Review

Shaping the landscape of interstitial lung disease in idiopathic inflammatory myopathies: state of the art, evidence gaps and a need for clinical trials

D. Rivero Gallegos[1], F.M. Pais[2], T.-Y. Lan[3], C. Papadopoulou[4], E.K. Joerns[5], J. Paul[6], J. Rojas Serrano[1], T. Kulkarni[7], P.C. Gandiga[8], H. So[9], K. Houghton[10], N. Bagri[11], M. Jansen[12], B. Bader-Meunier[13], E.M. Wilfong[14], R. Aggarwal[15], R.W. Hallowell[16], V. Nagaraja[17]

Affiliations: see page 373.

*Daphne Rivero Gallegos, MD, MS**
*Faye M. Pais, MD**
Ting-Yuan Lan, MD
Charalampia Papadopoulou, MD, PhD
Elena K. Joerns, MD, MS
Jisna Paul, MD
Jorge Rojas Serrano, MD, PhD
Tejaswini Kulkarni, MD
Prateek C. Gandiga, MD
Ho So, MD, MS
Kristin Houghton, MD
Narendra Bagri, MD
Marc Jansen, MD, PhD
Brigitte Bader-Meunier, MD
Erin M. Wilfong, MD, PhD
Rohit Aggarwal, MD, MS
*Robert W. Hallowell, MD***
*Vivek Nagaraja, MD***

**Contributed equally as co-first authors.*
***Contributed equally as senior authors.*

Please address correspondence to:
Vivek Nagaraja
Division of Rheumatology,
Mayo Clinic Arizona,
13400 E Shea Blvd.,
Scottsdale, AZ 85259, USA.
Email: nagaraja.vivek@mayo.edu

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ABSTRACT

Interstitial lung disease (ILD) affects a significant proportion of adults and children with idiopathic inflammatory myopathies (IIM-ILD and JIIM-ILD). Despite its major impact on mortality and therapeutic decision-making, robust studies and clinical trials to inform evidence-based practice are strikingly scarce. Heterogeneous clinical manifestations, variable testing practices, and lack of widely accepted nomenclature and standardised endpoint definitions magnify the challenges to design clinical trials for this novel disease subtype. Thus, the Myositis Clinical Trials Consortium (MCTC) developed the IIM-ILD working group (WG) to bridge the gaps and address the challenges unique to these patients. The IIM-ILD WG will accomplish these objectives by leveraging MCTC's global network of over 960 members, including physicians from multiple specialties, researchers, industry collaborators, and patient-support organisations. Collectively, the paper emphasises the need for structured phenotyping, unified terminology, and validated outcome measures as indispensable prerequisites for designing rigorous, multicentre trials in patients with IIM-ILD and JIIM-ILD. By leveraging the MCTC platform, the IIM-ILD Working Group will accelerate therapeutic development and ultimately improve outcomes for adults and children afflicted with IIM-associated ILD.

Introduction

Interstitial lung disease (ILD) is the foremost driver of morbidity and mortality in adults and children with idiopathic inflammatory myopathy (IIM), occurring in 20–100% of patients (1, 2). Juvenile idiopathic inflammatory myopathy associated ILD (JIIM-ILD) mirrors this burden, producing comparable detriments to mortality and quality of life in children. Despite the life-threatening disease impact, there is a striking scarcity of robust observational and natural history studies to inform our understanding of IIM-ILD. Consequently, therapeutic decision-making rests on limited evidence, retrospective series, and case reports (3, 4). IIM-ILD management is highly variable, reflecting both institutional practice patterns and the disease's intrinsic heterogeneity. Pulmonary involvement can be purely inflammatory, fibrotic, or a mixture of both, and may affect the parenchyma, airways, and respiratory musculature, including the diaphragm. This phenotypic diversity translates into a wide spectrum of clinical presentations, functional and physiological impairments noted on pulmonary function tests, oxygen requirements, six-minute walk distance, dyspnoea scores, and imaging features (5, 6). This phenotypic heterogeneity, together with variable antibody profiles, impedes timely diagnosis and the development of standardised screening, diagnostic, and treatment algorithms. Although recent societal guidelines address screening, monitoring, and management of ILD in systemic autoimmune rheumatic diseases (SARD) (3), the applicability and utility in adult and juvenile IIM-ILD have yet to be determined.

