Myositis-associated interstitial lung disease: a comprehensive approach to diagnosis and management

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ABSTRACT

Interstitial lung disease (ILD) frequently complicates the inflammatory myopathies and at times is the most prominent clinical feature. Over the years, there has been a growing recognition for the strong association between seropositivity of several myositis-specific antibodies (MSAs) and lung involvement. Growing literature suggests that individual MSAs may influence the risk of developing ILD and are associated with pulmonary disease severity and various clinical sub-phenotypes. The presence of ILD in patients with myositis correlates with increased morbidity and mortality. As such, it presents a unique treatment challenge for both the rheumatology and pulmonary communities and requires a multidisciplinary approach to management. This review will discuss the role of serologies and invasive and non-invasive testing modalities utilised to diagnose and monitor patients with myositis-ILD. Current studies pertaining to the wide array of immunomodulatory therapies utilised in cases of progressive disease are also highlighted in detail.

Interstitial lung disease in myositis

Interstitial lung disease (ILD) is a common complication of polymyositis (PM) and dermatomyositis (DM), with a prevalence ranging from 19.9% to 42.6% (1-3). ILD is the presenting feature and has been reported to precede signs of clinical myopathy in 7.2% to 37.5% of cases (2, 4, 5). However, even in the presence of active immunosuppression, ILD can develop at any point in the course of myositis, with a median time to development of 16.9–18 months (6, 7). Furthermore, it is not uncommon for ILD that is initially stable or improving on immunosuppression to ultimately progress, with one study demonstrating a subsequent worsening of pulmonary function tests (PFTs) occurring in up to a third of patients (8). Despite the fact that ILD was not included in the recently validated ACR/EULAR classification criteria for idiopathic inflammatory myopathies (IIM) (9), it is the leading cause of hospitalisation (10) and death in patients with PM/DM (3), carrying a reported mortality rate that ranges from 7.5% to 44% (2, 11, 12). Consequently, treatment decisions must often centre around lung-specific therapies. Patients with myositis-ILD present unique diagnostic and therapeutic challenges that are best approached through multidisciplinary collaborations involving experienced rheumatologists and pulmonologists (13). This review will highlight these challenges while providing current treatment strategies.

Myositis classification criteria

Ideally, treatment algorithms of myositis and associated ILD would be determined by the characterisations that exist within the different clinical subgroups of these disease entities. However, due to the heterogeneity of both myositis and ILD, there is no all-encompassing classification criteria that has been uniformly adopted by rheumatologists or pulmonologists. The Bohan and Peter Classification in 1975 first laid the groundwork for classifying the IIMs (14, 15). Since then, multiple classification and diagnostic criteria have proposed modifications to those originally put forth by Bohan and Peter, including the incorporation of myositis-specific antibodies(16). In 2017, a validated classification criteria of myositis was approved by the American College of Rheumatology and European League Against Rheumatism (9). While these criteria were a significant update from 1975, they in-

cluded only anti-Jo1 of the known myositis-specific antibodies (MSAs) and did not integrate ILD into the criteria. More recently, in 2018, Mariampillai *et al*. proposed developing a new classification system for IIM based on clinical findings and inclusion of an expanded MSA panel. In their study, IIM could be sorted into four major clusters, one of which was comprised predominantly of patients with evidence of the anti-synthetase syndrome and positivity for either the anti-Jo1 or anti-PL-7 antibody. Every patient in this cluster reportedly had pulmonary involvement, and the authors concluded that the incorporation of MSAs into the classification of myositis seemed to be more beneficial than the morphologic features obtained on muscle biopsy (17).

Myositis specific antibodies and ILD

Are autoantibodies associated with sub-phenotypes?

Antisynthetase antibodies are the most common autoantibodies seen in patients with either DM or PM, with an average prevalence in this disease population of 20% and 29%, respectively (18). To date, there are eight known anti-synthetase antibodies directed against the aminoacyl-tRNA synthetase enzyme (ARS-Abs) (Table I). Although the term "anti-synthetase syndrome" has historically been used to describe patients positive for one of these antibodies, some emerging literature argues against this terminology; indeed, it is not uncommon for clinical features thought to be characteristic of the so-called "syndrome" to be minimal or lacking at various stages of the disease (19-22). Additionally, characteristic features of the syndrome may be just as common in the presence of non-ARS myositis-associated antibodies (18). Moreover, select data suggest that each of these ARS-Abs may be associated with unique sub-phenotypes (Table I) (19, 23).

