitis, it can also be used safely along with biologic DMARDs.

4. Mycophenolate mofetil

MMF has become an increasingly popular treatment in CTD-ILD. The first series advocating for MMF in CTD-ILD was comprised of 28 subjects and demonstrated that MMF was well tolerated and associated with preservation of lung function among a diverse spectrum of CTD-ILD (62). A very small prospective study in SSc-ILD (63) used MMF 2000 mg/day with prednisolone ≤10 mg/day in six diffuse cutaneous SSc patients, five of whom had a recent diagnosis of “alveolitis”. At 4-6 months, improvement in FVC (from 65.6% to 76.2% of predicted [p=0.057]) and DLco (from 64.2% to 75.4% of predicted [p=0.033]) were noted and concomitant thoracic HRCT improvement was noted at 6-8 months. Several other retrospective studies report the use of MMF (2000 mg/day with or without low dose prednisone) in SSc-ILD (most with evidence of alveoli-

tis either on BAL or thoracic HRCT), showing trends towards significant improvement of PFT parameters and thoracic HRCT findings (62, 64-66). The largest study of MMF use for CTD-ILD was recently published (67) and included a heterogeneous cohort comprised of 125 CTD-ILD patients (including 44 SSc-ILD, 32 IIM-ILD, 18 RA-ILD). The mean age was 60.4±11.6 years, 42% were women, and most were treated with MMF 3000 mg/day over a 3-year period. In this large and diverse CTD-ILD retrospective cohort, MMF treatment was associated with effective CS dose tapering (at MMF initiation, median prednisone dose was 20 mg/day and at 12 months from MMF initiation, median prednisone dose was 5 mg/day [p<0.0001]). Along with its steroid-sparing effects, treatment with MMF was also associated with longitudinal improvements in FVC and DLco and was found to be a very well tolerated therapy (~90% adherence rate). In our experience, similar to AZA, MMF can also be safely combined with biologic DMARDs in individuals in whom the extra-thoracic disease (e.g., synovitis) necessitates a more intense and targeted approach with a biologic therapy.

5. Calcineurin antagonists

Cyclosporine and tacrolimus are commonly used immunosuppressive medications for CTD-ILD. No controlled data exist to guide their use, but retrospective studies lend support for their efficacy. A retrospective review of 32 centers in Japan from 1989 to 2000 report 32 IIM-ILD patients using CS and cyclosporine for the treatment of ILD (68). One out of 9 polymyositis (PM) patients and 9 out of 17 dermatomyositis (DM) patients (7 of whom had an acute presentation) died during the observation period (mean 25.7 months). To explain the high rate of death in the DM patients, the investigators assessed the timing of introduction of cyclosporine: the group with early combination treatment (cyclosporine within 2 weeks of diagnosis) versus those with late introduction lived longer (p=0.049). Another small study of 14 patients with IIM assessed PFT and thoracic HRCT scans one year after treatment with a combination of prednisone 1 mg/kg/day and cyclosporine 4 mg/kg/day instituted within 14 days of diagnosis of ILD. The study showed a significant improvement in HRCT scores, FVC (p=0.001) but not DLco (p=NS) when comparing values before and one year after treatment initiation (69).
Tacrolimus can be an effective agent for the spectrum of CTD-ILD and, perhaps, in IIM-associated ILD in particular. A retrospective study of 13 patients with both myositis and ILD (70) were treated with tacrolimus for a mean period of 51.2 months. Twelve were anti-Jo1 positive and one was anti-PL12 positive. Subjects in this small series demonstrated improvement in myositis as well as pulmonary function: both FVC and DLco statistically improved and were maintained during 150 weeks of follow-up. Other observations demonstrate potential efficacy in refractory cases previously treated with combination therapies including CYC and cyclosporine (68, 71, 72).

6. Rituximab

RTX is a chimeric monoclonal antibody targeting the cell-surface receptor CD20, found on B cells before their differentiation to memory and plasma cells. Treatment with RTX leads to B cell depletion, reduction of autoantibody generation, modifications of inflammatory cytokines, and T cell function alterations; making this agent a potent treatment option for many different autoimmune diseases (e.g. systemic vasculitis and RA), and is often used in severe and refractory cases of other CTDs (73). Extending its use beyond non-Hodgkin lymphoma and RA, RTX is now used in many different autoimmune diseases (74) and is largely very well tolerated (75). A small retrospective series of eleven patients with anti-synthetase syndrome (76), all with ILD, 3 with acute presentations, and 10 with positive anti-Jo1 antibody, were treated with RTX as a rescue therapy after failure of CYC and/or other immunosuppressive therapies. Nine patients received the RA regimen and two received 375 mg/m^2 per week for four consecutive weeks. Comparing the PFT data obtained in the eight months preceding treatment with PFT data obtained in the seven months following treatment, six patients had in improvement of >10% of their FVC and three had in increase of >15% of their DLCO. Three to six months following infusion, the thoracic HRCT showed a regression of the ground glass opacities in four patients and progression in one patient. Keir et al. (77) reported eight cases of CTD-ILD (5 with IIM; median FVC 45%

of predicted and median DLco 25% of predicted) in which RTX 1000 mg IV twice at 2-week interval was used as rescue therapy. Six of these patients had serial PFT: prior to RTX infusion, all had decline in FVC and DLco, and post-RTX infusions, a median DLco improvement of 22% of predicted (p=0.04) and a median FVC improvement of 18% of predicted (p=0.03) was noted. The same group recently reported their experience with RTX infusions in fifty cases of severe and refractory ILD; thirty-three of these cases had CTD-ILD (10 IIM, 8 SSc, 9 undifferentiated connective tissue disease) (44). This was a very severely impacted cohort: forty-nine out of fifty had received prior immunosuppression with cytotoxic medications, four required mechanical ventilation, mean DLco was 24.5% of predicted and mean FVC was 44.0% of predicted. In the CTD-ILD sub-group, 85% of the patients (most with IIM) were classified as responders. In the 6-12 month period prior to RTX, a median decline in FVC of 13.3% of predicted and in DLco of 18.8% of predicted was noted compared to the 6-12 month period post-RTX therapy, where an improvement of 8.9% of the FVC in % of predicted (p<0.01) and a stabilization of the DLco (p<0.01) was noted.

There are several small studies of RTX in SSc-ILD. With secondary endpoints of PFT and thoracic HRCT measures, fifteen patients with diffuse cutaneous SSc and mild-moderate ILD (patients with a FVC or DLco <50% of predicted were excluded) received RTX 1000 mg infusions at days 0 and 14. At six months, the FVC, DLco and the HRCT remained stable in this SSc population at high risk of progressive ILD (78). Daoussis et al. reported the results of a small randomized controlled trial of fourteen SSc-ILD patients: eight subjects treated with RTX 375 mg/m^2 per week for four consecutive weeks and then again six months later were compared with six subjects in the "control group" that received standard treatment (including prednisone, MMF, CYC and bosentan) (79). At one year, the FVC in the RTX group increased from 68.1±19.7 to 75.6±19.7% of predicted (p=0.0018), an improvement of 10.3% compared to the control group losing 5.0% of predicted (p=0.23). The DLco also improved significantly in those that were treated with RTX (from 52.3±20.7 to 62.0±23.2% of predicted [p=0.017], improvement of 19.5%) compared to a decrease of 7.5% in the control group (p=0.25). Follow up of the RTX-treated patients at two years from the first infusion (80) showed significant improvement maintenance for both FVC and DLco (p<0.0001 for both values). Another small prospective series of five SSc-ILD patients refractory to CYC were treated with RTX at a lower but more frequent dosing schedule (500 mg at days 0 and 14 every 3 months for a year). RTX treatment was associated with a significant increase in both FVC (48.5±6.7 to 66.0±4.0 % of predicted [p<0.001]) and DLco (72.0±5.2 to 89.0±3.2% of predicted [p<0.004]) at one year follow up (81).