High-quality clinical trials require standardised nomenclature and accept-

ed definitions of disease improvement, stability, relapse, and progression; elements notably absent in IIM-ILD. Moreover, no defined endpoints or validated assessment tools exist to capture changes in pulmonary and systemic organ involvement in adult or juvenile IIM-ILD. These critical gaps severely hinder clinical trial development and perpetuate therapeutic delays.

In this manuscript, we systematically review the current state of knowledge, detail key gaps in disease characterisation and outcome assessment for both adult and paediatric IIM-ILD and propose a strategic roadmap prioritising standardised clinical phenotypes and longitudinal outcome measures. The framework we develop aims to underpin future guidelines, disease assessment tools, therapeutic advances, and targeted clinical trials in adults and juveniles with IIM-ILD.

Clinical phenotypes and treatments in IIM-ILD

Epidemiology and risk factors

Interstitial lung disease (ILD) drives morbidity and mortality in IIM: mortality ranges from 13% to 33%, with rapidly progressive ILD (RP-ILD) and anti-MDA5 positivity conferring nearly sixfold increase in the odds of death (7-10). Across this spectrum, IIM-ILD phenotypes are heterogeneous in both disease behaviour and radiologic patterns, ranging from slowly to rapidly progressive courses and from predominantly inflammatory patterns, such as non-specific interstitial pneumonia (NSIP) and organising pneumonia (OP), to fibrotic patterns, such as usual interstitial pneumonia (UIP). The presence of ILD markedly increases the risk of respiratory failure, infection, and ICU admission, lowering one-year survival from 95% (IIM without ILD) to 86% (IIM with ILD) (10). In adults, the estimated global prevalence of IIM-ILD is 31–65%, rising to 65% in Asian populations and in high-risk subtypes such as antisynthetase syndrome (ASyS) and clinically amyopathic dermatomyositis (CADM) (2, 11, 12). In children, juvenile dermatomyositis (JDM) accounts for most cases, with an annual incidence of 2.5-4.1 per million (8, 9). ILD prevalence in JDM ranges from 8–23%, reaching ~30 % in East Asian cohorts (8, 13, 14). Although more frequent in patients with myositis-specific autoantibodies (MSAs) such as anti-MDA5 and anti-synthetase antibodies (anti-PL7, anti-PL12) (7, 8, 13, 15, 16), ILD can occur in any JDM patient regardless of antibody status (9, 17). Paediatric ILD risk factors include anti-Ro52 co-positivity, elevated ESR, ferritin levels, IL-10 levels, and Asian ancestry (8, 13).

Clinical and radiologic phenotypes

Radiographically, adult IIM-ILD most commonly manifests as NSIP or OP (18, 19). NSIP presents with basal and peripheral ground glass opacities and reticulation, while OP appears as diffuse patchy consolidations, especially in anti-MDA5 and anti-SAE antibody carriers and in CADM. A minority of patients with anti-PL7 or anti-PL12 antibodies develop UIP. NSIP/OP overlap patterns are frequent in IIM-ILD versus other connective tissue disease ILDs (20). Paediatric patterns include OP, NSIP, diffuse alveolar damage, and mixed changes (8, 10); anti-MDA5-positive children often demonstrate peripheral ground glass opacities and consolidation correlating with RP-ILD (10, 21, 22). RP-ILD is relatively rare; most paediatric cases follow a chronic or subacute course and achieve stabilisation or improvement with prompt immunosuppression (16, 23). Fibrotic remodelling is uncommon in children, with honeycombing or traction bronchiectasis typically appearing only after delayed or prolonged disease. Children generally exhibit greater recovery potential, and resolution of interstitial changes is common with adequate therapy (23). Longitudinal outcome data in paediatric cohorts remain sparse.

Current treatment strategies and screening

Treatment in adult IIM-ILD is extrapolated from observational cohorts and from therapy patterns in systemic sclerosis (SSc). The 2023 ACR/CHEST guideline lists mycophenolate, azathioprine, rituximab, or calcineurin inhibitors (with or without glucocorticoids) as first line agents; JAK inhibitors or cyclophosphamide are considered in moderate to severe disease (3). If progression occurs on a first line drug, switching or combining compatible agents (*e.g.* mycophenolate + rituximab) is recommended. RP-ILD warrants high dose intravenous glucocorticoids plus 1-2 of the aforementioned agents; anti-MDA5 associated RP-ILD often demands early triple therapy (*e.g.* glucocorticoids, calcineurin inhibitor, cyclophosphamide, rituximab), with JAK inhibitors and plasmapheresis for refractory disease; intravenous immunoglobulin is variably used in refractory cutaneous-pulmonary overlap (9). Paediatric treatment largely follows adult protocols, employing high dose corticosteroids, tacrolimus or cyclosporine, rituximab, cyclophosphamide, and increasingly JAK inhibitors (8, 17, 24-27).

