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Management of interstitial lung disease (ILD) in myositis syndromes: A practical guide for clinicians

Puja Mehta [a, b, *], Rohit Aggarwal [c], Joanna C. Porter [a, d], Harsha Gunawardena [e, **]

[a] Centre for Inflammation and Tissue Repair, UCL Respiratory, Division of Medicine, University College London (UCL), London, UK
[b] Department of Rheumatology, University College London Hospital (UCLH), UK
[c] Division of Rheumatology and Clinical Immunology, Department of Medicine, University of Pittsburgh, Pittsburgh, PA, USA
[d] Department of Respiratory Medicine, University College London Hospital (UCLH), UK
[e] Department of Rheumatology, North Bristol NHS Trust and University of Bristol, Bristol, UK

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A B S T R A C T

Inflammatory myopathies are heterogeneous clinico-serological syndromes, with variable clinical manifestations. Interstitial lung disease (ILD) is a major cause of morbidity and mortality in patients with myositis. The clinical manifestation of myositis-ILD is heterogeneous, e.g., with acute-on-chronic presentations, as well as the chronic aftermath of acute disease. Here, we have largely divided myositis-ILD into three main prognostic groups which require different treatment approaches: mild-moderate (subacute), severe or progressive (acute or subacute) and rapidly progressive, life-threatening. In current clinical practice, the treatment of myositis-ILD involves immunomodulation in an induction-maintenance treatment paradigm. There is now an option to add antifibrotics to slow the progression of established fibrosis in selected cases with chronic progressive phenotype. Here, we describe current concepts in myositis-ILD and aim to provide a practical guide for clinicians on how to approach assessment, including early identification of ILD, phenotyping of patients

* Corresponding author. Centre for Inflammation and Tissue Repair, UCL Respiratory, Rayne 9 Building, University College London, London, WC1E 6JF, UK.
** Corresponding author. Department of Rheumatology | Autoimmune CTD vasculitis, Brunel Building, Southmead Hospital, North Bristol NHS Trust and University of Bristol, Bristol, UK.
E-mail addresses: puja.mehta@ucl.ac.uk (P. Mehta), harsha.gunawardena@nbt.nhs.uk (H. Gunawardena).

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according to clinical trajectory and likely prognosis and stratified management adopting multi-disciplinary cross-speciality expertise, with close collaboration between rheumatology and respiratory physicians.

Introduction

Idiopathic inflammatory myopathies (IIM), collectively referred to as myositis, are a heterogenous group of systemic autoimmune diseases, i.e., connective tissue diseases (CTD), traditionally characterised by symmetrical, proximal muscle weakness, biochemical, neurophysiological and or histological evidence of muscle inflammation with extra-muscular manifestations, including rash and interstitial lung disease (ILD). Clinical features can vary between patients, some with clear overlap features and some with limited or predominant manifestations. Advances in our understanding of immunopathogenesis and identification and characterisation of autoantibody have heralded a move away from binary terminologies of 'polymyositis' or 'dermatomyositis' towards contemporary classification referring to clinico-serological syndromes [1–3]. ILD is a frequent pulmonary manifestation in myositis (myositis-ILD) and considerably influences morbidity and mortality. Myositis-ILD exhibits a wide clinical spectrum of severity with varying speed of progression, treatment response and prognosis, which can be difficult to predict at disease onset. The clinical course of ILD may be rapidly progressive (RP-ILD), which progresses over the course of days or weeks and may be refractory to standard immunomodulatory regimes; an acute or sub-acute sub-type, which progresses over the course of weeks or months and usually responds favourably to immunosuppressive treatment, but it may relapse after the de-escalation of treatment; and another more chronic sub-type, which could be stable on therapy or demonstrate slow progression. Expanding therapeutic options hold promise, however, there is an absence of randomised controlled trials and precision medicine strategies are challenging. Progress requires close collaboration between rheumatology and respiratory physicians [4]. Here, we describe current concepts in myositis-ILD and aim to provide a practical guide for clinicians on how to approach assessment, including early identification of ILD, phenotyping of patients according to clinical trajectory and likely prognosis and stratified management adopting multi-disciplinary cross-speciality expertise.