Finally, the results of ten RA-ILD subjects (4 with UIP and 6 with NSIP) treated with RTX (1000 mg for 2 infusions, two weeks apart, at six months intervals) has been recently reported (82). Of the seven subjects with data at baseline and 48 weeks (one had an infusion reaction at baseline, one died after hip fracture and one died of pneumonia), FVC and DLco worsened in one subjects, stabilized in four and improved by >10% in two subjects.

These retrospective and small prospective studies suggest that RTX may be a promising therapy for select cases of CTD-ILD and this agent warrants further study.

7. Intravenous immunoglobulin

Intravenous immunoglobulin (IVIg) is used in the treatment of a wide variety of diseases, with more than 75% of the IVIg in the United States administered to patients with autoimmune or inflammatory conditions (83). The immunomodulatory and anti-inflammatory effects of IVIg remain of unclear mechanisms, with many pathways in the innate and adaptive immune system being potentially targeted, going beyond simple antibody replacement and neutralization. There are few data in support of IVIg use in CTD-ILD. Five patients with severe IIM-ILD treated with high dose CS and other immunosuppressive agents were given IVIg as rescue therapy. Two patients improved and survived, two initially improved but deteriorated after seven days and died (none were retreated) and one deteriorated and died (84). Usually reserved for refractory muscle disease resistant to the combination of other agents or in severe cases necessitating aggressive initial therapy, more studies and reports are needed before being attributed any role in CTD-ILD.

Non-pharmacologic therapies and strategies for CTD-ILD

1. Cardio-pulmonary rehabilitation

Cardio-pulmonary rehabilitation is an important adjunctive therapy for several chronic lung diseases, including ILD (85). Although not formally studied in CTD-ILD, we find cardio-pulmonary rehabilitation to be useful for both the ILD component as well as some of the extra-thoracic disease components (e.g. muscle strengthening). In our experience, for those that are not limited significantly by their musculoskeletal disease components, cardio-pulmonary rehabilitation can be an effective, though often underutilized, adjunctive therapy in patients with CTD-ILD.

2. Oxygen supplementation

Though not formally studied in CTD-ILD, we believe that the need for supplemental oxygen should be evaluated in all patients with ILD, to ensure that the patient is not hypoxic while at rest, with exercise or with sleep. A few studies in ILD demonstrate improvement of exercise-capacity with oxygen supplementation but data on patient-related outcomes and survival are surprisingly lacking (86-88). In addition, given how commonly CS are used, and their Cushingoid side effects, consideration for obstructive sleep apnea is often warranted in this population.

3. Gastro-esophageal reflux disease

Gastro-esophageal reflux disease (GERD) is one of the most troublesome medical conditions encountered in individuals with CTD-ILD. Consideration and evaluation for GERD-associated lung injury and aspiration pneumonitis is particularly warranted in CTD-ILD. GERD and dysmotility of the esophagus are quite common in these cohorts (89-93), and can often be difficult to treat. General treatment measures such as avoidance of specific foods that decrease the lower esophageal sphincter tone (e.g., coffee, chocolate, mint), eating multiple smaller portions throughout the day rather than the traditional three meals a day, avoiding eating or drinking before going to bed and elevating the head of the bed are important measures to implement (94). Proton pump inhibitor and H2-receptor antagonist therapies are commonly required. Pro-motility agents (e.g., domperidone, metoclopramide, octreotide, cisapride, prucalopride) are sometimes needed as well. Finally, surgical approach with fundoplication is sometimes attempted, particularly with recurrent aspiration pneumonia or in anticipation of lung transplantation, but this procedure can worsen the esophageal dysmotility (95).

4. Pulmonary hypertension screening and treatment

Patients with ILD are at an increased risk of developing secondary PH at least in part related to chronic hypoxia (96). In addition, patients with SSc, SLE, and mixed connective tissue disease (MCTD) are at risk for a primary vasculopathy resulting in pulmonary arterial hypertension (PAH) (97). As exertional dyspnea is seen with ILD and PH, it is often difficult to dissect the relative contributions of these pulmonary manifestations in a given patient. In our opinion, periodic screening with echocardiography should be considered in all CTD-ILD patients, however there are limitations to echocardiography in patients with advanced lung disease (98). Arcasoy and colleagues assessed the sensitivity (85%), specificity (55%) and positive predictive value (52%) of a finding of PH in patients with advanced lung disease and found that the estimated systolic pulmonary artery pressure is frequently inaccurate (98). In patients with SSc-ILD, Steen has shown that a disproportionate reduction in the DLCO relative to the FVC (ratio of FVC%/DLCO% >1.6) suggests concomitant PH (99). In patients with SSc, elevations in the serum brain-natriuretic peptide level also suggest the presence of PH (100). In patients with CTD-ILD suspected to have PH based on non-invasive assessment, definitive evaluation with right-heart catheterization is warranted.

Because SSc patients have the highest prevalence of ILD and PAH (101, 102), most if not all of the controlled data from trials for CTD-ILD or CTD-PAH are based on studying CTD patients with SSc spectrum of disease. The controlled trials that have demonstrated efficacy for SSc-ILD therapies excluded patients with SSc-PAH, and trials that have demonstrated efficacy for PAH-targeted therapies

have excluded patients with SSc-ILD. As a result, there are no controlled data to inform evidence-based decisions for cohorts of CTD-ILD patients with co-existent PH. In practice, it is not uncommon to combine immunosuppressive regimens for ILD with PAH-targeted therapies (e.g. prostanoids, phosphodiesterase-inhibitor therapy, endothelin-antagonist therapy) but these strategies are only based on anecdotal evidence (103, 104) and recent data suggest these approaches may be ineffective (105).

5. Acute ILD exacerbation assessment and management

Similar to other forms of ILD, patients with CTD-ILD can also have disease exacerbations (106), but these are neither well-characterized nor understood. In our experience, they are typically associated with a poor outcome. When a patient with CTD-ILD develops acute or subacute worsening breathlessness or cough, ILD exacerbation is a concern, and comprehensive evaluation is indicated to exclude more common entities such as respiratory infection, thromboembolism, or acute cardiovascular events. Such evaluation may require a multidisciplinary approach and includes pulmonary physiologic re-assessment, thoracic HRCT imaging, and bronchoscopic evaluation. Certain scenarios require CT-angiography or ventilation/perfusion scanning, echocardiography, or other cardiac testing. Drug-induced pneumonitis associated with immunosuppressive agents (such as CYC associated pneumonitis) cannot be ignored as a possibility and is often difficult to prove. When thoracic HRCT imaging shows progression of the ILD, and infectious causes have been excluded, alteration and intensification of the immunosuppressive regimen is often indicated. Our approach is to use high-dose CS as a first-line approach, followed by consideration of altering the steroid-sparing therapies. There are no formal guidelines to follow, decisions are individualized to each patient, and we emphasize the importance of a thorough evaluation to exclude infection in these immunocompromised patients.

6. Immunizations and smoking cessation

Smoking cessation is a fundamental component of treating any chronic lung disease and CTD-ILD is no different. It is important to encourage and emphasize smoking cessation in all patients with CTD, and certainly those with associated ILD.