While baseline screening for ILD is not routine in IIM, the 2023 ACR/CHEST guideline recommends screening adults with high-risk features (specific antibodies, mechanic's hands, arthritis, ulcerations) (3, 24). In paediatrics, the SHARE guidelines advise baseline PFTs and HRCT for all JDM patients with respiratory symptoms or high-risk characteristics (anti-MDA5 positivity, abnormal auscultation, elevated inflammatory markers), with repeat testing guided clinically (3). However, accurate performance of PFTs may not be feasible in younger children and furthermore cooperation may be suboptimal, especially in children with pronounced musculoskeletal impairment.

Clinical trials in IIM-ILD

Current landscape

There are limited published RCTs in IIM-ILD, in contrast to similar disorders like SSc-ILD, where data from randomised controlled trials (RCTs) have demonstrated the efficacy of mycophenolate, cyclophosphamide (short-term efficacy), tocilizumab, and nintedanib (28). Current treatment strategies for IIM-ILD instead rely heavily on 'real-world evidence' with the common practice of GC combined with immunosuppressants as explained above. More recently, phase 2 studies have shown the potential of RCT in informing IIM-ILD treatment. One Japanese

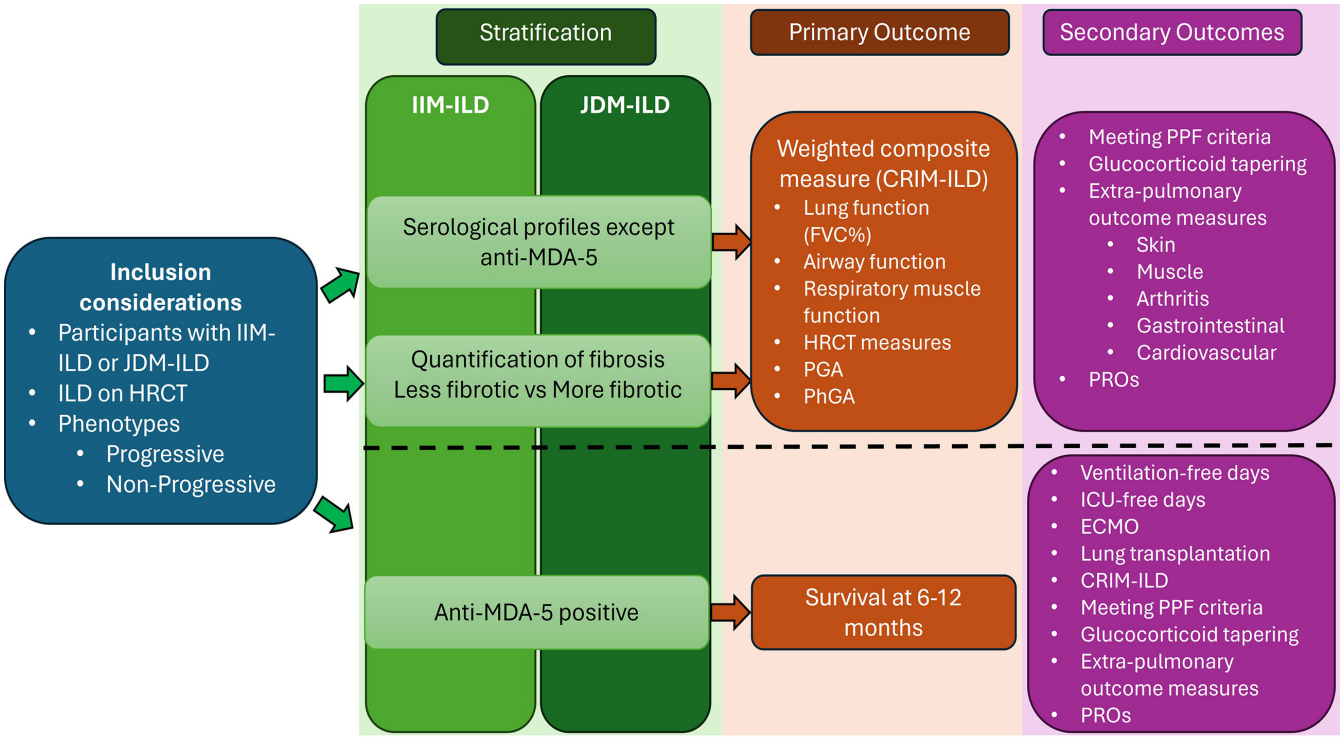

Fig. 1. A conceptual framework for clinical trials in IIM-ILD and JIIM-ILD.
IIM-ILD: idiopathic inflammatory myopathy associated interstitial lung disease; JIIM-ILD: juvenile idiopathic inflammatory myopathy-associated interstitial lung disease; JDM: juvenile dermatomyositis; HRCT: high-resolution chest computed tomography; CRIM-ILD: composite response index in myositis ILD; FVC%: forced vital capacity percentage predicted; PGA: patient global assessment; PhGA: physician global assessment; PPF: progressive pulmonary fibrosis; PROs: patient reported outcomes; ICU: intensive care unit; ECMO: extra-corporeal membrane oxygenation.

phase 2 randomised open-label trial of 58 IIM-ILD patients documented better efficacy of tacrolimus compared to cyclosporin (52-week PFS 87% *vs.* 71%) but also showed FVC% increased significantly in both groups at week 52 (16.9% and 19.7%, respectively), suggesting an overall efficacy of CNI (30). Another phase 2b trial, RECITAL, demonstrated comparable efficacy of cyclophosphamide and rituximab in progressive SARD-ILD, with rituximab being associated with fewer serious adverse events. Importantly, the RECITAL trial stratified randomisation by SARD diagnosis, and 45% of enrolled patients (44/97) were