Myositis-ILD: epidemiology and significance

ILD is one of the most important prognostic factors associated with poor survival in patients with myositis [5–7]. Mortality in patients with ILD is significantly higher, compared with those without ILD [8,9]. Reported estimates of the prevalence of myositis-ILD vary widely (ranging from 20 to 78% [10]), due to differences in populations studied, variable diagnostic methodology and reporting practices. A recent systematic literature review and meta-analysis of 34 studies (10,130 patients) demonstrated that the global prevalence of myositis-ILD was 0.41 (41%, 95% confidence interval [CI] 0.35–0.48) [11]. However, this prevalence varied with geographical locations and time trends. The prevalence of ILD was higher in Asia (0.5 (95% CI 0.42–0.57)), compared with America (0.23 (95% CI 0.15–0.31)) and Europe (0.26 (95% CI 0.18–0.34)), which highlights potential genetic and environmental contributions. Studies published after 2010 reported higher prevalence [11], suggesting changes in clinical practice due to increased recognition and diagnostic yield in higher risk phenotypes of myositis-ILD with more intensive screening programmes.

Assessment and management – step 1: identify risk factors

In a patient with myositis, the identification of factors that predict the development of ILD is important for early diagnosis. Equally identification of a 'myositis-associated' clinic-serological phenotype in a patient presenting with ILD is just as critical in order to improve clinical outcomes.

Clinical risk factors

A meta-analysis of 23 studies, which included 834 myositis patients, showed that older age at diagnosis (standardised mean difference, SMD, 0.35; 95% CI, 0.18–0.52; P < 0.0001), arthritis/arthralgia (OR, 3.17; 95% CI, 1.99–5.04; P < 0.00001), fever (OR, 2.31; 95% CI, 1.42–3.76; P = 0.0007), elevated erythrocyte sedimentation rate (ESR; SMD, 0.48; 95% CI, 0.32–0.64; P < 0.00001), and elevated C-reactive protein level (CRP; OR, 3.50; 95% CI, 1.48–8.28; P = 0.004) are associated with ILD. Meanwhile, cancer-associated myositis (OR, 0.36; 95% CI, 0.18–0.72; P = 0.004) reduced the risk of developing ILD [12]. Consideration should be given to younger patients presenting with ILD, especially women, where there may be an underlying myositis-associated syndrome [13].

Serological risk factors – 3 key phenotypes

Early characterisation of autoantibodies is a critical diagnostic step to define myositis-associated ILD syndromes [14] and has significant clinical utility in risk stratification and may serve as prognostic biomarkers (Table 1). Over the past few years, we have adopted terminology and description of myositis-specific autoantibodies (MSAs) which were originally described as specific for myositis syndromes and mutually exclusive, whereas myositis-associated autoantibodies (MAAs), e.g., anti-Ku, anti-RNP and anti-SSA, are frequently found in other CTDs associated with myositis [15]. We now recognise that several autoantibody specificities such as non-Jo1 anti-aminoacyl-tRNA synthetases (ARS) are more predictive of ILD and myositis can be absent [13,15], highlighting that nomenclature needs to change from myositis-specific to myositis-ILD related to facilitate clinician assessment.

ARS antibodies are associated with anti-synthetase syndrome, with clinical features, including inflammatory arthritis or arthralgia, fever, mechanic's hand, Raynaud phenomenon, myositis and ILD. Some antibodies have specific associations. For example anti-Jo-1 antibodies are strongly associated with myositis and ILD (OR, 3.34; 95% CI, 2.16–5.16; P < 0.00001 [12]). Skeletal muscle involvement is more common with anti-Jo1, anti-EJ, and anti-PL7 [16], but is less common (7–25%) with other anti-ARS antibodies, e.g., anti-PL12. In anti-PL12 antibody positive patients lung disease may predominate and although skeletal muscle manifestations are less common, other extra-muscular manifestations such as Raynaud's, mechanic's hands, or arthritis can feature [17,18].