Considering the presence of intrinsic lung disease and the fact that many patients with CTD have inherent immunodeficiency and are on chronic immunosuppressive treatment, basic infection prevention practices should be taught and emphasized, and appropriate vaccinations should be administered (Table 5). Unless otherwise contraindicated, the seasonal inactivated *Influenza* vaccine should be administered annually to all patients with CTD-ILD and the *Pneumococcal* vaccine should also be given to all CTD-ILD patients (107-109). Usual vaccination recommendations should also be followed, with ideal timing of inactivated vaccine administration being before starting immunosuppression. Because of its higher incidence in CTDs in general (110, 111), its potential for long term morbidity and its prevention easiness, *Herpes Zoster* vaccine, which is safe in this population (112), should be considered in all CTD patients independently of age and prior episode status (107). However, because the *Herpes Zoster* vaccine is a live attenuated vaccine, administering this vaccine to those on chronic immunosuppressive therapy may be controversial and seeking expert advice (such as with an infectious disease specialist) may be helpful to guide individual decisions (108).

6. Pneumocystis prophylaxis

Patients with CTD-ILD are more prone to infection, respiratory and otherwise. Also, due to the chronic role of potent immunosuppressive therapies used in these patients, they are at risk for both typical and atypical pathogens. *Pneumocystis jiroveci* pneumonia (PjP) is one of the atypical infections that can be encountered in CTD-ILD and with potentially devastating consequences (113, 114). This infection may be more difficult to diagnose in the rheumatologic population and may be associated with a worse prognosis compared to the HIV/AIDS population (115). PjP prophylaxis is usually recommended when two immunosuppressive therapies (including CS ≥20 mg/day of prednisone equivalent (116)) are used. Some practitioners also recommend this approach when using CS at ≥20 mg/day of prednisone equivalent alone for any sustained period of time. In general, we initiate PjP prophylaxis in those treated with CYC or in those on a secondary

agent such as MMF or AZA along CS ≥20 mg/day of prednisone equivalent. Importantly, it is important to consider possible PjP infection in any CTD patient with new infiltrative lung disease.

8. Bone health measures

It is important to consider bone health aspects in CTD-ILD patients as many are at substantially increased risk of bone density loss and ultimately fracturing. We encourage "good bone habits" (diet, exercise, alcohol and tobacco avoidance, etc.), ensure that calcium and vitamin D intakes are sufficient and prescribe supplements as needed and, in certain cases, add a bone anti-resorptive agent prophylactically. Baseline and longitudinal bone densitometry is important to quantify bone mineral density status as well. It is important to keep in mind that even low doses of CS (≤5 mg daily of prednisone equivalent) are associated with an increased fracture risk (117) and many patients treated for CTD-ILD will remain on CS for many months or even years. Guidelines about who should be prophylactically treated have been published (118) but there is controversy surrounding the use of anti-resorptive agents in patients <50 years of age. As usual, working in a multidisciplinary model and engaging primary care and rheumatology among other bone health specialists is an important adjunctive measure needed for the comprehensive care of CTD-ILD.

9. Lung transplantation

Lung transplantation is a last resort in the management of CTD-ILD. Careful selection of suitable CTD-ILD patients for lung transplantation is a complex and tedious process and thorough evaluations are needed. Notable manifestations that can complicate or preclude transplantation include concurrent PH, heart failure, renal disease, thromboembolic disease, chest wall skin thickening and, particularly, severe GERD with dysmotility or aspiration. Furthermore, the overall activity of the extra-thoracic CTD manifestations need to be considered as well as degree of associated functional impairment or disability attributable to the extra-thoracic disease features (e.g., destructive arthropathy or severly thickened skin). Studies of carefully selected patients do show that mortality in SSc-ILD transplanted patients is comparable to IPF at 2 years (38% in SSc versus 33% in IPF) (119). Another study showed no survival difference at one year between SSc and IPF patients but rates of acute graft rejection were significantly increased for the SSc compared with the IPF group (HR 2.91, p<0.007) contrary to other adverse effects such as chronic graft rejection, infection and pulmonary function for which there was no difference (120).

Summary

The intersection of the CTDs and the ILDs is complex. Although often considered as a single entity, "CTD-ILD" actually reflects a heterogeneous spectrum of diverse CTDs and a variety of patterns of interstitial pneumonia. The evaluation of patients with CTD that develop ILD, or the assessment for underlying CTD in those presenting with so-called "idiopathic" ILD can be challenging and these evaluations can be optimized by effective multidisciplinary collaboration. When a diagnosis of CTD-ILD is confirmed, careful and thorough assessments to determine extra versus intra-thoracic disease activity, and degrees of impairment are needed. Pharmacologic intervention with immunosuppression is the mainstay of therapy for all forms of CTD-ILD, but should be reserved only for those that demonstrate clinically significant and/or progressive disease. The management of CTD-ILD is not yet evidence based and there is a desperate need for controlled trials across the spectrum of CTD-ILD. Non-pharmacologic management strategies (e.g., supplemental oxygen and cardiopulmonary rehabilitation) and addressing comorbidities or aggravating factors (e.g., GERD, aspiration, bone health, PH, PJP prophylaxis) should be part of a comprehensive treatment plan for individuals with CTD-ILD.

References

1. Solomon JJ, Fischer A. Idiopathic interstitial pneumonia and connective tissue disease-associated interstitial lung diseases: similarities and differences. In: Meyer KC, Nathan SD, editors. Idiopathic pulmonary fibrosis : a comprehensive clinical guide. 1st ed. New York, NY: Springer; 2014. p. xv, 451 pages.
2. Elhai M, Meune C, Avouac J, Kahan A, Allanore Y. Trends in mortality in patients with systemic sclerosis over 40 years: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford).