IIM-ILD, making this trial highly relevant to the IIM community (29). The EvER-ILD trial further showed the benefit of adding rituximab to mycophenolate in SARD-ILD or NSIP-pattern ILD, although only eight IIM-ILD patients were included, limiting the generalisability to patients with IIM (31). A recently published pilot study, ATtackMy-ILD, showed favourable trends in FVC% and symptoms with abatacept at week 48 in ASyS-ILD. The primary endpoint defined by a 24-week FVC% change was not met (32). An ongoing investigator-initiated phase 3 trial is also comparing cyclophosphamide followed by azathioprine with tacrolimus for patients with ASyS (NCT03770663) (33).

Approximately 20–30% of IIM-ILD patients meet PF-ILD criteria, making antifibrotic therapy an appealing treatment strategy (34, 35). Despite real-world studies suggesting possible efficacy, IIM-ILD patients remain underrepresented in large phase 3 antifibrotic trials, including INBUILD and FIBRONEER-ILD (36, 37). In the INBUILD subgroup analysis, nintedanib consistently reduced FVC% decline across SARD-ILD, but the study primarily included RA-ILD and SSc-ILD, with only two IIM-ILD patients enrolled (36). Current efforts now target IIM-ILD specifically, such as the MINT trial, a hybrid design evaluating the effects of nintedanib on symptoms and quality of life (NCT05799755), and a phase 3 RCT evaluating the effect of pirfenidone specifically for amyopathic dermatomyositis (NCT02821689) (38, 39). In patients with JIIM-ILD, there are no RCTs to date and treatments are mainly driven by single-centre studies, case series, or extrapolation from IIM-ILD trial data in adults.

Limitations, unmet needs and outcome measures

The design of clinical trials in IIM-ILD and JIIM-ILD is very challenging due to several factors. First, there is no consensus on how to define 'progression', 'improvement', or 'remission' in IIM-ILD. Unlike SSc-ILD, where a ≥10% FVC decline is widely used as a primary endpoint, FVC% in myositis is often confounded by respiratory muscle weakness (40). Historically, myositis trials have assessed pulmonary involvement only through physician or patient VAS scores (MDAAT form), and no standardised composite outcome for IIM-ILD exists (41). Recent studies, such as EvER-ILD and ATtackMy-ILD, used FVC% change at week 24 as the primary endpoint, which may be too short to demonstrate change

(31, 32). Proposed composite endpoints for 'improvement' are currently being explored in an ongoing investigator-initiated trial (NCT03770663) (33).