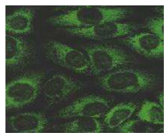
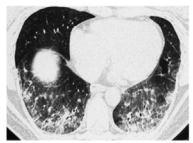
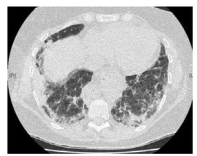
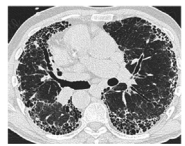
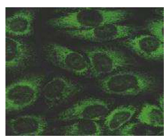
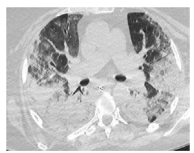
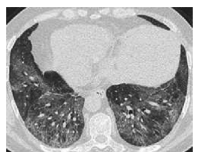
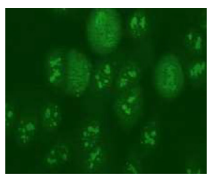
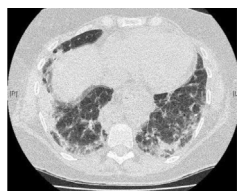
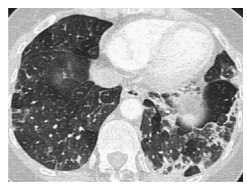
Anti-MDA5 antibodies are associated with typical DM rash, characteristic mucocutaneous ulceration and a variable spectrum of ILD (OR, 18.26; 95% CI, 9.66–34.51; P < 0.00001) (11). Original descriptions and subsequent reports clearly highlight the combination of clinically amyopathic DM (CADM) and RP-ILD with a higher prevalence in certain ethnic groups (Japan, Korea and China). Although there remains an association with RP-ILD across ethnic groups [19], less severe subacute ILD is seen in Caucasian cases [20].

Anti-PM-Scl antibodies are seen in overlap systemic sclerosis-myositis cases with variable clinical presentation and a frequency of <10% in patients with predominant myositis. In this latter group (patients with predominant myositis), a key observation is phenotypic similarity to anti-synthetase syndrome with mechanic's hands, Raynaud's along with ILD [21].

Poor prognostic factors risk factors

Several poor prognostic factors for myositis-ILD have been reported, including male gender, older age at disease onset, CADM, cutaneous involvement (rash), fever, skin ulceration, periungual erythema, elevated creatine kinase, raised ferritin >500 ng/mL, chest high-resolution computed tomography (HRCT) patterns (absence of ground-glass attenuation but predominant fibrosis), low oxygen saturations at presentation and presence of anti-MDA5 antibodies, although the populations and endpoints varied between studies, which were mostly of small sample size [10,22–25]. A recent multicentre retrospective cohort from Japan of 497 patients used multivariate analysis with a stepwise selection of parameters to generate a predictive model and identified the following independent risk factors for ILD mortality: age at onset ≥60 years [hazard ratio (HR) 4.3, 95% CI: 2.4–7.5], CRP ≥10 mg/l (HR 2.6, 95% CI: 1.5–4.8), peripheral capillary oxygen saturation <95% (HR 2.0, 95% CI: 1.2–3.4) and MDA5 antibody (HR = 7.5, 95% CI: 2.8–20.2) [26].

Table 1
Serological risk factors – 3 key phenotypes.

Clinical phenotype	Syndrome manifestations	Autoantibody	Autoantigen target	ANA HEp-2 pattern	Current available confirmation test	Predominant ILD subtypes	Other ILD subtypes
Anti-synthetase	Myositis, arthritis, ILD, mechanic's hands, Gottron's lesion, fever, Raynaud's	Anti-Jo1 Anti-PL7 Anti-PL12 Anti-EJ Anti-OJ Anti-KS Anti-Ha Anti-Zo	Intracytoplasmic amino-acyl tRNA synthetases	Cytoplasmic 	ELISA (Jo1) Myositis immunoblot (Jo1, PL7, PL12, EJ, OJ) Immunoprecipitation (KS, Ha, Zo)	NSIP  OP + NSIP 	UIP 
Anti-MDA5	Rapidly progressive ILD > acute | subacute ILD, mucocutaneous ulcerating lesions, clinically amyopathic DM	Anti-MDA5	Intracytoplasmic MDA5	Cytoplasmic 	Myositis immunoblot	AIP 	NSIP 
Anti-PM-Scl	Scleroderma, myositis, Raynaud's, mechanic fingers, arthritis	Anti-PM-Scl	Multi-protein 75/100 intracellular nucleolar complex	Nucleolar 	Myositis immunoblot or Scleroderma immunoblot	OP + NSIP 	Fibrotic OP 

Abbreviations: NSIP, non-specific interstitial pneumonia; UIP, usual interstitial pneumonia; OP, organising pneumonia; AIP, acute interstitial pneumonia.

Current clinical practice in terms of ILD screening and inter-specialty referrals (rheumatology/respiratory input) are highly variable [27]. Moving forward, combining all risk factors (clinical, serological, poor prognostic markers) will aid screening paradigms at the onset of diagnosis (Fig. 1).

