

Special article

Myositis-associated interstitial lung disease

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ABSTRACT

Introduction/Objective: To review the epidemiology, general clinical aspects and diagnosis, impact on morbidity and mortality, and general treatment approaches for myositis-associated ILD.

Materials and methods: The relevant literature was reviewed.

Results: The clinical, radiographic, and histopathological features of interstitial lung disease (ILD) in idiopathic inflammatory myopathies (IIM) are similar to idiopathic ILD. Patients with a known diagnosis of myositis require prompt clinical evaluation including the determination of myositis-associated autoantibodies. Patients possessing autoantibodies associated with ILD or those with any pulmonary symptoms should undergo a pulmonary function test and high-resolution CT (HRCT) scanning of their lungs.

Conclusion: Despite the lack of placebo-controlled trials, systemic glucocorticoids are considered the mainstay of initial treatment of myositis-associated ILD. Glucocorticoid-sparing agents are often concomitantly administered, particularly in patients with severe disease. The first-line conventional immunosuppressive drugs include either mycophenolate mofetil or azathioprine. If these agents fail or if the pulmonary features are severe or rapidly progressive, then more aggressive immunosuppressive or immunomodulatory therapy including cyclophosphamide, tacrolimus or cyclosporine, rituximab, IVIg, or tofacitinib can be considered. Further investigations are required to assess the role of novel therapies in the treatment of myositis-associated ILD.

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Enfermedad pulmonar intersticial asociada a miositis

RESUMEN

Introducción/objetivo: Revisar la epidemiología, los aspectos clínicos generales, el diagnóstico, el impacto en la morbilidad y la mortalidad y los enfoques generales de tratamiento para la enfermedad pulmonar intersticial (EPI) asociada a miositis.

Materiales y métodos: Se revisó la literatura relevante.

Palabras clave:

Miositis

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Tratamiento

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Resultados: Las características clínicas, radiográficas e histopatológicas de la EPI en las miopatías inflamatorias idiopáticas (MII) son similares a las de la EPI idiopática. Los pacientes con un diagnóstico conocido de miositis requieren una evaluación clínica inmediata que incluya la determinación de autoanticuerpos asociados a la miositis. Los pacientes que poseen autoanticuerpos asociados con EPI o aquellos con cualquier síntoma pulmonar deben someterse a una prueba de función pulmonar y una tomografía computarizada de alta resolución (TCAR) de sus pulmones.

Conclusión: A pesar de la falta de ensayos controlados con placebo, los glucocorticoides sistémicos se consideran el pilar del tratamiento inicial de la EPI asociada a miositis. Los agentes ahorradores de glucocorticoides a menudo se administran de forma concomitante, particularmente en pacientes con enfermedad grave. Los fármacos inmunosupresores convencionales de primera línea incluyen micofenolato mofetilo o azatioprina. Si estos agentes fallan o si las características pulmonares son graves o rápidamente progresivas, se puede considerar una terapia inmunosupresora o inmunomoduladora más agresiva que incluya ciclofosfamida, tacrolimus o ciclosporina, rituximab, IgIV o tofacitinib. Se requieren más investigaciones para evaluar el papel de las nuevas terapias en el tratamiento de la EPI asociada a la miositis.

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Introduction

Adult polymyositis (PM) and dermatomyositis (DM) are idiopathic inflammatory myopathies (IIM) frequently associated with interstitial lung disease (ILD). ILD is a major cause of morbidity and mortality in patients with PM and DM.^{1,2} The clinical, radiographic, and histopathologic features of ILD in PM and DM are similar to idiopathic ILD with an immunologic and fibrotic targeting of the interstitial, alveolar, and airway structures. Similar to the idiopathic interstitial pneumonias, the patterns of lung pathology in PM or DM-associated ILD include nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), organizing pneumonia (OP) [i.e. cryptogenic organizing pneumonia (COP), previously termed bronchiolitis obliterans organizing pneumonia (BOOP)], and acute interstitial pneumonia (AIP) with diffuse alveolar damage (DAD).³

In this article, we review the epidemiology, general clinical aspects and diagnosis, impact on morbidity and mortality, and general treatment approaches for myositis-associated ILD (MA-ILD).