Anti-Jo1 is the most common and well-described ARS-Ab, comprising up to 60% of all ARS-Abs detected (23, 24). It has been associated with an increased rate of arthralgias (18, 19, 23, 25), mechanics hands (18, 19), and myositis (18, 22, 23, 25). In one large cohort evaluating 225 anti-Jo1 patients, arthritis was present at the time of disease onset in 64.5% of cases, with 76.5% exhibiting signs of joint disease by the end of follow-up. Although ILD was not present at baseline in roughly half the cohort, it ultimately developed in 84% of all patients, including the majority of those initially presenting with isolated arthritis as the only defining feature of the anti-synthetase syndrome (26).

Anti-PL-12 has been associated with the development of Raynaud's phenomenon (19) and isolated ILD (19). Anti-PL-7 is associated with the development of a heliotrope rash, myositis (19, 20), ILD preceding a diagnosis of myositis (19, 27), and pericardial effusions (20). Both anti-PL-12 and anti-PL-7 have been associated with more frequent and severe lung involvement when compared with anti-Jo1 (22, 25). Anti-OJ antibodies are associated with ILD (19, 28), more frequent and severe myopathy (28, 29), and a lower incidence of Raynaud's phenomenon compared with the other ARS-Abs (28). Given the relative rarity of anti-EJ, anti-KS, anti-Zo, and anti-Ha antibodies, it is difficult to draw definitive conclusions regarding their clinical features. However, anti-KS appears to be associated with isolated ILD (19).

It should be noted that many of the systemic features in patients with ARS-Ab develop over the course of months or years (26, 30, 31), and clinical profiles at the end of follow-up can be different than at study onset. As a result, studies using a small window of time to define the clinical features of a particular autoantibody may inherently be flawed. Furthermore, many of the sub-phenotypes identified in the earlier, smaller studies have not been reproduced in the larger cohorts of anti-synthetase patients. For instance, in the largest study of patients positive for an ARS-Ab to date that included over 800 patients, there was no significant difference between most antibody types with regards to survival or frequency of myositis, ILD, or accompanying clinical findings (*e.g*. fevers, mechanic's hands, or Raynaud's) (31). Therefore, it remains debatable whether the individual ARS-Abs confer distinct clinical features or fit within a cohesive named syndrome.

Autoantibodies in dermatomyositis-associated ILD

While most autoantibodies in DM, such as anti-Mi-2, anti-TIF-1-gamma, and NXP-2, are associated with a lower risk of ILD, anti-MDA-5 confers a higher risk of severe, progressive ILD. Anti-MDA5 antibodies are more common in both Asian populations and in patients with clinically amyopathic dermatomyositis (CADM) compared to those with classic DM (32-37), and their presence is associated with rapidly progressive ILD (32, 34-36, 38) and death (32, 36, 37, 39) in these cohorts. Historically, the overall response rate to therapy has been felt to be lower in patients with DM compared to PM (40-42). However, these studies did not account for the presence or absence of MDA-5 antibodies, which occur almost exclusively in DM patients. As such, perhaps MSA profile, and not the underlying type of myositis, determines prognosis in these ILD patients. Although the classic skin changes of palmar papules, deep ulcerations with punched out borders, and areas of frank skin necrosis have come to be almost pathognomonic for the presence of MDA-5 (33, 38, 43), these findings are not always present at the onset of disease, and we recommend testing for this antibody in all patients with underlying myositis or ILD.

Myositis-associated antibodies in overlap myositis with ILD

Anti-Ku and anti-PM-Scl antibodies have been associated with ILD, though they most frequently occur in patients with overlap myositis and features of systemic lupus erythematosus or systemic sclerosis, respectively (44, 45). The prevalence of ILD in patients with anti-PM-Scl antibodies has reportedly ranged from 38%-78% (18, 46-48), with lower rates of 27% being reported for those with anti-Ku antibodies (18). Both antibodies share many clinical features that overlap with those classically associated with the anti-synthetase syndrome (18, 46). However, myositis-specific and myositis-associ-

Table I. Antisynthetase antibodies and associated clinical manifestations.

Autoantigen	Prevalence in myositis (123)	% of ARS antibodies detected (5-7, 19, 20, 22, 23, 25, 27, 117, 124-134)	Distinct features (18-20, 22, 23, 25, 28, 29)
Histidyl t-RNA synthetase (Jo-1)	20-30%	22-73	Arthritis, mechanics hands, myositis
Threonyl t-RNA synthetase (PL-7)	2-5%	10-18	Heliotrope rash, severe ILD, myositis, pericardial effusions
Alanyl t-RNA synthetase (PL-12)	2-5%	6-17	Raynaud's, isolated ILD
Glycl t-RNA synthetase (EJ)	1%	2-23	
Isoleucyl t-RNA synthetase (OJ)	1%	2-5	Severe myopathy, lower incidence of Raynaud's
Asparaginyl t-RNA synthetase (KS)*	1%	3-8	Isolated ILD
Phenylalanyl t-RNA synthetase (ZO)*	NA	Infrequent	
Tyrosyl t-RNA synthetase (HA/YRS)*	NA	Infrequent	

*Not commercially available.

ated antibodies (MAAs) can co-exist, and the presence of anti-Ku or anti-PM-Scl should prompt a comprehensive serologic workup and a careful evaluation for evidence of disease involvement beyond the muscle and lungs.