2012;51(6):1017-26. Epub 2011/09/09. doi: 10.1093/rheumatology/ker269. PubMed PMID: 21900368.
3. Taborda AL, Azevedo P, Isenberg DA. Retrospective analysis of the outcome of patients with idiopathic inflammatory myopathy. A long-term follow up. Clinical and experimental rheumatology. 2014. Epub 2014/01/23. PubMed PMID: 24447373.
4. Marigliano B, Soriano A, Margiotta D, Vadacca M, Afeltra A. Lung involvement in connective tissue diseases: a comprehensive review and a focus on rheumatoid arthritis. Autoimmunity reviews. 2013;12 (11):1076-84. Epub 2013/05/21. doi: 10.1016/j.autrev.2013.05.001. PubMed PMID: 23684699.
5. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. American journal of respiratory and critical care medicine. 2002;165(2):277-304. Epub 2002/01/16. doi: 10.1164/ajrccm.165.2.ats01. PubMed PMID: 11790668.
6. Olson AL, Brown KK, Fischer A. Connective tissue disease-associated lung disease. Immunology and allergy clinics of North America. 2012; 32(4): 513-36. Epub 2012/10/30. doi: 10.1016/j.iac.2012.09.002. PubMed PMID: 23102064.
7. Cottin V. Significance of connective tissue diseases features in pulmonary fibrosis. European respiratory review : an official journal of the European Respiratory Society. 2013;22(129):273-80. Epub 2013/09/03. doi: 10.1183/09059180.00003013. PubMed PMID: 23997055.
8. Doyle TJ, Hunninghake GM, Rosas IO. Subclinical interstitial lung disease: why you should care. American journal of respiratory and critical care medicine. 2012;185(11):1147-53. Epub 2012/03/01. doi: 10.1164/rccm.201108-1420PP. PubMed PMID: 22366047; PubMed Central PMCID: PMC3373068.
9. Fischer A, Richeldi L. Cross-disciplinary collaboration in connective tissue disease-related lung disease. Seminars in respiratory and critical care medicine. 2014;35(2):159-65. Epub 2014/03/29. doi: 10.1055/s-0034-1371530. PubMed PMID: 24668532.
10. Goh NS, Veeraraghavan S, Desai SR, Cramer D, Hansell DM, Denton CP, et al. Bronchoalveolar lavage cellular profiles in patients with systemic sclerosis-associated interstitial lung disease are not predictive of disease progression. Arthritis and rheumatism. 2007;56(6):2005-12. Epub 2007/05/29. doi: 10.1002/art.22696. PubMed PMID: 17530640.
11. Strange C, Bolster MB, Roth MD, Silver RM, Theodore A, Goldin J, et al. Bronchoalveolar lavage and response to cyclophosphamide in scleroderma interstitial lung disease. American journal of respiratory and critical care medicine. 2008;177(1):91-8. Epub 2007/09/29. doi: 10.1164/rccm.200705-655OC. PubMed PMID: 17901414; PubMed Central PMCID: PMC2176114.
12. Bouros D, Wells AU, Nicholson AG, Colby TV, Polychronopoulos V, Pantelidis P, et al. Histopathologic subsets of fibrosing alveolitis in patients with systemic sclerosis and their relationship to outcome. American journal of respiratory and critical care medicine. 2002;165(12):1581-6. Epub 2002/06/19. doi: 10.1164/rccm.2106012. PubMed PMID: 12070056.
13. Park JH, Kim DS, Park IN, Jang SJ, Kitaichi M, Nicholson AG, et al. Prognosis of fibrotic interstitial pneumonia: idiopathic versus collagen vascular disease-related subtypes. American journal of respiratory and critical care medicine. 2007;175(7):705-11. Epub 2007/01/16. doi: 10.1164/rccm.200607-912OC. PubMed PMID: 17218621.
14. Mittoo S, Gelber AC, Christopher-Stine L, Horton MR, Lechtzin N, Danoff SK. Ascertainment of collagen vascular disease in patients presenting with interstitial lung disease. Respir Med. 2009;103(8):1152-8. PubMed PMID: 19304475.
15. Castelino FV, Goldberg H, Dellaripa PF. The impact of rheumatological evaluation in the management of patients with interstitial lung disease. Rheumatology (Oxford). 2011;50(3):489-93. PubMed PMID: 20685802.
16. Fischer A, Meehan RT, Feghali-Bostwick CA, West SG, Brown KK. Unique characteristics of systemic sclerosis sine scleroderma-associated interstitial lung disease. Chest. 2006;130(4):976-81. Epub 2006/10/13. doi: 10.1378/chest.130.4.976. PubMed PMID: 17035427.
17. Fischer A, Swigris JJ, du Bois RM, Lynch DA, Downey GP, Cosgrove GP, et al. Anti-synthetase syndrome in ANA and anti-Jo-1 negative patients presenting with idiopathic interstitial pneumonia. Respiratory medicine. 2009;103(11):1719-24. Epub 2009/06/06. doi: 10.1016/j.rmed.2009.05.001. PubMed PMID: 19497723; PubMed Central PMCID: PMC2857337.
18. Fischer A, Du Bois RM. A practical approach to connective tissue disease-associated lung disease. In: Baughman RP, Du Bois RM, editors. Diffuse lung disease : a practical approach. 2nd ed. New York, NY: Springer; 2012. p. xii, 400 p.
19. Swigris JJ, Yorke J, Sprunger DB, Swearingen C, Pincus T, du Bois RM, et al. Assessing dyspnea and its impact on patients with connective tissue disease-related interstitial lung disease. Respiratory medicine. 2010; 104(9): 1350-5. Epub 2010/05/18. doi: 10.1016/j.rmed.2010.03.027. PubMed PMID: 20471238; PubMed Central PMCID: PMC2914213.
20. Eaton T, Young P, Milne D, Wells AU. Six-minute walk, maximal exercise tests: reproducibility in fibrotic interstitial pneumonia. American journal of respiratory and critical care medicine. 2005; 171(10): 1150-7. Epub 2005/01/11. doi: 10.1164/rccm.200405-578OC. PubMed PMID: 15640367.
21. Hallstrand TS, Boitano LJ, Johnson WC, Spada CA, Hayes JG, Raghu G. The timed walk test as a measure of severity and survival in idiopathic pulmonary fibrosis. The European respiratory journal. 2005; 25(1): 96-103. Epub 2005/01/11. doi: 10.1183/09031936.04.00137203. PubMed PMID: 15640329.
22. Buch MH, Denton CP, Furst DE, Guillevin L, Rubin LJ, Wells AU, et al. Submaximal exercise testing in the assessment of interstitial lung disease secondary to systemic sclerosis: reproducibility and correlations of the 6-min walk test. Annals of the rheumatic diseases. 2007; 66(2): 169-73. Epub 2006/07/27. doi: 10.1136/ard.2006.054866. PubMed PMID: 16868020; PubMed Central PMCID: PMC1798506.
23. Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, et al. Interstitial lung disease in systemic sclerosis: a simple staging system. American journal of respiratory and critical care medicine. 2008;177(11):1248-54. Epub 2008/03/29. doi: 10.1164/rccm.200706-877OC. PubMed PMID: 18369202.
24. Dawson JK, Fewins HE, Desmond J, Lynch MP, Graham DR. Predictors of progression of HRCT diagnosed fibrosing alveolitis in patients with rheumatoid arthritis. Annals of the rheumatic diseases. 2002;61(6):517-21. Epub 2002/05/15. PubMed PMID: 12006324; PubMed Central PMCID: PMC1754108.
25. Lynch DA. Quantitative computed tomography of diffuse lung disease. Journal of thoracic imaging. 2013;28(5):264-5. Epub 2013/08/24. doi: 10.1097/RTI.0b013e3182a14fd8. PubMed PMID: 23966091.
26. Flaherty KR, Mumford JA, Murray S, Kazerooni EA, Gross BH, Colby TV, et al. Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. American journal of respiratory and critical care medicine. 2003;168(5):543-8. Epub 2003/05/30. doi: 10.1164/rccm.200209-1112OC. PubMed PMID: 12773329.
27. Kocheril SV, Appleton BE, Somers EC, Kazerooni EA, Flaherty KR, Martinez FJ, et al. Comparison of disease progression and