Epidemiology

The prevalence of ILD among patients with PM and DM varies from 5 to 78 percent.¹⁻¹⁷ The wide variation is likely related to varying methods of ascertainment, and the IIM subsets that are analyzed. The prevalence of ILD is lower when HRCT is not used. PM and DM patients with anti-synthetase autoantibodies (Jo-1 and non-Jo-1) are clearly associated with a higher frequency of ILD. For example, in a series of 90 anti-Jo-1 antibody-positive patients with PM or DM, 77 (86%) met the authors criteria for ILD.¹⁸ In another investigation, evidence of pulmonary fibrosis was noted in

73% of patients with anti-Jo-1 autoantibodies and 81% of patients with non-Jo-1 anti-synthetase antibodies.¹⁹ The frequency of anti-synthetase antibodies has been reported to be higher in females compared to males (70% vs. 30%).¹⁹ ILD is also associated with other myositis autoantibodies, specifically anti-melanoma differentiation-associated gene 5 (MDA5). Clinically amyopathic dermatomyositis (CADM), which is characterized by the typical cutaneous manifestations of DM with no muscle involvement or only minimal muscle involvement is also associated with ILD and MA-ILD may be seen in patients with a normal serum creatine kinase (CK).²⁰ ILD is less frequent in patients with malignancy-associated myositis.^{21,22} In a multivariate analysis, older age (> 45 years) at onset predicted ILD in patients with myositis.¹⁶ Although the prevalence of ILD is similar in PM and DM, the prognosis is usually worse in DM-associated ILD.^{5,23}

Diagnostic approach

The diagnosis of ILD is generally suspected by clinical features, laboratory tests, pulmonary function tests, and imaging. Patients with a known diagnosis of PM or DM require early clinical evaluation for the presence of ILD including laboratory testing for myositis-associated autoantibodies. The detection of autoantibodies associated with MA-ILD should lead to pulmonary function tests and HRCT scanning.

Other mimickers of MA-ILD including infections and other connective tissue disease (CTD)-ILD such as Sjogren syndrome, systemic sclerosis, mixed connective tissue disease or rheumatoid arthritis-associated ILD, hypersensitivity pneumonitis, smoking-related ILD, occupational syndromes, or medication-related ILD with peripheral eosinophilia need to be ruled out.

Autoantibodies

The presence of specific myositis autoantibodies often correspond to particular clinical phenotypes and these autoantibody subsets may predict the risk of developing ILD as well as the clinical course and prognosis of IIM patients. Antisynthetase positive patients have a higher prevalence of ILD.^{8,12,22,24,25,27,29-34,35-37} The autoantibody target is one of the aminoacyl-transfer ribonucleic acid (tRNA) synthetase enzymes that catalyze the attachment of amino acids to the 3' end of their cognate tRNA. To date, 8 antisynthetase autoantibodies have been described which include anti-Jo-1 (histidyl-tRNA synthetase), anti-PL-7 (threonyl-tRNA synthetase), anti-PL-12 (alanyl-tRNA synthetase), anti-EJ (glycyl-tRNA synthetase), anti-OJ (isoleucyl-tRNA synthetase), anti-KS (asparaginyl-tRNA synthetase), anti-Ha (tyrosyl-tRNA synthetase), and anti-Zo (phenylalanyl-tRNA synthetase), all of which are associated with ILD.³⁸⁻⁴²

Anti-Jo-1 antibody is the most common antisynthetase autoantibody^{1,4} and in a series of 91 Jo-1-positive patients with antisynthetase syndrome, sixty-six patients (72.5%) had ILD.³⁷ Anti-Jo-1 patients with ILD had lower CK levels than those without ILD. In another study, 73% of patients with Jo-1 and 81% of patients with non-Jo-1 antisynthetase antibodies had evidence of pulmonary fibrosis. Moreover, non-Jo-1 antisynthetase antibody positive patients were shown to have decreased survival compared with Jo-1 patients.¹⁹ In another series of 95 patients with antisynthetase syndrome with anti-Jo-1 ($n=75$), anti-PL-7 ($n=15$), and anti-PL-12 ($n=5$) autoantibodies, ILD was identified in 90 percent of patients with the latter 2 autoantibody markers and 68 percent of Jo-1 positive patients.³⁵ In the anti-PL-7 or PL-12-positive patients, ILD was more often symptomatic at diagnosis compared to the Jo-1 positive patients. Furthermore, the ILD was more severe in the anti-PL-7 or PL-12 positive patients with less resolution of lung manifestations (5.6% vs. 29.4%).