Autoantibodies with primary lung involvement

In recent years, the growing availability of commercial myositis antibody panels, combined with an increased awareness of the anti-synthetase syndrome, has yielded a sizeable population of patients with positive autoantibodies and primary lung involvement. Oftentimes presenting with additional clinical features to suggest the possibility of an underlying rheumatologic process, these patients do not fulfil the criteria for an established connective tissue disease (CTD). Various terminology has evolved to capture these patients in the pulmonary field, including "undifferentiated CTD-associated ILD," (49) "lung-dominant CTD," (50) "autoimmune-featured ILD," (51) and, most recently, "idiopathic pneumonia with autoimmune features"(IPAF) (52). In a recent multicentre retrospective study, patients meeting IPAF criteria were stratified by the presence of MSAs and MAAs. Interestingly, survival was highest among patients who had MSAs, with outcomes that were indistinguishable from patients with overt IIM-ILD. The authors concluded that MSAs should perhaps be excluded from IPAF criteria, with these patients instead being treated in a similar fashion to those with a known myopathy (53).

Cancer-associated myositis

The association between PM/DM and malignancy is well known, and in some cases inflammatory myositis is considered a paraneoplastic process. Hill *et al*. evaluated 618 cases of DM and 914 cases of PM and found cancer rates of 32% and 15%, respectively, with non-Hodgkin lymphoma and ovarian, lung, pancreatic, stomach, and colorectal cancers being the most common types (54). The presence of certain MSAs themselves seem to be associated with an increased risk of malignancy. In 165 patients with ARS-ab, the rate of malignancy was 12%, without any appreciable difference between antibody subtypes. Patients were equally as likely to develop malignancy prior to, concurrent with, or following their diagnosis of ILD or myositis. Malignancy was listed as the cause of death in 18.8% of the 16 patients who died in this study (19). A large meta-analysis by Lega *et al*. demonstrated that the presence of an ARS-Ab was associated with a cancer prevalence ranging from 7–11%; other MSAs, including Mi2, SRP, PM-Scl, U1RNP, and Ku were associated with a cancer prevalence ranging from 0–48% depending on the study and specific antibody in question, though the risk of malignancy was not statistically different between these MSAs and the ARS-Abs (18). One study assessing over 200 patients with DM found that the presence of either NXP-2 or TIF-1γ identified 83% of the patients with cancer, and that the presence of one of these antibodies was associated with an increased risk of malignancy (odds ratio 3.78) (55). Lu *et al*. performed a meta-analysis of 28 PM/DM studies. They found that male sex, older age of disease onset (> 45 years), and more severe skin disease were risk factors for the presence of malignancy (56).

In our practice, we strongly emphasise the importance of routine age-appropriate cancer screening (pap smears, colonoscopies, mammograms, testicular exams). In patients with one of the above risk factors or the presence of either anti-NXP-2 or anti-TIF-1γ antibodies, we typically perform a screening CT scan of the chest, abdomen, and pelvis with a low threshold to pursue PET imaging in patients with unexplained weight loss, night sweats, or seemingly treatment-refractory disease. The presence of concurrent malignancy in a patient with active myositis or ILD can pose unique treatment challenges. Concerns about potential drug interactions between chemotherapy and immunomodulatory regimens may arise, and chemotherapeutic agents, including the new checkpoint inhibitors, are well known to be a cause of ILD and ILD flares (57). Furthermore, the risks of potentiating the growth or spread of cancer in the setting of robust immunosuppression must be weighed against the risk of a potential flare of the patient's underlying myositis or ILD. As

such, care is often taken to utilise the minimal effective immunosuppression dose, and close collaboration with the treating oncologic team is crucial.