Second, IIM-ILD is inherently heterogeneous, with subtypes showing different ILD trajectories (40). ASyS generally follows a chronic, but more treatment-responsive course (42), whereas anti-MDA5-positive ILD can be rapidly progressive and often fatal if not treated aggressively (1, 43). Recent studies have also identified distinct clinical phenotypic clusters among anti-MDA5-positive patients, with different patterns of cutaneous involvement, ILD severity, and prognosis, further underscoring the marked heterogeneity of IIM-ILD (44, 45). Even in ASyS there is heterogeneity, strongly associated with the autoantibody profile: patients with anti-Jo1 antibodies typically present with NSIP or OP and respond well to immunosuppressive therapy (46). On the contrary, patients positive for anti-PL7 or anti-PL12 have a greater fibrotic extent on HRCT (47), worse pulmonary function (48), and higher mortality (49). Moreover, Fu *et al*. described that no-Jo1 patients have a higher risk of progressive pulmonary fibrosis (PPF) compared to Jo1-positive patients, and PPF was strongly associated with mortality (50). This variability in disease severity and progression makes it difficult to design one trial applicable to all forms of IIM-ILD patients. Third, some cases with pulmonary-predominant disease with positive myositis-specific antibodies, may initially be classified as IPAF rather than IIM, creating challenges for consistent trial inclusion (51).

For future clinical trials in both IIM-ILD and JIIM-ILD, stratification of participants based on serological profiles and the nature of ILD (fibrotic *vs*. non-fibrotic or threshold of quantification of fibrosis based on percent involvement on HRCT) may need to be considered. This stratification approach accounts for variability in ILD trajectory and creates an opportunity for creating outcome measures specific to each arm, hence, allowing for the assessment of treatment effects and preserving the validity and interpretability of trial results.

The clinical complexity of myositis patients makes it challenging to detect pulmonary disease progression and to distinguish it from other manifestations, such as respiratory muscle weakness or extrapulmonary organ involvement. For this reason, the existing ILD progression criteria used by ATS or in most of the large international ILD clinical trials may not be ideally suited for this population. With multi-systemic diseases like IIM or JDM, it is imperative to have composite outcome measures to reflect and account for the key extra-pulmonary factors, principally myopathy (10, 40).

IIM-ILD Working Group: MCTC's lung centric initiative

The Myositis Clinical Trials Consortium (MCTC) established the IIM-ILD Working Group (IIM-ILD WG), a multi-disciplinary global initiative to address the gaps in clinical trial conceptualisation, framework and design in patients with IIM-ILD and JIIM-ILD. The multi-disciplinary experts in IIM-ILD WG include rheumatologists (adult and paediatric), pulmonologists (adult and paediatric), chest radiologists, lung pathologists, biostatisticians, with plans to include data scientists and experts in health informatics and artificial intelligence (Fig. 2). Collectively, the IIM-ILD component of the MCTC reinforces the recognition of lung involvement as a critical element of the disease, rather than a secondary manifestation.

The immediate short-term aims of the IIM-ILD WG are to: 1. synthesise available literature to propose uniform, globally accepted terminology for IIM-ILD; 2. define disease progression and improvement, differentiate between rapidly progressive forms and clarify the concepts of exacerbation and flare specific to IIM-ILD and 3. Perform deep phenotyping to allow for clinical characterisation and development of standardised case report forms utilisable in research and clinical practice; 4. Develop and validate outcome measures and entry criteria to support the design of multicentre clinical trials in IIM-ILD and JIIM-ILD (Fig. 2).

These steps will be accomplished through an initial systematic review of the literature to understand the existing literature and gaps on each of these themes. Subsequently, a Delphi exercise among experts with appropriate patient input around the world will be conducted to further define and elaborate the aims. For example, a Delphi consensus to define improvement, stability, relapse, and progression in IIM-ILD and JIIM-ILD. Ultimately, followed by data driven approach to validate the proposed definitions and outcomes.

Within this lung-centric initiative, the IIM-ILD WG has also begun to conceptualise a Composite Response Index in Myositis-ILD (CRIM-ILD) (Table I) to address many of the unmet needs described above. There is increasing recognition among pulmonologists and rheumatologists that primary outcome measures for IIM-ILD and JIIM-ILD trials may need to move beyond single surrogates such as FVC% decline (36) and instead adopt a weighted composite disease outcome measure. CRIM-ILD will encompass elements of lung function [improvement, stability, or progression of FVC% (highest ranked with variable weight based on degree of progression or improvement)], respiratory muscle functions (for example: maximal inspiratory pressure and maximal expiratory pressure), HRCT measures (variable weight for improvement, stability, or progression), patient global assessment, and physician global assessment. Given the temporary steroid responsiveness of IIM-ILD coupled with severe long-term morbidity, concomitant steroid reduction is increasingly being viewed as an important secondary end point. CRIM-ILD has an opportunity to capture, on a weighted numerical or logarithmic scale, the evolution of IIM-ILD, including improvement. The premise of this approach is to be inclusive of all IIM-ILD and JIIM-ILD subsets, namely: improved, stable and progressive disease (52). This approach would, for example, assign a higher response score to a >10% increase in FVC% with radiologic improvement and the ability to taper prednisone to <5mg/day by week 52, compared with stabilisation of FVC% that requires higher steroid doses.