Assessment and management – step 2: define patient and extent of disease

To optimise and standardise patient care, including interpretation of immunological, physiological and imaging tests, it is imperative to integrate services encompassing rheumatology, respiratory medicine (ILD, pulmonary arterial hypertension (PAH) transplantation), radiology, laboratory immunology and palliative care. A framework to approach a patient with suspected myositis-ILD is summarised in Fig. 2. A thorough clinical assessment regarding respiratory symptoms (cough, dyspnoea and reduced exercise tolerance) is required alongside a review for extra-respiratory muscle, skin and joint disease. It is notable to remember that symptoms may be influenced by concomitant myopathy and confounded by chest wall weakness. Whilst all patients with respiratory symptoms warrant investigations to interrogate differential diagnoses irrespective of autoantibody status, we would recommend that all patients with anti-synthetase and anti-MDA5 autoantibodies are screened for ILD at baseline, with an HRCT chest and pulmonary function and 6-min walk tests.

Immunological testing

Careful robust interpretation of autoantibodies is imperative. Standard techniques for antinuclear antibody (ANA) testing include immunofluorescence (IIF) on human epithelial cells (Hep-2 cells) and generic or antigen-specific enzyme-linked immunosorbent assays (ELISA). We recommend ANA is screened by Hep-2 IIF, because associated autoantigen targets have specific cytoplasmic or nucleolar patterns that will be missed by alternative ANA techniques (Table 1) [1]. For example, a patient with myositis, Raynaud's, skin changes and lung infiltrates, a nucleolar staining pattern suggests

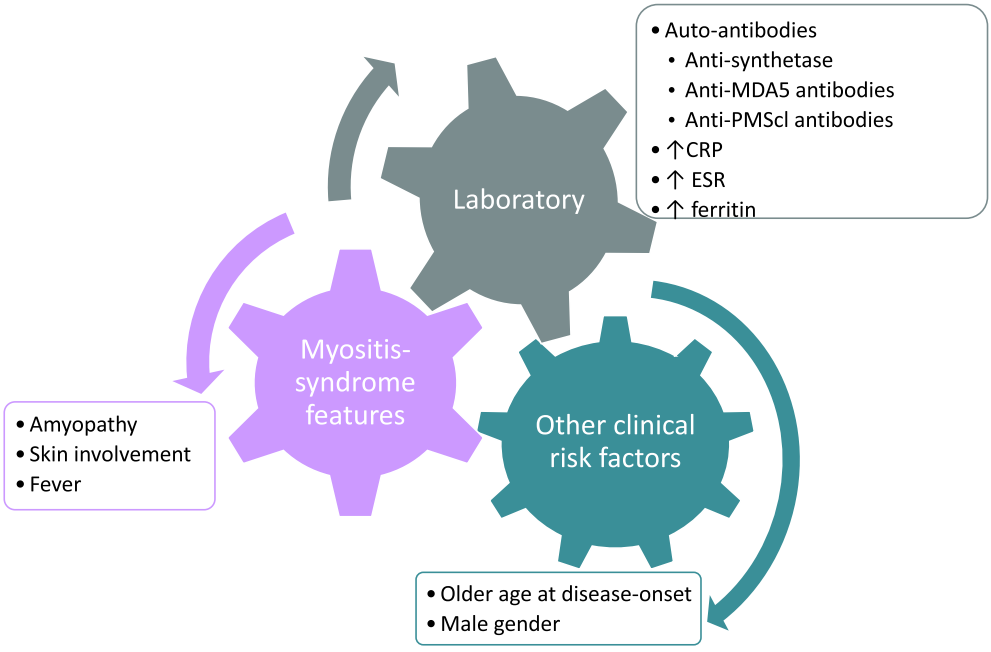


Fig. 1. Risk factors for developing myositis-ILD.