Diagnostic assessment of ILD in myositis

Routine pulmonary screening

- Pulmonary function tests (PFTs)

We recommend that all patients with myositis, regardless of respiratory symptoms, receive full PFTs at the time of diagnosis and annually thereafter. In general, PFTs alone are not considered an adequate screening tool for detecting ILD in patients with an underlying CTD, with one study of scleroderma patients reporting a sensitivity of 63% and 85% for spirometry or a combination of spirometry and diffusion capacity, respectively (58). However, establishing a PFT at baseline is important, since a decline in pulmonary function over time may alert the provider to the development of subclinical parenchymal changes and prompt the acquisition of CT imaging. Patients with known ILD who are receiving active treatment for their disease are typically followed with PFTs every 3–4 months to ensure disease stability; in patients with new or worsening dyspnoea, PFTs are repeated more acutely.

Providers should be aware that interpreting PFTs in patients with myositis comes with certain caveats. In up to a third of cases, ILD is the initial manifestation of an underlying inflammatory myopathy, with overt muscle involvement developing later in the course of disease (2, 4-6, 41). As such, a declining FVC could be secondary to either worsening ILD or the development of myositis with subsequent respiratory muscle weakness. Conversely, an improvement in respiratory symptoms and spirometry may reflect an improvement in myopathy while partially masking a concurrent worsening of underlying lung inflammation. Therefore, PFTs in patients with myositis-ILD should be interpreted with caution and in the context of muscle enzyme trends and strength testing of proximal muscles. Intermittent screening for diaphragmatic weakness can be considered by performing spirometry in both the upright and supine position. MIPs/MEPs may also provide useful information regarding diaphragm strength in patients with suspected respiratory muscle weakness as a result of profound inflammatory muscle involvement. Full lung volumes to assess for an elevated RV/TLC ratio may also be useful.

- CT imaging

Although we do not recommend obtaining a high resolution CT scan as an initial screening test in all patients with myositis in the absence of respiratory symptoms or known ILD, we have a very low threshold to perform such imaging in any patient with unexplained dyspnoea, persistent chronic cough, crackles or rhonchi heard on auscultation, an FVC or DLCO <80% predicted upon initial screening, or a cumulative decline in FVC or DLCO of greater than 10% from initial baseline (58).

- Echocardiography

Pulmonary hypertension is a known complication of ILD, including patients with the anti-synthetase syndrome, and its presence is associated with decreased survival (59, 60). We typically order an echocardiogram to screen for pulmonary hypertension in patients with physical exam findings concerning for elevated pulmonary pressures (*e.g.* visible jugular venous distension, lower extremity oedema, palpable parasternal heave), new or worsening dyspnoea that is not readily explained by progression of their ILD, ambulatory desaturations in the clinic or on a formal 6-minute walk test, a fall in DLCO that is out of proportion to the decline in FVC, a decline in DLCO despite stable CT imaging, or an initial DLCO that is less than 40% predicted (61, 62).

- The role of bronchoscopy.

Bronchoscopy typically plays a limited role in the diagnosis of myositis-ILD. Cell counts and differentials do not reliably differentiate between the various histologic patterns seen in these patients, and the small sample size and crush artifact of tissue obtained via transbronchial biopsy renders this technique frequently inadequate to distinguish between usual interstitial pneumonia (UIP) and non-specific interstitial pneumonia (NSIP), the two patterns most commonly seen in the presence of an underlying CTD. As such, we typically only perform bronchoalveolar lavage when it is clinically and radiographically impossible to distinguish between a superimposed infection and an acute ILD exacerbation (63, 64).

- The role of surgical lung biopsy.

Histopathology in patients with myositis-ILD can present in a variety of patterns, though NSIP is by far more common than organising pneumonia, diffuse alveolar damage, or UIP, comprising 61–81.8% of cases in the largest series (2, 41, 65). Several pathologic features distinguish the UIP seen in patients with an underlying CTD from those with IPF, namely increased inflammation in a pattern consisting of plasma cells, lymphoid follicles, and germinal centres, combined with less prominent fibrosis and smaller honeycomb spaces (66-68). As a result, patients with myositis-ILD typically receive immunomodulatory therapy irrespective of their underlying pathology, and as will be discussed below, the decision to initiate an anti-fibrotic agent in this patient population is based up on radiographic evidence or PFT evidence of significant progression of the fibrotic component of disease. Therefore, given a morbidity that ranges from 9.3–12.6% (69), an in-hospital mortality of roughly 1.7% following a thoracic procedure and, with an underlying diagnosis of CTD being associated with worse outcomes (70), surgical lung biopsy is typically avoided in patients with myositis-ILD.

Agents used in the treatment of myositis-ILD

To date, there are no prospective, randomised studies comparing the efficacy of the various steroid-sparing agents. Some data suggests that the first-line agents are equivocal in their response rate and potentially interchangeable (Table II) (40, 71, 72). In one study, patients initially receiving either MMF, AZA, or cyclophosphamide were switched to an alternative agent either due to toxicity (n=8) or a failed clinical response (n=5).