However, within the broader strategy of stratifying participant recruitment by serological profile, the anti-MDA5-ILD

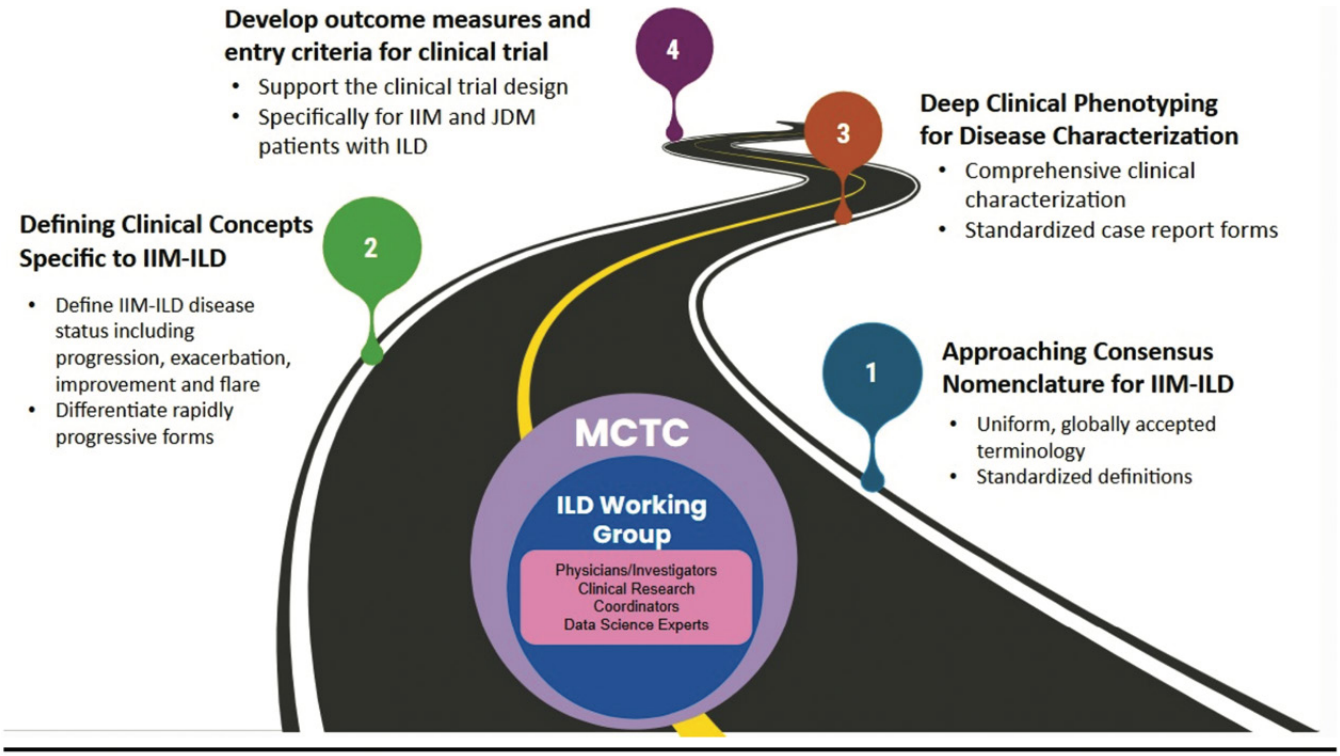

Fig. 2. The structure and roadmap of the ILD working group.
MCTC: Myositis Clinical Trials Consortium.

Table I. Proposed domains for composite response index in myositis-ILD (CRIM-ILD).