Anti-SAE (anti-small ubiquitin-like modifier activating enzyme 1 and 2) is another autoantibody targeting 40-kDa and 90-kDa proteins in DM patients. Anti-SAE antibody has been associated with a low frequency of ILD.^{38,39} Anti-SRP, anti-Mi-2 and anti-NXP-2 antibodies are other autoantibodies that are considered to be less associated with ILD.³⁸⁻⁴²

A more recently identified autoantibody, anti-MDA5, has been increasingly associated with ILD,^{28,43-45} particularly rapidly progressive ILD in some Asian populations.^{28,43} In one published series of 160 DM patients, most anti-MDA5-positive patients had overt clinical myopathy and ILD, but not rapidly progressive ILD.⁴⁵ However, data from our center shows that anti-MDA5 is associated with rapidly-progressive interstitial lung disease and poor survival in U.S. patients with amyopathic and myopathic dermatomyositis,⁴⁶ similar to that reported in Asian studies. Given the variable prognosis and associated clinical features, further studies are warranted to further elucidate the role of anti-MDA5 antibody as a biomarker of ILD and prognosis in the U.S. Caucasian myositis population.

Pulmonary function tests

In MA-ILD, pulmonary function tests (PFTs) typically show a restrictive pattern with a reduction in total lung capacity (TLC), forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and diffusing capacity (DLCO). The FEV1/FVC ratio is typically normal or increased.¹ In a series of 71 patients with DM, all patients with ILD ($n=16$) had a reduced DLCO⁴⁷ and 18 (25%) had a low DLCO in the absence of lung CT findings showing ILD. A disproportionately low DLCO relative to lung volume may be suggestive of pulmonary hypertension.

Patients with early ILD may have normal PFTs. On the other hand, PFT abnormalities may reflect other conditions such as respiratory muscle weakness where a restrictive pattern with a normal DLCO and no radiographic features of ILD are noted. However, slight reductions in the DLCO may occur with respiratory muscle weakness where the diaphragm, intercostal muscles, and accessory muscles are affected. Measurements of maximal inspiratory pressure (MIP) and maximum expiratory pressure (MEP) can distinguish respiratory muscle weakness from ILD. Thus, PFT results should be interpreted with caution.

Serial PFTs are a minimally invasive method to follow ILD activity or progression as well as responsiveness to treatment. In general, and due to the variability and reproducibility of DLCO and FVC% measurements, a change of at least 15% and 10% respectively is required to identify a significant change in ILD activity.^{48,49} Lower values for vital capacity and diffusing capacity have been shown to predict a poor prognosis.²⁶ The OMERACT special interest group of CTD-ILD has proposed preliminary consensus-driven core domains and instruments to be considered for future randomized clinical trials in CTD-ILD. Moreover, this group has proposed a progression free survival definition as possible outcomes for a clinical trial assessing treatment response in CTD-ILD. The progression free survival is defined as the time to first occurrence of either $\geq 10\%$ relative decline in FVC% or ≥ 5 -10% relative decline in FVC% and $\geq 15\%$ relative decline in DLCO% or death.⁴⁹

Imaging

Abnormalities on the chest radiograph include diffuse reticular, nodular or mixed reticulo-nodular patterns, predominantly at the lung bases.⁵⁰ Patients with rapidly progressive disease may have patchy ground glass opacities or diffuse white-out of the lungs.

HRCT, which involves volumetric imaging with ≤ 1.5 mm slice thickness, has greater sensitivity and superior diagnostic accuracy compared to routine chest radiography in the diagnosis of ILD.⁵¹ Both supine and prone images are sometimes necessary to verify ILD as opposed to dependent atelectasis. Radiographic abnormalities on HRCT may reflect the underlying histopathology in UIP only, whereas for other histopathological variants, such as NSIP, the radiographic patterns are not very specific. A UIP histopathology is suggested on HRCT by the presence of subpleural, basal predominant reticular abnormalities with honeycombing with or without traction bronchiectasis (along with the absence of features

listed as inconsistent with UIP pattern).⁵² Although not specific, patchy ground glass opacities may reflect NSIP while patchy consolidation or opacification suggests COP.

In a study of 64 patients, the characteristic CT findings of patients with anti-synthetase antibody positive ILD were areas of ground-glass attenuation and reticulation, predominantly distributed as lower and peribronchovascular lesions, which is compatible with NSIP.⁵³ In a retrospective study of 51 patients newly diagnosed with PM/DM-ILD, lower consolidation/ground-glass attenuation pattern was observed in 21 patients (41%), lower reticulation was observed in 23 patients (45%), random ground-glass attenuation was observed in four patients (8%).⁵⁴

In evaluating MA-ILD, it is important to serially review all previous imaging to temporally characterize the onset and progression of ILD. HRCT scans correlate with PFT findings and the clinical severity of respiratory impairment,⁵⁵ and some believe serial HRCTs are necessary only if there is clinical suspicion of infection or worsening ILD or a decline in the PFT parameters.