mortality of connective tissue disease-related interstitial lung disease and idiopathic interstitial pneumonia. Arthritis and rheumatism. 2005;53(4):549-57. Epub 2005/08/06. doi: 10.1002/art.21322. PubMed PMID: 16082627.
28. Lynch DA. Quantitative CT of fibrotic interstitial lung disease. Chest. 2007; 131(3): 643-4. Epub 2007/03/16. doi: 10.1378/chest.06-2955. PubMed PMID: 17356073.
29. Kremer JM, Alarcon GS, Weinblatt ME, Kaymakcian MV, Macaluso M, Cannon GW, et al. Clinical, laboratory, radiographic, and histopathologic features of methotrexate-associated lung injury in patients with rheumatoid arthritis: a multicenter study with literature review. Arthritis and rheumatism. 1997;40(10):1829-37. Epub 1997/10/23. doi: 10.1002/1529-0131(199710) 40:10< 1829::AID-ART16>3.0.CO;2-T. PubMed PMID: 9336418.
30. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis care & research. 2012;64(5):625-39. Epub 2012/04/05. doi: 10.1002/acr.21641. PubMed PMID: 22473917.
31. Bykerk VP, Akhavan P, Hazlewood GS, Schieir O, Dooley A, Haraoui B, et al. Canadian Rheumatology Association recommendations for pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs. The Journal of rheumatology. 2012;39(8):1559-82. Epub 2011/09/17. doi: 10.3899/jrheum.110207. PubMed PMID: 21921096.
32. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Annals of the rheumatic diseases. 2014;73(3):492-509. Epub 2013/10/29. doi: 10.1136/annrheumdis-2013-204573. PubMed PMID: 24161836; PubMed Central PMCID: PMC3933074.
33. Hanrahan PS, Scrivens GA, Russell AS. Prospective long term follow-up of methotrexate therapy in rheumatoid arthritis: toxicity, efficacy and radiological progression. British journal of rheumatology. 1989;28(2):147-53. Epub 1989/04/01. PubMed PMID: 2706419.
34. Hargreaves MR, Mowat AG, Benson MK. Acute pneumonitis associated with low dose methotrexate treatment for rheumatoid arthritis: report of five cases and review of published reports. Thorax. 1992;47(8):628-33. Epub 1992/08/01. PubMed PMID: 1412121; PubMed Central PMCID: PMC463926.
35. Golden MR, Katz RS, Balk RA, Golden HE. The relationship of preexisting lung disease to the development of methotrexate pneumonitis in patients with rheumatoid arthritis. The Journal of rheumatology. 1995;22(6):1043-7. Epub 1995/06/01. PubMed PMID: 7674228.
36. Searles G, McKendry RJ. Methotrexate pneumonitis in rheumatoid arthritis: potential risk factors. Four case reports and a review of the literature. The Journal of rheumatology. 1987;14(6):1164-71. Epub 1987/12/01. PubMed PMID: 3325643.
37. Taylor PC, Feldmann M. Anti-TNF biologic agents: still the therapy of choice for rheumatoid arthritis. Nature reviews Rheumatology. 2009;5(10):578-82. Epub 2009/10/03. doi: 10.1038/nrrheum.2009.181. PubMed PMID: 19798034.
38. Karampetsou MP, Liossis SN, Sfikakis PP. TNF-alpha antagonists beyond approved indications: stories of success and prospects for the future. QJM : monthly journal of the Association of Physicians. 2010; 103(12): 917-28. Epub 2010/08/31. doi: 10.1093/qjmed/hcq152. PubMed PMID: 20802008.
39. Wallis RS, Broder MS, Wong JY, Hanson ME, Beenhouwer DO. Granulomatous infectious diseases associated with tumor necrosis factor antagonists. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2004; 38(9): 1261-5. Epub 2004/05/06. doi: 10.1086/383317. PubMed PMID: 15127338.
40. Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Fu B, Ustianowski AP, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special emphasis on risks in the elderly. Rheumatology (Oxford). 2011;50(1):124-31. Epub 2010/08/03. doi: 10.1093/rheumatology/keq242. PubMed PMID: 20675706; PubMed Central PMCID: PMC3105607.
41. Salmon-Ceron D, Tubach F, Lortholary O, Chosidow O, Bretagne S, Nicolas N, et al. Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. Annals of the rheumatic diseases. 2011;70(4):616-23. Epub 2010/12/24. doi: 10.1136/ard.2010.137422. PubMed PMID: 21177290.
42. Hadjinicolaou AV, Nisar MK, Bhagat S, Parfrey H, Chilvers ER, Ostor AJ. Non-infectious pulmonary complications of newer biological agents for rheumatic diseases--a systematic literature review. Rheumatology (Oxford). 2011;50(12):2297-305. Epub 2011/10/25. doi: 10.1093/rheumatology/ker289. PubMed PMID: 22019799.
43. Panopoulos ST, Sfikakis PP. Biological treatments and connective tissue disease associated interstitial lung disease. Current opinion in pulmonary medicine. 2011;17(5):362-7. Epub 2011/05/21. doi: 10.1097/MCP.0b013e3283483ea5. PubMed PMID: 21597375.
44. Keir GJ, Maher TM, Ming D, Abdullah R, de Lauretis A, Wickremasinghe M, et al. Rituximab in severe, treatment-refractory interstitial lung disease. Respirology. 2013. Epub 2013/11/30. doi: 10.1111/resp.12214. PubMed PMID: 24286447.
45. Ando K, Motojima S, Doi T, Nagaoka T, Kaneko N, Aoshima M, et al. Effect of glucocorticoid monotherapy on pulmonary function and survival in Japanese patients with scleroderma-related interstitial lung disease. Respiratory investigation. 2013;51(2):69-75. Epub 2013/06/26. doi: 10.1016/j.resinv.2012.12.002. PubMed PMID: 23790734.
46. Horai Y, Isomoto E, Koga T, Okada A, Kawashiri SY, Tamai M, et al. Early diagnosis and treatment for remission of clinically amyopathic dermatomyositis complicated by rapid progress interstitial lung disease: a report of two cases. Modern rheumatology / the Japan Rheumatism Association. 2013;23(1):190-4. Epub 2012/03/31. doi: 10.1007/s10165-012-0637-6. PubMed PMID: 22460910.
47. Steen VD, Medsger TA, Jr. Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. Arthritis and rheumatism. 1998;41(9):1613-9. Epub 1998/09/29. doi: 10.1002/1529-0131(199809)41:9<1613::AID-ART11>3.0.CO;2-O. PubMed PMID: 9751093.
48. Silver RM, Warrick JH, Kinsella MB, Staudt LS, Baumann MH, Strange C. Cyclophosphamide and low-dose prednisone therapy in patients with systemic sclerosis (scleroderma) with interstitial lung disease. The Journal of rheumatology. 1993;20(5):838-44. Epub 1993/05/01. PubMed PMID: 8336309.
49. Schnabel A, Reuter M, Gross WL. Intravenous pulse cyclophosphamide in the treatment of interstitial lung disease due to collagen vascular diseases. Arthritis and rheumatism. 1998;41(7):1215-20. Epub 1998/07/15. doi: 10.1002/1529-0131 (199807) 41:7<1215::AID-ART11>3.0.CO;2-Y. PubMed PMID: 9663478.
50. Akesson A, Scheja A, Lundin A, Wollheim FA. Improved pulmonary function in systemic sclerosis after treatment with cyclophosphamide. Arthritis and rheumatism. 1994;37(5):729-35. Epub 1994/05/01. PubMed PMID: 8185701.
51. White B, Moore WC, Wigley FM, Xiao HQ, Wise RA. Cy-