Table II. Doses and standard monitoring of therapeutic agents used in the treatment of myositis-ILD

Medication	Use	Dose	Medication toxicity monitoring
Corticosteroids	Standard initial treatment for acute disease	0.5-1 mg/kg per day of prednisone Rapidly progressive ILD: pulse dose steroids 0.5-1 g/daily for 3 days	Glucose monitoring, annual bone density testing
Mycophenolate mofetil*	First-line steroid sparing agent*	Minimum efficacious dose of 2 g/daily, uptitration to 3 g/daily	CBC and LFTs every 2 weeks for the first 4 weeks, and once stable dose, every 4 weeks on stable therapy Yearly comprehensive skin exam with dermatologist to evaluate for cancerous moles (squamous)
Azathioprine*	First-line steroid sparing agent*	1.5-2.5 mg/kg daily	CBC and LFTs every 2 weeks for the first 4 weeks, and once stable dose, every 4 weeks on stable therapy Yearly comprehensive skin exam with dermatologist to evaluate for cancerous moles
Tacrolimus*	Second-line steroid sparing agent to be used in patients who are refractory to MMF or AZA, or in select cases of severe disease	Start at 0.5 mg PO BID, adjust to serum trough 5-10 ng/ml	CBC, CMP, Tacrolimus level every week for first 4 weeks, then every 4 weeks. Yearly comprehensive skin exam with dermatologist to evaluate for cancerous moles
IVIG	Adjunctive treatment	2 g/kg given over 3-5 days every 4 weeks	BMP, CBC every 4 weeks
Rituximab	Adjunctive treatment and/or second-line steroid sparing agent	1000mg IV Day 0, and then Day 14	CD 19/20 levels and serologic testing for viral hepatitis before treatment. Immunoglobulin levels before redosing if patient has received multiple doses
Cyclophosphamide	Third-line steroid sparing agent	2 mg/kg PO daily	CBC, CMP every 2 weeks, UA monthly, yearly urine cytology

*Steroid sparing agents are typically initiated at the start of therapy with corticosteroids.

Those who switched due to toxicity maintained a parallel clinical response regardless of the agent to which they switched; those who failed to respond also failed on the new agent (71). While there are reports in the literature of providers changing from AZA to MMF and vice versa in cases of ILD progression (6, 73), convincing evidence to support this approach is lacking. Consequently, it is not uncommon for patients with refractory pulmonary disease to require concurrent therapy with multiple steroid-sparing agents in order to prevent disease progression (40, 74-76).

Prednisone

Corticosteroids, both due to their relatively rapid onset of action and provider familiarity, have historically been utilised as first-line therapy in doses ranging from 0.75-1.0 mg/kg for the treatment of myositis-ILD. However, prolonged exposure to steroids is associated with significant side effects. Moreover, the response rate of myositis-ILD to steroids as monotherapy has reportedly ranged from 37.5% to 52%, with significantly lower rates in patients with DM compared to PM (42, 77). As such, there is typically a very low threshold to add an additional immunosuppressing agent early in the disease course.

Azathioprine

Historically, azathioprine (AZA) has been the most commonly used steroid-sparing agent reported in the treatment of myositis-ILD (7, 22, 40). In one study, a little over half of the patients receiving AZA as treatment for myositis-ILD with anti-Jo1 positivity demonstrated a positive response (6). Another retrospective study involving 35 patients with myositis-ILD receiving AZA and steroids demonstrated a similar response rate of roughly 54% (40). Huapaya *et al*. performed a retrospective analysis of myositis-ILD patients, of which 66 received AZA and 44 received MMF as the sole steroid-sparing agent. Although both groups demonstrated an improvement in % predicted FVC and a reduction in total prednisone dose over several years, only the AZA group experienced an improvement in % predicted for DLCO, and the final dose of prednisone at 36 months was lower on average by 6.6 mg. However, patients in the AZA group experienced a higher rate of adverse events (33.3% *vs*. 13.6%) and drug discontinuation, which was largely related to nausea and transaminitis (78).

Mycophenolate

One retrospective study evaluating the effectiveness of mycophenolate (MMF) in the treatment of CTD included 32 patients with myositis-ILD. Following the initiation of MMF, these patients maintained stable lung function after

52 weeks despite a significant decrease in average prednisone dose, thus establishing MMF as an effective steroid-sparing agent (73). In another study that included 11 patients with myositis ILD that received MMF as steroid-sparing agent, 54.5% demonstrated a clinical response, a rate similar to those receiving AZA and methotrexate (MTX) (40). Other small case series have also demonstrated that MMF is effective at improving lung function and reducing prednisone doses in patients with myositis ILD (79-81).