Regarding prognosis, survival is best in patients with ground glass opacities (a pattern consistent with NSIP) and worse in those with honeycombing or reticular changes (likely UIP).^{26,56} However, in a retrospective study of 17 patients with PM-associated ILD and 16 with DM-associated ILD, patients with primarily ground-glass attenuation and reticular opacity on HRCT had a poorer prognosis compared to those with a predominantly fibrotic pattern.⁵⁷ In another study, automated computer scoring of HRCT scans objectively identified RA-ILD and was helpful in quantifying the radiographic severity of lung disease in patients with pulmonary fibrosis.⁵⁸ In a recent study of 211 MA-ILD patients, OP pattern on HRCT was associated with FI. This could be related to more acute and subacute presentation of OP.⁵⁹ The role of HRCT in MA-ILD is an area requiring further research, particularly as it relates to quantifying disease progression.

Lung biopsy

It is not common to perform a lung biopsy in a patient with MA-ILD as other less invasive tools (such as clinical evaluation, laboratory analysis, HRCT) can guide treatment decisions. Lung biopsy is typically reserved for selected cases mainly to exclude neoplasms, lymphoproliferative disorders, and certain infections (preferably through BAL).⁶⁰ Lung biopsy may be helpful in MA-ILD especially when there are diagnostic dilemmas (e.g. infection versus disease activity) or an unfavorable response to therapeutic intervention challenges where the prognosis is unclear. For example, when imaging is discordant with the clinical picture, tissue may help with establishing the features of UIP and NSIP or the other histopathologic variants of ILD mentioned earlier. In cases where the clinical presentation and HRCT imaging is consistent with UIP, one can avoid lung biopsy. Some case series have described the presence of usual interstitial pneumonia (UIP) in histology, but the most frequently reported patterns in several studies are NSIP and OP.⁶¹⁻⁶³ VATs or surgical lung biopsy is preferred over transbronchial biopsy in most cases of MA-ILD. Transbronchial biopsy and/or lavage can be used to rule out

sarcoidosis and/or infection or malignancy in cases where the parenchymal abnormalities are central. Overall, lung biopsies are performed when the cause or diagnosis of the ILD is unclear, and their indication needs to be evaluated by a multidisciplinary team due to the risk of complications involved.

The Envisia genomic classifier, a clinically validated molecular diagnostic test, differentiates UIP from non-UIP pathology in transbronchial biopsies, potentially allowing patients to avoid invasive surgical lung biopsy.⁶⁴⁻⁶⁷ The test utilizes total RNA extracted from transbronchial biopsy samples to perform Next Generation RNA Sequencing. The gene count data from 190 genes are then input to the Envisia genomic classifier, a machine learning algorithm, to distinguish between UIP and non-UIP. It's noteworthy that The Envisia genomic classifier is not widely available and requires careful interpretation by a multidisciplinary team. There is currently no recommendation either in favor or against this diagnostic method.⁶⁸

Glucocorticoid therapy

Despite the lack of controlled trials, glucocorticoids are considered the mainstay of initial treatment of MA-ILD as at least one-half of the patients respond favorably.² Glucocorticoid therapy is usually initiated with prednisone at a dose of 1 mg/kg/day, often in divided doses and generally not exceeding 80 mg daily. After 4-6 weeks of high-dose glucocorticoid therapy, prednisone is slowly tapered based on the response to therapy and using the general guideline of tapering the existing dose by 20-25% every month. The total duration of therapy with prednisone is generally at least 12 months and when the daily prednisone dose reaches 5-10 mg/day the tapering is generally held.

Patients with rapidly progressive ILD require pulse intravenous methylprednisolone (1000 mg daily for three consecutive days) followed by the aforementioned high dose oral glucocorticoid regimen⁶⁹ in combination with a second immunosuppressive agent, generally cyclophosphamide (intravenous or oral) or rituximab with a transition to mycophenolate mofetil (MMF) or another immunosuppressive agent as outlined below and Fig. 1.