Domain	Variable	Categories
Lung function	FVC% predicted (absolute change from baseline) at week 24.	Improved: ≥10% Stable: 5%-10% Worsened: ≤5%
HRCT extent	ILD extension (%): (overall/ fibrotic/ inflam-matory) assessed annually or earlier if clinically indicated.	**Complete remission** Total disappearance of consolidations and ground-glass opacities without increase in fibrotic extent. **Partial resolution/stable:** <30% change in residual OP lesion extent and no significant increase in fibrotic component **Progression:** ≥30% increase in fibrotic abnormalities (traction bronchiectasis or honeycombing) or appearance of new fibrotic lesions
Patient global assessment	Patient global VAS (0-10)	
Physician global assessment	Physician global VAS (0-10)	
Glucocorticoid exposure	Prednisone daily dose and cumulative dose	Tapering to ≤5 mg/day by week 24.
Respiratory muscle function	MIP/MEP	Improved Stable Worsened

MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure.

phenotypes, both in adults and juveniles with a RP-ILD, will warrant a different primary outcome measure. Due considerations need to be given to the severity, rapid progression, and poor prognosis of this condition (53-56). For this reason, survival at 6–12 months is a suitable primary outcome, with key secondary outcomes such as CRIM-ILD, ventilation-free days, ICU-free days, ECMO, and lung transplantation. This approach allows for continued evaluation of longitudinal FVC% for comparability across the CTD-ILD trials.

Currently, PPF is being used as entry criteria in CTD-ILD trials, however, this approach assumes that patients with stable disease would not have

ability to show improvement. Again, this concept is borrowed from SSc-ILD and being imposed on IIM-ILD patients as part of CTD-ILD. IIM-ILD patients have varied trajectories, and quite often, stable patients show improvement with an appropriate combination of immunosuppressives.

Moreover, although recent criteria for PPF have been proposed (57), no formal validation procedure has been realised in patients with IIM-ILD. Standardised definitions are essential both as outcome measures and as inclusion criteria in future trials. From a holistic approach, secondary outcome measures that include skin, joint, gastrointestinal, muscle, and cardiovascular involvement may be considered, given many immunomodulatory and anti-fibrotic approaches may provide benefit in organs other than the lungs. Figure 1 depicts a conceptual framework for clinical trials in IIM-ILD and JIIM-ILD.

Recently, clinical trial investigators, regulatory representatives, and patients with idiopathic pulmonary fibrosis came together to propose clinical trial outcomes that would better reflect the lived experience of patients (58).While a change in FVC% has long been the preferred ILD primary endpoint, these groups discussed focusing on endpoints that reflect 'Feels, Function, Survive' parameters that are most important to patients (58). Such metrics would include patient reported outcomes and dyspnoea scales to augment traditional endpoints such as PFTs and quantitative CT changes. The suggested approach to design a composite measure like CRIM-ILD is born out of themes from such patient-centred stakeholder discussions. Future studies should also aim to identify and validate biomarkers that portend IIM-ILD progression and treatment response. A final strategic priority is assessing how to best minimise cumulative GC dose exposure in IIM-ILD and JIIM-ILD patients. At present, glucocorticoid doses in IIM-ILD are higher than for most other organ and life threatening systemic rheumatic diseases. Prior clinical trials in lupus nephritis (59) and ANCA vasculitis (60) established that lower doses of GC are safe and effective. For ANCA vasculitis, avacopan further reduced GC exposure with sustained efficacy (61), which resulted in significantly less GC toxicity (62). A similar approach is warranted in IIM-ILD and JIIM-ILD patients. MCTC's integrated and comprehensive platform will allow IIM-ILD WG to ideate and design pragmatic trials that are truly global promoting equitable access and accelerating therapeutic discovery in IIM and JDM related ILD.

Through MCTC, the IIM-ILD WG is uniquely positioned to promote clinical advancements, research opportunities, and harmonisation of care strategies in IIM-ILD. Participation of members at various levels of training enables early-career physicians and scientists to develop expertise in this multifaceted and underrecognised field. In essence, the IIM-ILD Working Group of the MCTC is the first, global collaborative platform dedicated to improving outcomes and building clinical trial readiness in adult IIM-ILD and juvenile IIM-ILD.

Conclusion

ILD in IIM is frequent, life-threatening, yet widely heterogeneous in both adults and paediatrics. There is an urgent need for systematic, uniform deep phenotyping across specialised centres worldwide. Effective, evidence-based therapies for IIM-ILD and juvenile IIM-ILD will profoundly improve outcomes for both adult and paediatric patients. Achieving this goal hinges on three foundational steps: 1. creating robust deep clinical phenotyping that captures the spectrum of disease presentations; 2. establishing universally accepted terminology for IIM-ILD activity; and 3. defining standardised metrics for disease progression and treatment response.