clophosphamide is associated with pulmonary function and survival benefit in patients with scleroderma and alveolitis. Annals of internal medicine. 2000;132(12):947-54. Epub 2000/06/17. PubMed PMID: 10858177.
52. Steen VD, Lanz JK, Jr., Conte C, Owens GR, Medsger TA, Jr. Therapy for severe interstitial lung disease in systemic sclerosis. A retrospective study. Arthritis and rheumatism. 1994;37(9):1290-6. Epub 1994/09/01. PubMed PMID: 7945491.
53. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, et al. Cyclophosphamide versus placebo in scleroderma lung disease. The New England journal of medicine. 2006;354(25):2655-66. Epub 2006/06/23. doi: 10.1056/NEJMoa055120. PubMed PMID: 16790698.
54. Tashkin DP, Elashoff R, Clements PJ, Roth MD, Furst DE, Silver RM, et al. Effects of 1-year treatment with cyclophosphamide on outcomes at 2 years in scleroderma lung disease. American journal of respiratory and critical care medicine. 2007;176(10):1026-34. Epub 2007/08/25. doi: 10.1164/rccm.200702-326OC. PubMed PMID: 17717203; PubMed Central PMCID: PMC2078679.
55. Goldin J, Elashoff R, Kim HJ, Yan X, Lynch D, Strollo D, et al. Treatment of scleroderma-interstitial lung disease with cyclophosphamide is associated with less progressive fibrosis on serial thoracic high-resolution CT scan than placebo: findings from the scleroderma lung study. Chest. 2009;136(5):1333-40. Epub 2009/11/07. doi: 10.1378/chest.09-0108. PubMed PMID: 19892673; PubMed Central PMCID: PMC2773360.
56. Roth MD, Tseng CH, Clements PJ, Furst DE, Tashkin DP, Goldin JG, et al. Predicting treatment outcomes and responder subsets in scleroderma-related interstitial lung disease. Arthritis and rheumatism. 2011; 63(9): 2797-808. Epub 2011/05/07. doi: 10.1002/art.30438. PubMed PMID: 21547897; PubMed Central PMCID: PMC3910296.
57. Hoyles RK, Ellis RW, Wellsbury J, Lees B, Newlands P, Goh NS, et al. A multicenter, prospective, randomized, double-blind, placebo-controlled trial of corticosteroids and intravenous cyclophosphamide followed by oral azathioprine for the treatment of pulmonary fibrosis in scleroderma. Arthritis and rheumatism. 2006;54(12):3962-70. Epub 2006/11/30. doi: 10.1002/art.22204. PubMed PMID: 17133610.
58. Mira-Avendano IC, Parambil JG, Yadav R, Arrossi V, Xu M, Chapman JT, et al. A retrospective review of clinical features and treatment outcomes in steroid-resistant interstitial lung disease from polymyositis/dermatomyositis. Respiratory medicine. 2013; 107(6): 890-6. Epub 2013/03/23. doi: 10.1016/j.rmed.2013.02.015. PubMed PMID: 23517887.
59. Yamasaki Y, Yamada H, Yamasaki M, Ohkubo M, Azuma K, Matsuoka S, et al. Intravenous cyclophosphamide therapy for progressive interstitial pneumonia in patients with polymyositis/dermatomyositis. Rheumatology (Oxford). 2007;46(1):124-30. Epub 2006/06/07. doi: 10.1093/rheumatology/kel112. PubMed PMID: 16754626.
60. Berezne A, Ranque B, Valeyre D, Brauner M, Allanore Y, Launay D, et al. Therapeutic strategy combining intravenous cyclophosphamide followed by oral azathioprine to treat worsening interstitial lung disease associated with systemic sclerosis: a retrospective multicenter open-label study. The Journal of rheumatology. 2008; 35(6): 1064-72. Epub 2008/05/09. PubMed PMID: 18464307.
61. Dheda K, Lalloo UG, Cassim B, Mody GM. Experience with azathioprine in systemic sclerosis associated with interstitial lung disease. Clinical rheumatology. 2004;23(4):306-9. Epub 2004/08/05. doi: 10.1007/s10067-004-0906-7. PubMed PMID: 15293090.
62. Swigris JJ, Olson AL, Fischer A, Lynch DA, Cosgrove GP, Frankel SK, et al. Mycophenolate mofetil is safe, well tolerated, and preserves lung function in patients with connective tissue disease-related interstitial lung disease. Chest. 2006; 130(1): 30-6. Epub 2006/07/15. doi: 10.1378/chest.130.1.30. PubMed PMID: 16840379.
63. Liossis SN, Bounas A, Andonopoulos AP. Mycophenolate mofetil as first-line treatment improves clinically evident early scleroderma lung disease. Rheumatology (Oxford). 2006;45(8):1005-8. Epub 2006/02/24. doi: 10.1093/rheumatology/kei211. PubMed PMID: 16490756.
64. Gerbino AJ, Goss CH, Molitor JA. Effect of mycophenolate mofetil on pulmonary function in scleroderma-associated interstitial lung disease. Chest. 2008; 133(2): 455-60. Epub 2007/12/12. doi: 10.1378/chest.06-2861. PubMed PMID: 18071023.
65. Koutroumpas A, Ziogas A, Alexiou I, Barouta G, Sakkas LI. Mycophenolate mofetil in systemic sclerosis-associated interstitial lung disease. Clinical rheumatology. 2010; 29(10): 1167-8. Epub 2010/06/10. doi: 10.1007/s10067-010-1498-z. PubMed PMID: 20532938.
66. Zamora AC, Wolters PJ, Collard HR, Connolly MK, Elicker BM, Webb WR, et al. Use of mycophenolate mofetil to treat scleroderma-associated interstitial lung disease. Respiratory medicine. 2008; 102(1): 150-5. Epub 2007/09/08. doi: 10.1016/j.rmed.2007.07.021. PubMed PMID: 17822892.
67. Fischer A, Brown KK, Du Bois RM, Frankel SK, Cosgrove GP, Fernandez-Perez ER, et al. Mycophenolate mofetil improves lung function in connective tissue disease-associated interstitial lung disease. The Journal of rheumatology. 2013;40(5):640-6. Epub 2013/03/05. doi: 10.3899/jrheum.121043. PubMed PMID: 23457378; PubMed Central PMCID: PMC3676865.
68. Takada K, Nagasaka K, Miyasaka N. Polymyositis/dermatomyositis and interstitial lung disease: a new therapeutic approach with T-cell-specific immunosuppressants. Autoimmunity. 2005;38(5):383-92. Epub 2005/10/18. doi: 10.1080/08916930500124023. PubMed PMID: 16227154.
69. Kotani T, Takeuchi T, Makino S, Hata K, Yoshida S, Nagai K, et al. Combination with corticosteroids and cyclosporin-A improves pulmonary function test results and chest HRCT findings in dermatomyositis patients with acute/subacute interstitial pneumonia. Clinical rheumatology. 2011;30(8):1021-8. Epub 2011/02/23. doi: 10.1007/s10067-011-1713-6. PubMed PMID: 21340495.
70. Wilkes MR, Sereika SM, Fertig N, Lucas MR, Oddis CV. Treatment of antisynthetase-associated interstitial lung disease with tacrolimus. Arthritis and rheumatism. 2005;52(8):2439-46. Epub 2005/07/30. doi: 10.1002/art.21240. PubMed PMID: 16052580.
71. Ochi S, Nanki T, Takada K, Suzuki F, Komano Y, Kubota T, et al. Favorable outcomes with tacrolimus in two patients with refractory interstitial lung disease associated with polymyositis/dermatomyositis. Clinical and experimental rheumatology. 2005; 23(5): 707-10. Epub 2005/09/22. PubMed PMID: 16173253.
72. Oddis CV, Sciurba FC, Elmagd KA, Starzl TE. Tacrolimus in refractory polymyositis with interstitial lung disease. Lancet. 1999;353(9166):1762-3. Epub 1999/05/29. doi: 10.1016/S0140-6736(99)01927-3. PubMed PMID: 10347992; PubMed Central PMCID: PMC2977932.
73. Braun-Moscovici Y, Butbul-Aviel Y, Guralnik L, Toledano K, Markovits D, Rozin A, et al. Rituximab: rescue therapy in life-threatening complications or refractory autoimmune diseases: a single center experience. Rheumatology international. 2013; 33(6): 1495-504. Epub 2012/12/15. doi: 10.1007/s00296-012-2587-x. PubMed PMID: 23239037.
74. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. The New England journal of medicine. 2010;363(3):221-32. Epub 2010/07/22. doi: 10.1056/NEJMoa0909905. PubMed PMID: 20647199; PubMed Central PMCID: PMC3137658.
75. Tony HP, Burmester G, Schulze-Koops H, Grunke M, Henes J,