Glucocorticoid-sparing drugs

Most patients with symptomatic MA-ILD will require the addition of a second immunosuppressive, either for enhancing the treatment response or for a glucocorticoid-sparing effect. Early initiation of a second immunosuppressive is typically performed in patients anti-synthetase syndrome, anti-MDA5-associated ILD, and patients with severe pulmonary disease upon presentation.^{70,71} These agents are often initiated concomitantly with glucocorticoid therapy, particularly with moderate or severe ILD. The first-line glucocorticoid-sparing agents include mycophenolate mofetil (MMF) or azathioprine. If these agents fail or the patient worsens, then subsequent immunosuppressive options include cyclophosphamide, tacrolimus or cyclosporine, rituximab or intravenous immune globulin (IVIg).

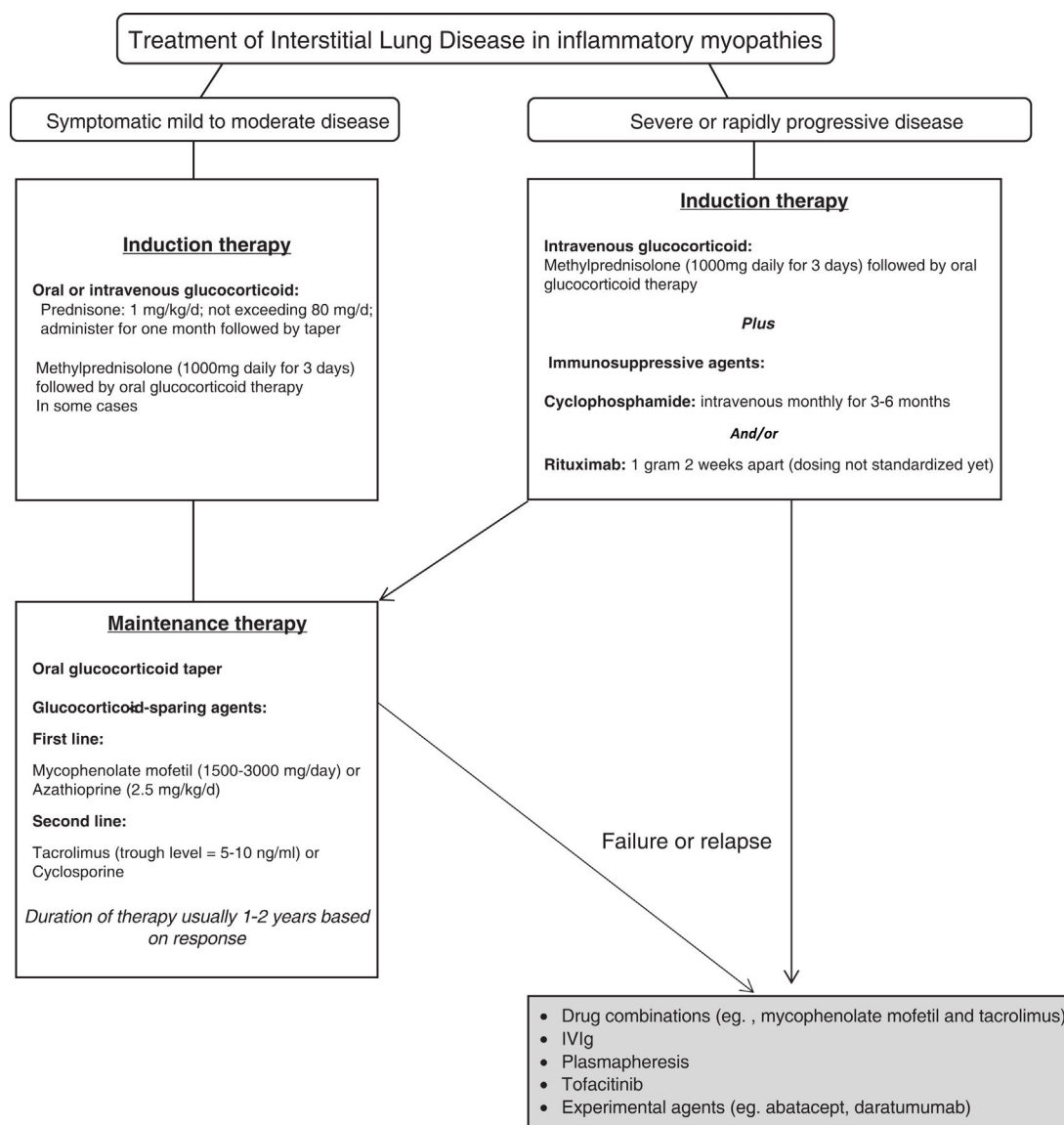


Fig. 1 – Treatment of interstitial lung disease in inflammatory myopathies.