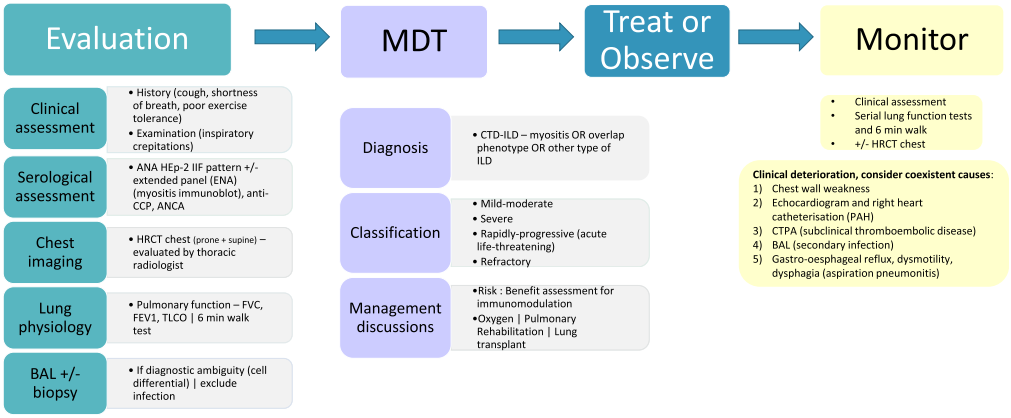


Fig. 2. Framework for overall management of myositis-ILD. Abbreviations: Anti-CCP, anti-cyclic citrullinated peptide protein antibody; ANCA, anti-neutrophil cytoplasmic antibody; CTPA, computerised tomography pulmonary angiography.

autoantibodies against the PM-Scl complex, whereas the absence of nuclear staining (negative ANA) with a strong cytoplasmic pattern with the similar clinical features suggests an anti-synthetase syndrome autoantibody. A patient with CADM, mucocutaneous ulceration and ILD with negative ANA and cytoplasmic stain on Hep-2 IIF is indicative of anti-MDA5 antibodies. Therefore, distinctive Hep-2 patterns inform the interpretation of extended myositis immunoblot panels and should be correlated with clinical manifestations to bring together a consensus diagnosis, as false positivity or misinterpretation of immunology may result in inappropriate management.

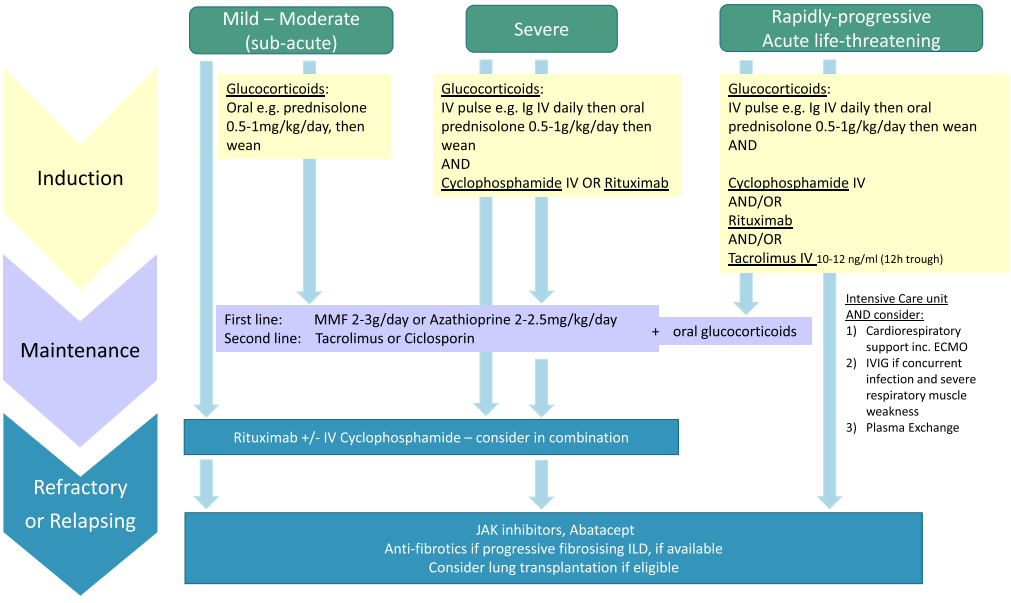


Fig. 3. Treatment approach for myositis-ILD according to ILD phenotype characterisation. In clinical practice, steroid and cyclophosphamide regimens vary. Severe disease is usually defined by FVC<70%, TLCO <55% and/or HRCT extent >20%.

Respiratory physiology testing

Lung function tests may demonstrate a restrictive pattern of spirometry and decreased gas transfer (Table 2), and they are helpful for assessing the severity of ILD at baseline, evaluating extra-thoracic restriction due to myopathy, monitoring disease progression and reducing the need for serial HRCT chest scans, unless there is clinical and/or physiological deterioration. The transfer factor for carbon monoxide (TLCO) is a measure of overall gas transfer across the alveolar-capillary membrane. The KCO, transfer co-efficient, is an expression of the gas transfer per unit volume of lung. The TLCO and KCO may be helpful to distinguish between ILD (where the TLCO is usually low with a preserved KCO) and chest wall weakness (where the TLCO may be normal or low and the KCO may be elevated). The development of secondary pulmonary hypertension can result in further reduction in TLCO and a drop in KCO, which may be disproportionate to FVC decline. Six-minute walk tests are an important adjunctive measure at presentation and serial progression. Combining 3 key measures; predicted % FVC, TLCO and oxygen saturation on walk test guides clinicians to fully assess disease burden.