Kotter I, et al. Safety and clinical outcomes of rituximab therapy in patients with different autoimmune diseases: experience from a national registry (GRAID). Arthritis research & therapy. 2011;13(3):R75. Epub 2011/05/17. doi: 10.1186/ar3337. PubMed PMID: 21569519; PubMed Central PMCID: PMC3218885.
76. Sem M, Molberg O, Lund MB, Gran JT. Rituximab treatment of the anti-synthetase syndrome: a retrospective case series. Rheumatology (Oxford). 2009; 48(8):968-71. Epub 2009/06/18. doi: 10.1093/rheumatology/kep157. PubMed PMID: 19531628.
77. Keir GJ, Maher TM, Hansell DM, Denton CP, Ong VH, Singh S, et al. Severe interstitial lung disease in connective tissue disease: rituximab as rescue therapy. The European respiratory journal. 2012; 40(3): 641-8. Epub 2012/01/28. doi: 10.1183/09031936.00163911. PubMed PMID: 22282550.
78. Lafyatis R, Kissin E, York M, Farina G, Viger K, Fritzler MJ, et al. B cell depletion with rituximab in patients with diffuse cutaneous systemic sclerosis. Arthritis and rheumatism. 2009;60(2):578-83. Epub 2009/01/31. doi: 10.1002/art.24249. PubMed PMID: 19180481; PubMed Central PMCID: PMC2637937.
79. Daoussis D, Liossis SN, Tsamandas AC, Kalogeropoulou C, Kazantzi A, Sirinian C, et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. Rheumatology (Oxford). 2010;49(2):271-80. Epub 2009/05/19. doi: 10.1093/rheumatology/kep093. PubMed PMID: 19447770; PubMed Central PMCID: PMC2806066.
80. Daoussis D, Liossis SN, Tsamandas AC, Kalogeropoulou C, Paliogianni F, Sirinian C, et al. Effect of long-term treatment with rituximab on pulmonary function and skin fibrosis in patients with diffuse systemic sclerosis. Clinical and experimental rheumatology. 2012;30(2 Suppl 71):S17-22. Epub 2012/01/17. PubMed PMID: 22244622.
81. Moazedi-Fuerst F, Kielhauser S, Brickmann K, Hermann J, Lutfi A, Meilinger M, et al. Rituximab for systemic sclerosis: arrest of pulmonary disease progression in five cases Results of a lower dosage and shorter interval regimen. Scandinavian journal of rheumatology. 2014. Epub 2014/03/13. doi: 10.3109/03009742.2013.869617. PubMed PMID: 24611681.
82. Matteson E, Bongartz T, Ryu J, Crowson C, Hartman T, Dellaripa PF. Open-Label, Pilot Study of the Safety and Clinical Effects of Rituximab in Patients with Rheumatoid Arthritis-Associated Interstitial Pneumonia. Open Journal of Rheumatology and Autoimmune Diseases. 2012;2(3):53-8. doi: 10.4236/ojra.2012.23011.
83. Gelfand EW. Intravenous immune globulin in autoimmune and inflammatory diseases. The New England journal of medicine. 2012;367(21):2015-25. Epub 2012/11/23. doi: 10.1056/NEJMra1009433. PubMed PMID: 23171098.
84. Suzuki Y, Hayakawa H, Miwa S, Shirai M, Fujii M, Gemma H, et al. Intravenous immunoglobulin therapy for refractory interstitial lung disease associated with polymyositis/dermatomyositis. Lung. 2009;187(3):201-6. Epub 2009/04/24. doi: 10.1007/s00408-009-9146-6. PubMed PMID: 19387736.
85. Johnson-Warrington V, Williams J, Bankart J, Steiner M, Morgan M, Singh S. Pulmonary rehabilitation and interstitial lung disease: aiding the referral decision. Journal of cardiopulmonary rehabilitation and prevention. 2013;33(3):189-95. Epub 2013/04/19. doi: 10.1097/HCR.0b013e31828db112. PubMed PMID: 23595005.
86. Bye PT, Anderson SD, Woolcock AJ, Young IH, Alison JA. Bicycle endurance performance of patients with interstitial lung disease breathing air and oxygen. The American review of respiratory disease. 1982; 126(6):1005-12. Epub 1982/12/01. PubMed PMID: 7181219.
87. Harris-Eze AO, Sridhar G, Clemens RE, Gallagher CG, Marciniuk DD. Oxygen improves maximal exercise performance in interstitial lung disease. American journal of respiratory and critical care medicine. 1994;150(6 Pt 1):1616-22. Epub 1994/12/01. doi: 10.1164/ajrccm.150.6.7952624. PubMed PMID: 7952624.
88. Visca D, Montgomery A, de Lauretis A, Sestini P, Soteriou H, Maher TM, et al. Ambulatory oxygen in interstitial lung disease. The European respiratory journal. 2011;38(4):987-90. Epub 2011/10/04. doi: 10.1183/09031936.00190710. PubMed PMID: 21965506.
89. Ntoumazios SK, Voulgari PV, Potsis K, Koutis E, Tsifetaki N, Assimakopoulos DA. Esophageal involvement in scleroderma: gastroesophageal reflux, the common problem. Seminars in arthritis and rheumatism. 2006;36(3):173-81. Epub 2006/10/19. doi: 10.1016/j.semarthrit.2006.08.002. PubMed PMID: 17045629.
90. Fagundes MN, Caleiro MT, Navarro-Rodriguez T, Baldi BG, Kavakama J, Salge JM, et al. Esophageal involvement and interstitial lung disease in mixed connective tissue disease. Respiratory medicine. 2009; 103(6): 854-60. Epub 2009/02/10. doi: 10.1016/j.rmed.2008.12.018. PubMed PMID: 19201182.
91. Miura Y, Fukuda K, Maeda T, Kurosaka M. Gastroesophageal reflux disease in patients with rheumatoid arthritis. Modern rheumatology / the Japan Rheumatism Association. 2014;24(2):291-5. Epub 2013/11/21. doi: 10.3109/14397595.2013.843749. PubMed PMID: 24252041.
92. Mandl T, Ekberg O, Wollmer P, Manthorpe R, Jacobsson LT. Dysphagia and dysmotility of the pharynx and oesophagus in patients with primary Sjogren's syndrome. Scandinavian journal of rheumatology. 2007; 36(5): 394-401. Epub 2007/10/27. doi: 10.1080/03009740701607638. PubMed PMID: 17963171.
93. Gaal J, Varga J, Szabados L, Garai I, Galuska L, Suranyi P, et al. High prevalence of oesophageal involvement in patients with undifferentiated connective tissue disease using radionuclide oesophageal transit scintigraphy. Nuclear medicine communications. 2005; 26(12): 1113-7. Epub 2005/11/03. PubMed PMID: 16264359.
94. Bredenoord AJ, Pandolfino JE, Smout AJ. Gastro-oesophageal reflux disease. Lancet. 2013;381(9881):1933-42. Epub 2013/03/13. doi: 10.1016/S0140-6736(12)62171-0. PubMed PMID: 23477993.
95. Weinstein WM, Kadell BM. The Gastrointestinal Tract in Systemic Sclerosis. In: Clements PJ, Furst DE, editors. Systemic sclerosis. 2nd ed. Philadelphia, PA: Lipincott Williams & Wilkins; 2004. p. xvii, 430 p.
96. Nathan SD, Hassoun PM. Pulmonary hypertension due to lung disease and/or hypoxia. Clinics in chest medicine. 2013;34(4):695-705. Epub 2013/11/26. doi: 10.1016/j.ccm.2013.08.004. PubMed PMID: 24267299.
97. Ahmed S, Palevsky HI. Pulmonary arterial hypertension related to connective tissue disease: a review. Rheumatic diseases clinics of North America. 2014;40(1):103-24. Epub 2013/11/26. doi: 10.1016/j.rdc.2013.10.001. PubMed PMID: 24268012.
98. Arcasoy SM, Christie JD, Ferrari VA, Sutton MS, Zisman DA, Blumenthal NP, et al. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. American journal of respiratory and critical care medicine. 2003;167(5):735-40. Epub 2002/12/14. doi: 10.1164/rccm.200210-1130OC. PubMed PMID: 12480614.
99. Steen V, Medsger TA, Jr. Predictors of isolated pulmonary hypertension in patients with systemic sclerosis and limited cutaneous involvement. Arthritis and rheumatism. 2003;48(2):516-22. Epub 2003/02/07. doi: 10.1002/art.10775. PubMed PMID: 12571862.
100. Allanore Y, Borderie D, Avouac J, Zerkak D, Meune C, Hachulla E, et al. High N-terminal pro-brain natriuretic peptide levels and low diffusing capacity for carbon monoxide as independent predictors of the occurrence of precapillary pulmonary arterial hypertension in patients with systemic sclerosis. Arthritis and rheumatism. 2008;58(1):284-91. Epub 2008/01/01. doi: 10.1002/art.23187. PubMed PMID: 18163505.
101. Castelino FV, Varga J. Interstitial lung disease in connective tissue