Mycophenolate mofetil (MMF)

Over the past decade, MMF has gained popularity in treating MA-ILD. In a case series of four patients with DM-associated ILD receiving prednisone, the addition of MMF was associated with normalization of the PFTs and resolution of dyspnea in three patients after one year of follow up, along with improvement in the DLCO in the other patient.⁷² In another retrospective study, MMF was shown to preserve lung function in CTD-ILD.⁷³ In the largest cohort of connective tissue disease-associated ILD (CTD-ILD), 125 patients with CTD-ILD (32 with PM or DM) received MMF for a median of 897 days and showed significant improvements in FVC at 52, 104, and 156 weeks and DLCO at 52 and 104 weeks after the initiation of MMF therapy.⁷⁴ Trends toward significance and statistically significant improvements in FVC% were noted among subjects with PM or DM at 52 weeks ($5.7 \pm 3.7\%$; $p = 0.1$), 104 weeks ($7.7 \pm 3.4\%$; $p = 0.02$), and 156 weeks ($9.7 \pm 4.9\%$; $p = 0.04$). There

were similar trends for DLCO% improvement for the PM/DM group.

MMF is administered orally starting at 250–500 mg twice daily and increased by 250–500 mg increments every 1–2 weeks to the target dose of 1500–3000 mg/day. A lower dose is administered in patients with renal insufficiency.

Azathioprine

Azathioprine was one of the first-line conventional immunosuppressive agents used in the management of PM or DM. Several small retrospective case series of PM/DM patients with ILD have suggested efficacy for azathioprine in treating MA-ILD.^{2,22} In one report of 70 patients with MA-ILD, azathioprine use in 25 patients was associated with clinical improvement and the survival was better than observed for control subjects with idiopathic UIP.²² In a retrospective study, 66 patients with MA-ILD were treated with azathioprine and

44 with MMF. At treatment initiation, mean FVC% predicted and DLCO% predicted were significantly lower in the azathioprine group than in the MMF group. In both groups, FVC% predicted improved and the prednisone dose was reduced over 2–5 years; however, for DLCO% predicted, only the AZA group improved. The adjusted model showed no significant difference in posttreatment FVC% predicted or DLCP% predicted between groups, but a 6.6-mg lower dose of prednisone at 36 months in the AZA group.⁷⁵

Screening for thiopurine methyltransferase (TPMT) deficiency is recommended prior to treatment with azathioprine. Azathioprine is given orally starting at 50 mg/day with dose escalation by 50 mg increments every 1–2 weeks up to 2.5 mg/kg/day. The target dose is lower in patients with renal insufficiency.

Tacrolimus and cyclosporine

T-cells have been suggested as therapeutic targets in MA-ILD. In one study, infiltrating lymphocytes in myositis-associated NSIP patients revealed activated CD8+ T-cells.⁷⁶ In another study, CD8+ T-cells were increased in bronchial lavage fluid of patients with PM or DM.⁷⁷ A more recent study showed a decrease in regulatory T-cells in interstitial pneumonitis associated with rheumatic disease.⁷⁸

Tacrolimus and cyclosporine use have been frequently reported in MA-ILD.^{79–84} In a series of eight patients with myositis (6 with anti-Jo-1 and 2 with anti-SRP antibodies; 5 with ILD), tacrolimus use was associated with an improvement in PFT parameters in three of five patients with ILD.⁸⁴ In a follow-up report, 13 patients with antisynthetase-associated ILD (12 with anti-Jo-1) were treated with tacrolimus for an average of 51 months and showed improvement in PFTs.⁸⁵ Tacrolimus has also been used as an initial glucocorticoid-sparing agent⁸⁶ but its use is generally reserved for patients with severe disease due to concerns regarding toxicity. In three small case series of patients with MA-ILD, tacrolimus was beneficial in patients resistant to cyclosporine.^{79,87,88} In a retrospective study of 49 previously untreated MA-ILD patients treated with tacrolimus plus conventional therapy or only with conventional therapy (prednisolone, IV cyclophosphamide and/or cyclosporin), the tacrolimus group had significantly longer event-free survival as compared with the conventional therapy group.⁸⁹ In a retrospective cohort, 23 patients in whom conventional treatment had failed, 18 of whom subsequently received adjunctive tacrolimus. Ninety-four percent had improvements in ILD and 72% showed improvement in both myositis and ILD. The mean doses of prednisone decreased from baseline by 65% at 3–6 months and 81% at 1 year.⁹⁰

In a recent prospective open-label, randomized, phase 2 trial, patients with MA-ILD were randomly allocated to receive prednisolone plus tacrolimus or prednisolone plus cyclosporine.⁹¹ The progression free rates at 52 weeks were 87% in the tacrolimus group and 71% in the cyclosporine group which was not statistically significant.