HRCT imaging

We recommend HRCT chest (non-contrast with prone, supine views and inspiratory/expiratory scans) as the gold standard diagnostic investigation for ILD. Patterns include more 'inflammatory' ILD with focal multi-lobar consolidation (due to organising pneumonia, OP) and/or ground-glass opacification (GGO) with reticulation suggesting a non-specific interstitial pneumonia (NSIP). A more fibrotic NSIP may also present with GGO, albeit in this case due to fine fibrosis, or signs of reticulation (i.e., intralobular reticular opacities, interlobular septal thickening, traction, or non-septal linear or plate-like opacities) [28]. More established fibrosis leads to traction bronchiectasis and honeycombing (usual interstitial pneumonia, UIP), which, although less common, is seen particularly in non-Jo1 anti-synthetase syndromes (anti-PL12 and anti-PL7) (personal observations) [29]. Careful interpretation of HRCT evaluated by a thoracic radiologist can establish where a patient sits along this OP-NSIP-UIP

Table 2
Interpretation of lung function tests.

		FEV1	FVC	FEV1: FVC	TLCO/DLCO	KCO	(Other)
Monitored in ILD			<70% or serial reduction >10%		<55% or serial reduction >15%		(6MWT − desaturation <90% or serial decline)
Type of lung disease							
Obstructive	Asthma	↓ ↔	↔↑	↔↓	↔ ↑	↑↔	
	COPD	↓↓	↔↑	↓	↓↓ with emphysema	↓↓ with emphysema	
Restrictive	Intrapulmonary (e.g., ILD)	↓	↓↓	↔ ↑	↓↓	↓	
	Extrapulmonary (e.g., chest wall muscle weakness)	↓	↓	↔ ↑	↔(↓)	↑↑	
Other	Pulmonary haemorrhage/ polycythaemia	↔	↔	↔	↔ ↑	↑	
Other	Pulmonary HT	↔	↔	↔	↔ ↓	↓	

Note: FEV_1: forced expiratory volume in 1 s; total volume of air a patient is able to exhale in the first second during maximal effort; a normal result is approximately 80%. FVC: forced vital capacity; determination of vital capacity from a maximally forced expiratory effort, i.e., the amount of air that can be forcibly exhaled after maximal inspiration. A 'normal' result is approximately 80−120%. The FEV_1/FVC ratio: the percentage of the FVC expired in 1 s. TLCO (also referred to as DLCO) = Transfer factor, i.e., measure of overall gas transfer Measure of gas transfer across the alveolar-capillary membrane. KCO = Transfer co-efficient − an expression of the gas transfer per unit volume of lung. The TLCO and KCO may be helpful to distinguish between ILD (where the TLCO and KCO are usually low) and chest wall weakness (where the TLCO may be normal or low and the KCO may be elevated). 6MWT; 6-min walk test is also added as an assessment of severity or progression NB: Direction of arrows indicates decrease (downward arrow), increase (upward arrow) or stability (horizontal arrow) of the specified parameter.

spectrum, assessing the degree of inflammatory change and background fibrosis alongside the extent of lung involved. In some cases, there may be radiological uncertainty, which may then lead to further assessment, including bronchoalveolar lavage (BAL) with differential cell count or even lung biopsy. However, in clinical practice, myositis-ILD patients rarely require characterisation by surgical biopsy and when clinico-serological phenotype fits the radiological interstitial pneumonia pattern, especially with serological positivity for MSA or MAA (e.g., anti-PM-Scl syndrome and OP ± NSIP, anti-synthetase syndrome and OP + NSIP ± progressive fibrosis), most clinicians and patients opt for a trial of immunosuppressive therapy to treat and stabilise ILD.

Treatment of myositis-ILD

A multi-disciplinary team approach to diagnosis and characterisation of the ILD phenotype is critical, with members including physicians with expertise in ILD including radiology, respiratory and rheumatology [30–32]. MDT discussions incorporate (a) clinical features – lung and overlap manifestations, (b) respiratory function with lung function and walk test parameters, (c) interstitial pneumonia and ILD extent in order to provide a consensus treatment pathway for the patient. As we develop closer collaboration between physicians with expertise in myositis-ILD, stratified treatment plans will become further refined to determine the treatment regimens employed or alternatively a watchful surveillance observational approach (outlined below, Fig. 3). Clinicians must also consider reasons for unexplained clinical deterioration (e.g., worsening shortness of breath and exercise tolerance), without progressive ILD HRCT changes and with appropriate investigations, e.g., respiratory muscle weakness, PAH (which may be primary or secondary to ILD), subclinical pulmonary embolic disease, concomitant infection and gastrointestinal causes (e.g., gastroesophageal reflux and dysmotility, which can lead to centrilobular fibrosis secondary to aspiration).