Calcineurin inhibitors

Although less commonly used in the United States, there is evidence that cyclosporine (CsA) may be an effective therapy in patients with myositis, with one study even suggesting an improved adjusted mortality in patients who receive the steroid-sparing agent at the time of ILD diagnosis compared with patients receiving CsA later in the course of their disease (82). In one retrospective analysis of 17 patients with steroid-refractory anti-Jo-1-positive ILD, treatment with CsA was associated with an average improvement in CT imaging and PFTs at a median follow-up of 96 months. Moreover, the median prednisone dose was decreased from 25 mg to 2.5 mg daily (83). Another retrospective study included 15 patients with antisynthetase syndrome–associated ILD, of which 11 demonstrated refractory disease despite treatment with a steroid-sparing agent. 13/15 patients demonstrated either stabilisation or improvement in FVC following the addition of either TAC or CsA, though no distinction was made between the two agents (84).

Similar to CsA, all of the data supporting the use of tacrolimus for the treatment of myositis-ILD comes in the form of case series and retrospective studies (85). However, tacrolimus has a greater potency and half-life than CsA (86), and there are reports of its efficacy in patients failing initial therapy with alternative steroid sparing agents, including CsA, MTX, AZA, and MMF (74, 86-88). Kurita *et al*. performed a retrospective analysis of 49 patients with myositis-ILD and determined that the use of tacrolimus was associated with longer event-free survival compared with traditional therapy comprised of either corticosteroid monotherapy or steroids combined with either cyclosporine or IV cyclophosphamide (89). Sharma *et al*. retrospectively analysed myositis-ILD patients who received prednisone in combination with either AZA, MTX, or MMF. Among those who initially failed to respond to this conventional therapy, 94% demonstrated improved lung function and an average decrease in prednisone dose of 65% following the addition of tacrolimus. The average dose of traditional steroid sparing agent was also decreased, with several patients able to discontinue their original DMARD completely (40).

Rituximab

While there are rare reports of its use as first-line therapy in patients with myositis-ILD (90), rituximab (RTX) has increasingly been combined with traditional steroid-sparing agents for refractory cases (76, 90). Bauhammer *et al*. evaluated 10 anti-Jo1 positive patients with ILD who received rituximab, and VC and DLCO increased significantly in all of them, with resolution of alveolitis on CT imaging in the 6 patients that had follow up imaging. As was seen in other cohorts (91, 92), the presence of Ro-52 antibodies was associated with more refractory ILD that failed to respond to traditional immunosuppression. However, an improvement in ILD was seen in all 7 patients with high Ro-52 titres following the administration of rituximab (90). Another study reviewing 10 patients with ILD in the setting of anti-synthetase antibodies further supports the notion that RTX may be beneficial in treating refractory disease. Allenbach *et al*. reported at least a 10% improvement in FVC in 50% of patients with stabilisation in the remaining 40%. Importantly, all patients in the study had failed a combination of both corticosteroids and at least two other immunosuppressive agents (75). To date, one of the largest retrospective studies evaluating the use of rituximab in the treatment of ILD involved 24 patients with either myositis or the antisynthetase syndrome, the majority of which had disease refractory to standard steroid-sparing agents. The group as a whole experienced a clinically significant improvement in FVC, DLCO, and CT abnormalities. However, the use of additional immunosuppressants both immediately prior to and following the administration of rituximab confound the results (76).

Intravenous immunoglobulin

Although there are numerous trials demonstrating improved muscle and skin findings in patients with inflammatory myositis treated with intravenous immunoglobulin (IVIG) (93-97), the data for its use in the treatment of myositis associated ILD is limited to only a few case reports (98, 99) and case series, with interpretation of the latter being confounded by the concurrent use of other immunosuppressant drugs that make it difficult to determine whether or not the positive effects seen were secondary to the addition of IVIG (100, 101). The largest study to date is a retrospective analysis by Huapaya *et al*., which retrospectively analysed 17 myositis-ILD patients, of which 82% had disease refractory to previous therapy with corticosteroids and two immunosuppressing agents. Roughly 40% of patients experienced an FVC % increase of at least 10%, and the mean prednisone dose decreased by more than 50%. Of note, 16/17 patients in this study were receiving concurrent therapy with at least one steroid-sparing immunosuppressing agent in addition to the IVIG (102). Therefore, although the data is limited, IVIG is often added as salvage therapy in patients with refractory ILD given that it is not considered to be as immunosuppressing.