Cyclophosphamide

Cyclophosphamide is generally reserved for myositis patients with severe or rapidly progressive ILD. In a series of seventeen patients with MA-ILD, patients received monthly intravenous cyclophosphamide (300–800 mg/m² monthly) for at least six months in addition to daily prednisone.⁹² Eleven of the 17 patients improved with less dyspnea and, among seven patients requiring supplemental oxygen, six discontinued its use. Twelve patients showed improvements in FVC of at least 10 percent. Cyclophosphamide use in MA-ILD has been reported in a few more case reports and small series.^{93,94}

Rituximab

In the last decade there have been several case series and a randomized control trials demonstrating significant efficacy of rituximab in PM/DM patients, however, efficacy data of rituximab specific to ILD is evolving. Nevertheless, a beneficial effect of rituximab in MA-ILD has been suggested in case reports and case series.^{95,96} In a retrospective assessment of 50 patients with severe progressive ILD (10 with MA-ILD), rituximab use was associated with a median improvement in FVC of 6.7% ($p < 0.01$) and stability of the DLCO (0% change; $p < 0.01$) in the 6–12-month period following B cell depletion.⁹⁷ The highest proportion of CTD-ILD patients with an improvement following rituximab was seen in the myositis patients with five (50%) experiencing an increase in FVC of > 10% and/or DLCO of > 15%, compared with 4 out of 22 (18.2%) with other CTDs. A retrospective study of 24 rituximab-treated anti-synthetase patients with severe ILD, reported improved PFTs after a median 52 months follow-up post-rituximab.⁹⁸ HRCT analysis showed a median 34% reduction in ILD extent post-rituximab. The best outcome was observed in patients with a disease duration < 12 months and/or acute onset/exacerbation of ILD. Rituximab has been used for management of antisynthetase-associated ILD.^{99–101} A retrospective analysis of patients who received rituximab for CTD-ILD, patients with myositis overlap or antisynthetase syndrome appeared to respond well to treatment, with four patients showing clinically significant improvement in FVC > 10% [M]. In a recent retrospective study of 62 patients with antisynthetase-associated ILD, 34 patients received 2–12 monthly IV cyclophosphamide, followed by standard immunosuppressive therapy in 30 cases (88%).¹⁰² Twenty-eight patients received rituximab, day 1–day 15 infusions, followed by rituximab infusions every 6 months in 26 cases (93%) and 15 patients (54%) concomitantly received another immunosuppressive therapy. Although rituximab and cyclophosphamide demonstrated similar progression-free survival at 6 months, rituximab was superior at 2 years. Rituximab has recently been successfully used for management of anti-MDA5-associated ILD.¹⁰³

Rituximab is usually administered as two 1-g doses two weeks apart but the dose and interval may vary.

IVIg

IVIg is an immunomodulatory agent that has demonstrated efficacy in DM and PM.^{104–106} Few case reports

have suggested efficacy for IVIg in the treatment of MA-ILD.^{107,108} In a retrospective analysis of 17 patients with antisynthetase-associated ILD (14 with refractory disease), the mean percent-predicted FVC% and percent-predicted DLCO% increased over time, while the mean prednisone dose ($p < 0.001$) decreased over time.¹⁰⁹ Seven patients achieved a $> 10\%$ increase in FVC%, including two who used IVIg as initial treatment.

IVIg is generally reserved as a salvage therapy in patients with severe ILD that is progressing despite conventional immunosuppressive therapy. IVIg is safe in the setting of an active infection and can be used concomitantly with other immunosuppressive drugs.