As outlined in previous sections, early diagnosis and characterisation are critical to identify patients with ILD, including those with poor prognostic features, i.e., progressive NSIP or acute interstitial pneumonia (AIP) RP-ILD pattern, with the aim to initiate intensive immunosuppression, whilst avoiding over-treatment and adverse events in patients with milder disease, who are likely to respond to modest immunomodulatory regimens. In the absence of data from randomised-controlled trials, the treatment of myositis-ILD is mainly eminence- and experience-based, extrapolated from the management of systemic sclerosis ILD, which has the larger evidence-base. In current clinical practice, the treatment of myositis-ILD is tailored according to ILD extent: mild-moderate (usually a subacute form), progressive and/or severe (can be subacute or acute) and life-threatening (generally acute) using an induction-maintenance treatment paradigm. Induction therapy involves oral or intravenous glucocorticoids, followed by maintenance therapy depending on the initial response, with tapering of glucocorticoids and the addition of glucocorticoid-sparing agents (e.g., mycophenolate mofetil, azathioprine, tacrolimus or ciclosporin). In some cases, where ILD extent is minimal and non-progressive, asymptomatic with no physiological compromise, corticosteroids (and their associated adverse event profile) may be avoided entirely. Most patients with progressive mild-moderate disease respond well to immunosuppression.

Severe or sub-acute disease with greater respiratory compromise requires intravenous corticosteroids with either intravenous rituximab or cyclophosphamide as induction therapy, depending on a number of factors, including the clinical severity, comorbidities and concomitant infection. Refractory or relapsing disease may respond to the combination of cyclophosphamide and rituximab or either of these with other agents such as mycophenolate or tacrolimus or cyclosporine. The key outcome in this cohort of patients is clinical and physiological stability.

Patients with life-threatening RP-ILD require intensive immunosuppressive treatment as early as possible, as early intervention results in better outcomes [33]. As outlined in the previous section, anti-MDA5 antibodies as well as some non-Jo1 antibody-positive patients can predict severe ILD, and this can be further strengthened by correlation with the degree of acute phase response with CRP and serum levels of ferritin at diagnosis [34]. A raised ferritin may be considered an acute phase response protein, but consideration should be given to hemophagocytic lymphohistiocytosis (HLH), which was observed in 4.2% (18 of 424) patients in the case-control study and fatal in 78% [35]. Risk factors for HLH included higher disease activity, acute exacerbation of ILD and infection [35] and may be indicated by

hyperferritinaemia, deranged liver function tests and cytopenias (or downward trends in full blood count indices) [36].

For RP-ILD, potent immunosuppression is usually needed for induction therapy with a combination of immunosuppressive agents such as high-dose glucocorticoids with combination agents (cyclophosphamide, calcineurin inhibitors (such as ciclosporin and tacrolimus) and/or rituximab) [37]. Patients should be managed in an intensive care or high-dependency unit setting, given the high fatality rate and with organ support when needed, e.g., extracorporeal membrane oxygenation (ECMO). Intravenous immunoglobulin should be considered as an adjuvant therapy, especially if there is a concurrent infection or severe myopathy, and plasma exchange has been beneficial as rescue therapy in some patients with anti-MDA5 disease [37]. JAK inhibitors (tofacitinib) [38] have been used successfully in some cases of myositis-ILD, particularly in anti-MDA5 positive patients. The effect of abatacept in ILD myositis needs to be evaluated in future trials. A randomised phase IIb trial reported that abatacept resulted in lower disease activity in nearly half of the patients' myositis [39]. However, although half of the trial population had ILD, lung outcomes with abatacept were not reported. There are ongoing clinical trials evaluating the role of abatacept NCT03215927 in ILD associated with antisynthetase syndrome and tocilizumab NCT02043548 in refractory myositis, so additional therapeutic strategies may evolve in time [33].