Methotrexate

Despite concerns that it carries a risk of inciting pneumonitis, methotrexate (MTX) has long been used as a steroid-sparing agent for the treatment of myositis-ILD, with some series reporting 26%-31% of patients having received the drug at some point in the course of their disease (7, 22). One trial involving 17 patients with myositis-ILD that received MTX and corticosteroids reported a clinical response of 47%, and represents the limited data to date on

the efficacy of this drug as a steroid-sparing agent (40).

Cyclophosphamide

Evidence for the use of cyclophosphamide in the treatment of myositis-ILD is limited to retrospective case series, and our practice is to favour alternative steroid-sparing agents given concerns for its underlying toxicity. In the largest review to date encompassing 5 non-randomised studies and 193 patients with myositis-ILD, Ge *et al*. found that on average, cyclophosphamide was associated with an improvement in vital capacity and DLCO in 64.3% and 67.3% of patients, respectively. A similar proportion of patients also experienced an improvement in CT scores (103). One of the studies included in this review was that by Yamasaki *et al*., which assessed 17 patients with myositis-ILD, 9 of which had disease refractory to either high-dose steroids or alternative immunosuppression. 6/7 patients requiring oxygen were able to wean off completely, and roughly half of them realised an improvement in vital capacity and HRCT scores after 6 months or more of cyclophosphamide therapy (104).

Tocilizumab

Tocilizumab, an IL-6 receptor antagonist, has been reported to be efficacious in the treatment of myositis in a small number of cases (105, 106). However, a recently completed 24-week phase IIb double blind randomised controlled trial of tocilizumab in myositis did not demonstrate efficacy as measured by a validated myositis response criteria (107). One multicentre retrospective study assessing tocilizumab in 28 patients with rheumatoid arthritis-associated ILD receiving at least one dose of the drug demonstrated stability in FVC over a follow-up period of 30 months (108). In a Phase 3 randomised double-blind placebo-controlled trial of tocilizumab in systemic sclerosis, the secondary endpoint of change in FVC at week 48 favoured those receiving tocilizumab (p=0.002). Currently, data specific to patients with myositis-associated ILD is limited to a case series of 6 patients who received tocilizumab for the treatment of refractory, rapidly progressive lung disease in the setting of anti-MDA5 positive DM. Five of six patients survived and one was lost to follow-up (109). Future placebo-controlled studies will be required to determine the true efficacy of tocilizumab in the treatment of myositis-ILD.

JAK inhibitors

Tofacitinib, a pan JAK inhibitor, was first described in a case report to be efficacious in treating recalcitrant DM (110). Since then, multiple case reports have demonstrated its efficacy in predominantly skin refractory DM (111-114), and an open label pilot study of 10 patients showed early promise in the treatment of DM using a validated Myositis Response Criteria (115). Evidence for the utility of tofacitinib in the treatment of ILD comes from a small study involving patients with MDA-5 associated DM. Although only compared with historical controls, the data was promising and demonstrated a marked mortality improvement in a patient population that typically associated with poor outcomes (116). Larger trials are needed to determine if JAK inhibitors have a place among the growing list of steroid-sparing immunomodulatory therapies.

Antifibrotic therapy

Immunosuppression is the mainstay of treatment for patients with myositis-ILD, in large part because patients almost always present with at least some degree of inflammation on CT imaging or biopsy. However, while an NSIP pattern of disease predominates, UIP is not uncommon, reported in 4.5- 45% of cases depending on the series and the presence or absence of ARS-Abs (2, 65, 117). Although trials assessing the efficacy of anti-fibrotic agents specifically in patients with myositis-ILD have yet to be completed, there is growing evidence that these therapies can be of benefit to patients with an underlying CTD or progressive fibrosing lung phenotype, even in the absence of a traditional IPF diagnosis. The SENSCIS trial randomised 576 patients with systemic sclerosis, ILD, and fibrosis affecting at least 10% of the lungs to receive either placebo or the anti-fibrotic agent nintedanib. The rate of FVC decline over 52 weeks was significantly lower in the nintedanib group than in the placebo group (-52.4 ml/year vs -93.3 ml/year) (118), and the side effect profile was similar to that seen in trials of nintedanib in IPF (119), despite the fact that roughly half the patients in each arm were receiving concurrent therapy with mycophenolate (118).