diseases: evolving concepts of pathogenesis and management. Arthritis research & therapy. 2010;12(4):213. Epub 2010/08/26. doi: 10.1186/ar3097. PubMed PMID: 20735863; PubMed Central PMCID: PMC2945045.
102. Shahane A. Pulmonary hypertension in rheumatic diseases: epidemiology and pathogenesis. Rheumatology international. 2013; 33(7): 1655-67. Epub 2013/01/22. doi: 10.1007/s00296-012-2659-y. PubMed PMID: 23334373.
103. Olschewski H, Ghofrani HA, Walmrath D, Schermuly R, Temmesfeld-Wollbruck B, Grimminger F, et al. Inhaled prostacyclin and iloprost in severe pulmonary hypertension secondary to lung fibrosis. American journal of respiratory and critical care medicine. 1999; 160(2): 600-7. Epub 1999/08/03. doi: 10.1164/ajrccm.160.2.9810008. PubMed PMID: 10430735.
104. Shapiro S. Management of pulmonary hypertension resulting from interstitial lung disease. Current opinion in pulmonary medicine. 2003;9(5):426-30. Epub 2003/08/09. PubMed PMID: 12904715.
105. Le Pavec J, Girgis RE, Lechtzin N, Mathai SC, Launay D, Hummers LK, et al. Systemic sclerosis-related pulmonary hypertension associated with interstitial lung disease: impact of pulmonary arterial hypertension therapies. Arthritis and rheumatism. 2011;63(8):2456-64. Epub 2011/05/04. doi: 10.1002/art.30423. PubMed PMID: 21538327.
106. Solomon JJ, Fischer A. Connective Tissue Disease-Associated Interstitial Lung Disease: A Focused Review. Journal of intensive care medicine. 2013. Epub 2013/12/29. doi: 10.1177/0885066613516579. PubMed PMID: 24371251.
107. Bridges CB, Coyne-Beasley T. Advisory committee on immunization practices recommended immunization schedule for adults aged 19 years or older: United States, 2014. Annals of internal medicine. 2014;160(3):190. Epub 2014/03/25. doi: 10.7326/M13-2826. PubMed PMID: 24658695.
108. van Assen S, Agmon-Levin N, Elkayam O, Cervera R, Doran MF, Dougados M, et al. EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. Annals of the rheumatic diseases. 2011;70(3):414-22. Epub 2010/12/07. doi: 10.1136/ard.2010.137216. PubMed PMID: 21131643.
109. Bombardier C, Hazlewood GS, Akhavan P, Schieir O, Dooley A, Haraoui B, et al. Canadian Rheumatology Association recommendations for the pharmacological management of rheumatoid arthritis with traditional and biologic disease-modifying antirheumatic drugs: part II safety. The Journal of rheumatology. 2012;39(8):1583-602. Epub 2012/06/19. doi: 10.3899/jrheum.120165. PubMed PMID: 22707613.
110. Veetil BM, Myasoedova E, Matteson EL, Gabriel SE, Green AB, Crowson CS. Incidence and time trends of herpes zoster in rheumatoid arthritis: a population-based cohort study. Arthritis care & research. 2013; 65(6): 854-61. Epub 2013/01/03. doi: 10.1002/acr.21928. PubMed PMID: 23281295; PubMed Central PMCID: PMC3674119.
111. Chakravarty EF, Michaud K, Katz R, Wolfe F. Increased incidence of herpes zoster among patients with systemic lupus erythematosus. Lupus. 2013; 22(3): 238-44. Epub 2012/12/22. doi: 10.1177/0961203312470186. PubMed PMID: 23257402.
112. Zhang J, Delzell E, Xie F, Baddley JW, Spettell C, McMahan RM, et al. The use, safety, and effectiveness of herpes zoster vaccination in individuals with inflammatory and autoimmune diseases: a longitudinal observational study. Arthritis research & therapy. 2011;13(5):R174. Epub 2011/10/26. doi: 10.1186/ar3497. PubMed PMID: 22024532; PubMed Central PMCID: PMC3308109.
113. Sepkowitz KA. Opportunistic infections in patients with and patients without Acquired Immunodeficiency Syndrome. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2002;34(8):1098-107. Epub 2002/03/27. doi: 10.1086/339548. PubMed PMID: 11914999.
114. Iikuni N, Kitahama M, Ohta S, Okamoto H, Kamatani N, Nishinarita M. Evaluation of Pneumocystis pneumonia infection risk factors in patients with connective tissue disease. Modern rheumatology / the Japan Rheumatism Association. 2006;16(5):282-8. Epub 2006/10/14. doi: 10.1007/s10165-006-0502-6. PubMed PMID: 17039308.
115. Sowden E, Carmichael AJ. Autoimmune inflammatory disorders, systemic corticosteroids and pneumocystis pneumonia: a strategy for prevention. BMC infectious diseases. 2004;4:42. Epub 2004/10/19. doi: 10.1186/1471-2334-4-42. PubMed PMID: 15488151; PubMed Central PMCID: PMC526257.
116. Vananuvat P, Suwannalai P, Sungkanuparph S, Limsuwan T, Ngamjanyaporn P, Janwityanujit S. Primary prophylaxis for Pneumocystis jirovecii pneumonia in patients with connective tissue diseases. Seminars in arthritis and rheumatism. 2011;41(3):497-502. Epub 2011/10/01. doi: 10.1016/j.semarthrit.2011.05.004. PubMed PMID: 21959291.
117. Van Staa TP, Leufkens HG, Abenhaim L, Zhang B, Cooper C. Use of oral corticosteroids and risk of fractures. June, 2000. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 2005;20(8):1487-94; discussion 6. Epub 2005/09/09. doi: 10.1359/jbmr.2005.20.8.1486. PubMed PMID: 16149171.
118. Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis. Arthritis care & research. 2010;62(11):1515-26. Epub 2010/07/28. doi: 10.1002/acr.20295. PubMed PMID: 20662044.
119. Schachna L, Medsger TA, Jr., Dauber JH, Wigley FM, Braunstein NA, White B, et al. Lung transplantation in scleroderma compared with idiopathic pulmonary fibrosis and idiopathic pulmonary arterial hypertension. Arthritis and rheumatism. 2006;54(12):3954-61. Epub 2006/11/30. doi: 10.1002/art.22264. PubMed PMID: 17133609.
120. Saggar R, Khanna D, Furst DE, Belperio JA, Park GS, Weigt SS, et al. Systemic sclerosis and bilateral lung transplantation: a single centre experience. The European respiratory journal. 2010;36(4):893-900. Epub 2010/03/31. doi: 10.1183/09031936.00139809. PubMed PMID: 20351032; PubMed Central PMCID: PMC2921556.