In 2015, two antifibrotics (pirfenidone and nintedanib) were licensed [40] for the treatment of idiopathic pulmonary fibrosis (IPF). These antifibrotics are now used worldwide as a standard of care in IPF with the aim to decelerate the progression of fibrosis, rather than reverse it. This led to studies of antifibrotics in progressive-fibrosing ILDs (PF-ILDs), of *known* cause, such as due to underlying autoimmune rheumatic disease (ARD). PF-ILDs included patients with UIP, but also those with fibrotic forms of inflammatory OP and NSIP. INBUILD was a double-blind, placebo-controlled phase 3 trial of nintedanib in 663 patients with PF-ILDs, including patients with ARD (170 patients, 25.6% [41]). The investigators defined the progression of ILD within 24 months as a relative decrease in FVC predicted greater than 10% from baseline or as a decrease in FVC between 5% and 10% combined with the deterioration of respiratory symptoms or increased extent of fibrosis on HRCT or third, as a deterioration of respiratory symptoms combined with the increased extent of fibrosis on HRCT. The primary endpoint was met and efficacy of nintedanib was demonstrated across the subgroups, including autoimmune ILD, and across the radiological subtypes (fibrotic OP-fibrotic NSIP-UIP) with a significant reduction of the rate of decline in FVC [42]. The autoimmune subgroup included 89 patients with rheumatoid arthritis-ILD (RA-ILD), 39 with systemic sclerosis-ILD, 19 with "mixed CTD-ILD", and the remainder with non-specified "other" autoimmune ILDs. Biologic or non-biologic disease-modifying anti-rheumatic drugs were permitted after 6 months of trial treatment, without increased adverse events, providing reassurance for the safety and tolerability of combination immunomodulatory therapy and nintedanib [43]. It is not clear how many patients had myositis-ILD; therefore, the results are difficult to directly extrapolate to patients with myositis, although a small retrospective cohort study ($n = 36$) in this population has demonstrated an efficacy signal [44]. Subgroup analysis of an open-label, prospective study of pirfenidone in patients with RP-ILD associated with CADM with matched historical controls indicated that the pirfenidone add-on had no impact on the survival of acute ILD patients (disease duration <3 months) (50% vs 50%, $p = 0.3862$); whilst for subacute ILD patients (disease duration 3–6 months), the pirfenidone add-on ($n = 10$) had a significantly higher survival rate compared with the control subgroup ($n = 9$) (90% vs 44.4%, $p = 0.0450$ [45]. There are ongoing clinical trials evaluating the efficacy of pirfenidone in patients with dermatomyositis–ILD (NCT02821689 and NCT03857854). Nintedanib was recently approved for the treatment of PF-ILDs in several parts of the world, including the USA and UK, and therefore both randomised controlled and real-world data are eagerly anticipated to help guide the clinical utility of anti-fibrotic therapy in clinical practice.

Finally, as per other ILDs, smoking cessation advice, pulmonary rehabilitation strategies and clinical psychology support should be employed and appropriately selected. Eligible patients should be referred early for consideration of lung transplantation [46], and palliative care support should be offered where appropriate.

Practice points

- ➢ Inflammatory myopathies are heterogeneous clinic-serological disorders, with a variety of clinical manifestations, including ILD, that require a multi-disciplinary approach involving both rheumatology and respiratory.
- ➢ ILD is a major cause of morbidity and mortality in patients with myositis. Myositis-ILD can be divided into three main prognostic groups which require different treatment approaches they are mild-moderate (subacute), severe or progressive (acute or subacute) and rapidly progressive, life-threatening
- ➢ In current clinical practice, the treatment of myositis-ILD involves immunomodulation in an induction-maintenance treatment paradigm of glucocorticoids, conventional and biological DMARDs. There is now an option to add antifibrotics to prevent the progression of established fibrosis in selected cases

Research agenda and future directions

- ➢ There remains a considerable unmet need for effective therapies, better understanding of the aetiopathogenesis and identification of biomarkers to predict treatment response and prognosis, allowing for a stratified and ultimately precision medicine treatment approach in myositis-ILD. Cross-speciality collaboration between rheumatology and respiratory medical teams is critical to drive progress.
- ➢ Controlled trials in myositis-ILD are needed to facilitate the generation of evidence-based, validated guidelines to refine treatment algorithms, including the role of anti-fibrotics, in order to achieve optimal disease control and improve prognosis.

Author contribution

PM drafted the review. JCP, RA and HG edited and approved the draft. All authors contributed to discussions and approved the final version of the manuscript.

Disclosures/conflicts of interest

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