Methotrexate

Methotrexate is not commonly used in the treatment of MA-ILD because of the risk of methotrexate-induced pneumonitis. However, there is no evidence that methotrexate results in more pulmonary toxicity in patients with myositis and ILD. In a report of synthetase positive patients with interstitial pneumonia, methotrexate use was associated with clinical improvement and no further impairment of the breathing pattern.¹¹⁰ A recent meta-analysis showed a small but significant increase in the risk of pneumonitis in patients with rheumatoid arthritis treated with methotrexate compared with other disease-modifying antirheumatic drugs and biologic agents (RR 7.81, 95% CI 1.76–34.72).¹¹¹ Thus, the rare methotrexate-induced pulmonary toxicity in a myositis patient with underlying ILD may present a diagnostic challenge and therefore, it should be used with caution.¹¹²

Other therapies

Combined immunosuppressive regimens have been used for rapidly progressive MA-ILD including anti-MDA5-associated disease. In a prospective multi-center study, anti-MDA5-positive DM with ILD ($n = 29$) were enrolled and treated with a regimen of high-dose glucocorticoids, tacrolimus, and IV cyclophosphamide.¹¹³ Plasmapheresis was used if a patient's condition worsened after the regimen started. A historical control group ($n = 15$) was used consisting of anti-MDA5-positive DM patients with ILD who received step-up treatment (high-dose GC and stepwise addition of immunosuppressant). The combined immunosuppressive regimen group showed significantly higher 6-month survival rates than the step-up treatment group (89% versus 33%; $p < 0.0001$).

Basiliximab is a monoclonal antibody that blocks the interleukin-2 (IL-2) receptor alpha chain (or CD25) on T and B lymphocytes and interferes with their replication and activation, respectively. In a recent case series of four anti-MDA5-positive patients with clinically amyopathic DM and rapidly progressive ILD despite treatment with prednisone, cyclosporine, and, in two patients, IVIg, the addition of basiliximab (two intravenous infusions of 20 mg, seven days apart) was associated with improvement in PFTs and HRCT findings in three patients.¹¹⁴ The fourth patient died after developing respiratory failure three days

after the first intravenous infusion of basiliximab. Prior treatment with prednisone and cyclosporine may have contributed to the respiratory improvement in the other three patients.

A few case reports of MDA5(+) patients describe improvement in ILD with tofacitinib, a janus kinase inhibitor, after failure of conventional immunosuppressive therapies.^{115–117} In an open-label study, patients with anti-MDA5-associated ILD were treated with tofacitinib (at a dose of 5 mg twice daily).¹¹⁸ A total of 32 patients who met the same criteria and received conventional treatments were historical controls. Survival 6 months after the onset of ILD was significantly higher among the patients in the prospective group (18 of 18, 100%) than among the patients in the control group (25 of 32, 78%) ($p = 0.04$). A recent retrospective analysis included 26 patients treated with tofacitinib and 35 treated with tacrolimus. The 6-month (38.5% vs 62.9%; $p = 0.03$) and 1-year (44.0% vs 65.7%; $p = 0.03$) mortality rates in the tofacitinib group were significantly lower than those in the tacrolimus group.

A recent report described a case of anti-MDA5-associated ILD who was initially treated with 1000 mg of methylprednisolone pulse, 500 mg of intravenous cyclophosphamide therapy followed by prednisolone 40 mg/day with tapering, and oral cyclosporine 200 mg/day.¹¹⁹ However, her ILD worsened. She was then initiated on plasma exchange as an additional treatment which led to improvement in the ILD, serum ferritin, and anti-MDA5 titer.

Another report suggested efficacy for daratumumab, an anti-CD38-antibody and anti-plasma cell agent, in a patient with rapidly progressive anti-MDA5-positive ILD in whom multiple immunosuppressive agents had failed including glucocorticoids, IVIg, tofacitinib, cyclophosphamide, cyclosporine, MMF and rituximab.¹²⁰ Significant pulmonary improvement was noticed after 4 weekly injections of 1800 mg. After 6 months of follow up, stable disease remission with significant pulmonary improvement and persistent depletion of CD38+ plasma cells and MDA5-antibody titers were noted.

Conclusion

ILD is a common and frequently devastating occurrence in myositis. The decision to start therapy for ILD in patients with IIM is generally based on the severity of dyspnea and its temporal progression along with functional studies (PFTs), imaging and the severity of the underlying myositis. Clearly, well-designed controlled trials are required to develop an evidence-based approach to the treatment of MA-ILD.⁴⁹ Efforts are underway with the development of CTD-ILD response criteria for clinical trials and novel agents are on the horizon to target inflammatory pathways and fibrosis, which will hopefully lead to well-designed clinical trials for CTD-ILD in general and MA-ILD in particular.⁴⁹

Ethical consideration

This review study does not involve experimentation on animals, patients or human subjects.

Conflict of interests

The authors declare that they have no conflict of interest.

Appendix A. Supplementary material

The Spanish translation of this article is available as supplementary material at doi:[10.1016/j.rcreu.2023.09.003](https://doi.org/10.1016/j.rcreu.2023.09.003).

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