The heterogeneity that has historically impeded progress in this field will only be overcome through coordinated, interdisciplinary collaboration between adult and paediatric investigators. The MCTC IIM-ILD Working Group offers an interactive platform for such collaboration, integrating expertise, fostering innovation, and generating the common language needed to design rigorously powered clinical trials. By prioritising the identification, characterisation, and standardised assessment of IIM-ILD, the working group lays the groundwork for future therapeutics that can meet the unmet needs of this novel yet treatable disease.

Affiliations

[1]Instituto Nacional de Enfermedades Respiratorias (INER), Mexico City, Mexico; [2]Division of Pulmonary, Critical Care and Sleep Medicine, University of Florida, College of Medicine, Gainesville, FL, USA; [3]National Taiwan University Hospital, Taipei, Taiwan; [4]Rheumatology Department, Great Ormond Street Hospital for Children NHS Foundation Trust and Great Ormond Street Institute of Child Health, University College London, UK; [5]Division of Rheumatology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA; [6]Division of Rheumatology and Immunology, The Ohio State University Wexner Medical Center, Columbus, OH, USA; [7]Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, The University of Alabama at Birmingham, AL, USA; [8]Division of Rheumatology, Emory Healthcare, Atlanta, GA, USA; [9]Division of Medicine and Therapeutics, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China; [10]Division of Rheumatology, Department of Paediatrics, University of British Columbia, Vancouver, Canada; [11]Division of Paediatric Rheumatology, Department of Paediatrics, All India Institute of Medical Sciences, New Delhi, India; [12]Department of Paediatrics Immunology and Rheumatology, Wilhelmina Children's Hospital, University Medical Center Utrecht, The Netherlands; [13]Meunier Department of Paediatric Immunology and Rheumatology, Necker Hospital, Assistance Publique-Hôpitaux de Paris, France; [14]Division of Rheumatology and Immunology, Division of Allergy, Pulmonary and Critical Care Medicine, Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, USA; [15]Division of Rheumatology and Clinical Immunology, Department of Medicine, University of Pittsburgh, PA, USA; [16]Division of Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [17]Division of Rheumatology, Mayo Clinic Arizona, Scottsdale, AZ, USA.

Competing interests

E.K. Joerns served on the ILD advisory board for Boehringer Ingelheim (BI) for content not related to this study. J. Paul has received research support/grants from

Nkarta, Argenix, and advisory board honoraria from Amgen. J. Rojas Serrano is member of BI speaker's bureau. T. Kulkarni has received consultation fees from BI, United Therapeutics, Bristol Myers Squibb, Avalyn Pharma, Rein Therpeutics, Puretech, Vicore, unrelated to current manuscript. P.C. Gandiga has served as an investigator or oversight committee member/safety officer for multiple industry-partnered and NIH-sponsored clinical trials in autoimmune myositis. He has received past honoraria from: BI, Howard Huges Medical Institutions (HHMI), Janssen Kezar Life Sciences, National Institutes of Health (NIH), Rheumatology Society of DC, The Myositis Association (TMA). E.M. Wilfong has received prior research support from BI, and has provided consulting services for Allogene, Arcellx, Astra Zeneca, BI and Merck. R. Aggarwal has received research grants from BI, Cabaletta Bio, Janssen, and PRoivant; consulting fees from Abcuro, Alexion, ANI Pharmaceutical, Argenx, Artiva Biotherapeutics, AstraZeneca, BI, Bristol Myers-Squibb, Cabaletta Bio, Capstanx, Century Therapeutics, CSL Behring, Dren Bio, EMD Serono, Fate Therapeutics Inc, Galapagos, GlaxoSmithKline LLC (GSK), Horizontal Therapeutics, Immunovant, Janssen, Janux Therapeutics, Kiniksa Pharmaceuticals, Lilly, Meiji Pharma, Novartis, Nkarta, Octapharma, OneFour Bio, Orna Therapeutics Inc, Ouro Medicines, Pfizer, PRoivant, SOBI, and Sun Pharmaceutical Industries. R. Hallowell has served on an advisory board for BI and has received consultation fees for Vicore and Merck. V. Nagaraja has received honoraria from BI as medical advisory board member.

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