A subsequent randomised trial of 663 patients with progressive fibrosing ILD of any cause other than IPF demonstrated a significant benefit from the addition of nintedanib over placebo, with an adjusted annual rate of FVC decline in the two groups of -80.8 ml/year and -187.8 ml/year, respectively. Although the cohort was not enriched for patients with myositis-ILD specifically, roughly a quarter of the patients in the study had been diagnosed with an underlying auto-immune disease (120). As a result of these trials, nintedanib has been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for not only the treatment of IPF, but for slowing the decline in FVC in patients with ILD associated with systemic sclerosis, and for the treatment of chronic fibrosing ILDs with a progressive phenotype.

Management

There are currently no standardised guidelines for the management of patients with myositis-ILD. Therapeutic algorithms are based on expert opinion and vary among academic centres (121, 122). Because of their rapid onset of action and ready availability, we use corticosteroids as an initial baseline therapy in all patients with myositis-ILD. Starting doses range from 0.5-1 mg/kg daily of prednisone equivalent depending on the severity of their disease and considerations about underlying comorbidities, such as diabetes and osteoporosis.

Given the long-term consequences of prednisone exposure, combined with the significant risk of disease flare and ultimate progression in these patients (8), we tend to prescribe either MMF (target dose 2,000-3,000 mg/day in divided doses) or AZA (target dose 2 mg/kg/day with a maximum of 200 daily) as first-line steroid-sparing agents concurrently with the initiation of pred-

nisone in the hopes that the latter can be weaned down to the lowest effective dose over the course of several months. Although no strong evidence supports the use of one agent over another, we tend to prefer MMF over AZA, since in our experience it less frequently leads to gastrointestinal symptoms and lab abnormalities (*e.g.* transaminitis).

We tend to add IVIG as adjunctive therapy to be used in addition to prednisone and a steroid-sparing agent for cases of refractory disease, severe skin involvement, or severe myositis. The standard dose is 2 g/kg of ideal body weight divided over three or five days. Careful pre-hydration with normal saline can often reduce the risk of infusion-related headaches.

In our practice, the use of tacrolimus is typically reserved for cases where patients fail to see an improvement or continue to exhibit signs of pulmonary function decline on PFTs after roughly 3-4 months of therapy with steroids and an anti-metabolite (MMF or AZA). Tacrolimus is occasionally chosen as a first-line steroid-sparing agent in cases of severe combined ILD and myositis. We favour the initial use of MMF or AZA when possible given concerns for long-term renal toxicity, neurotoxicity, and hyperglycaemia, combined with the fact that the need to monitor drug trough levels can be cumbersome to patients taking tacrolimus. We typically initiate a starting dose of 0.5 mg twice daily and titrate to target a 12-hour trough level of 5-10 ng/mL.

Rituximab is also used as add-on therapy in patients with progressive or persistent disease despite therapy with at least moderate dose prednisone (20 mg daily or more) and the use of an anti-metabolite or calcineurin inhibitor. The standard dose is 1000 mg given both on day zero and on day 14 (RA protocol). With rare exception, we avoid the use of cyclophosphamide given concerns about side effects and a lack of evidence that it is more effective than any other immunosuppressant for the treatment of ILD (71).

Despite appropriate treatment with immunomodulatory therapy, a subset of myositis-ILD patients will develop a progressive, fibrotic phenotype to their ILD. In cases where radiographic evidence suggests clear worsening of traction bronchiectasis or the development of honeycomb changes over time, we consider the addition of concurrent anti-fibrotic therapy with either nintedanib or pirfenidone.

In cases of rapidly progressive ILD (RP-ILD) with fulminant respiratory failure, we take an aggressive approach to management that includes the initiation of methylprednisolone 500-1000 mg/d for three days, AZA or MMF, and tacrolimus. Although we have had success substituting rituximab for tacrolimus in select cases, the latter may have a faster onset of action and is currently supported by stronger data for use in patients with refractory myositis-ILD (40, 74, 86-88).

Conclusion

ILD in myositis can portend a poor outcome when not recognised or treated early. In a patient with newly diagnosed myositis, clinicians should have a high level of suspicion for concurrent pulmonary involvement and a low threshold to perform serial PFTs or CT imaging, particularly in the presence of autoantibodies with a known ILD association. Given their clinical complexity, patients with established myositis-ILD benefit from co-management between pulmonary and rheumatology teams. While the immunosuppressive agents utilised to treat myositis-ILD tend to be similar to those used in patients with isolated myositis, a more aggressive treatment approach with higher dosing regimens or combination therapy is more commonplace in rapidly decompensating patients with underlying lung involvement. To date, solid evidence supporting the use of particular immunosuppressive agents is lacking, and the role of anti-fibrotic therapy in patients with progressive disease is still emerging. Collaboration between rheumatologists and pulmonologists will be required in order to perform the clinical trials needed to advance this field.

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