Review Article

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Predictors of progression in idiopathic inflammatory myopathies with interstitial lung disease

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ABSTRACT

The idiopathic inflammatory myopathies (IIMs) are a group of connective tissue diseases that affect multiple organ systems, including the lungs. Interstitial lung disease (ILD) is the most common and heterogeneous complication of IIMs, with its degree ranging from mild to fatal. Thus, it is critical to identify clinical features and validated biomarkers for predicting disease progression and prognosis, which could be beneficial for therapy adjustment. In this review, we discuss predictors for rapid progression of IIM-ILD and propose guidance for disease monitoring and implications of therapy. Systematic screening of myositis-specific antibodies, measuring serum biomarker levels, pulmonary function tests, and chest high-resolution computer tomography will be beneficial for the evaluation of disease progression and prognosis.

Key words: idiopathic inflammatory myopathies, interstitial lung disease, biomarker, prognosis, rapid progressive

INTRODUCTION

Idiopathic inflammatory myopathies (IIMs) are a group of connective tissue diseases that are characterized by skeletal muscle inflammation.[1] IIMs include dermatomyositis (DM), polymyositis (PM), inclusion body myositis, and immune-mediated necrotizing myopathy.[2] In addition to muscular involvement, IIMs can affect multiple organs, and involvement of the pulmonary system is a frequent and challenging issue. PM/DM-associated interstitial lung disease (PM/DM-ILD) is the most common and heterogeneous complication of IIMs, with its degree ranging from mild to fatal.[3,4] A subset of myositis patients with rapidly progressive ILD (RP-ILD), which is more devastating, also exists; hence, it is critical to identify clinical features and validated biomarkers for predicting patient prognosis, which could increase the efficiency of screening and diagnostic resources.[5-8]

Despite the established relationship between PM/DM-ILD and morbidity and mortality, risk prediction in the presence of ILD, RP-ILD, and unfavorable outcomes is essential yet challenging for clinicians due to heterogeneity in disease-specific and patient-specific variables.[9,10] The presence of characteristic skin lesions (Gottron's papules and heliotrope rash) and the absence of clinically significant muscle symptoms were reported to be associated with ILD in IIM patients.[11] Studies on predictive risk factors for RP-ILD in IIM patients revealed that biomarkers such as ferritin,[5] serum YKL-40 levels,[12,13] and myositis-specific autoantibodies (MSAs), including anti-aminoacyl-tRNA synthetase (ARS)[14] and antimelanoma differentiation-associated gene 5 (MDA5),[5,15,16] play important roles in evaluating disease activity

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and prognosis. In this review, we summarize the current understanding of disease pathogenesis and risk factors for IIM-ILD, discuss predictors of rapid progression in IIM-ILD, and propose guidance for disease monitoring and implications of therapy.

PATHOGENESIS OF IIM-ILD

Environmental risk factors

Multiple environmental factors, including ultraviolet radiation, viral infections, smoking, and medications, may trigger chronic immune activation in genetically susceptible individuals. A retrospective cross-sectional study revealed that ultraviolet radiation intensity was associated with increased odds of developing DM, and this effect was stronger in women.[17] Viral infections may play a role in triggering immune activation or disrupting immune tolerance, but tissues or serum test negative for the presence of infectious agents.[18] In a cross-sectional analysis of IIM cases from 11 countries, smoking was associated with the development of ILD in DM patients.[19] One study revealed that ultraviolet exposure and recent nonsteroidal anti-inflammatory drug use were significant predictors of DM flares.[20]

Genetic risk factors

Type II human leukocyte antigen (HLA) alleles play an important role in the pathogenesis of DM in Asian populations. A higher frequency of the HLA-DRB1*09:01 and HLA-DRB1*12:01 alleles was observed in adult Chinese patients with DM.[21] In addition, the DRB1*12:01[21] and *04:01[22] genotypes were significantly associated with the presence of anti-MDA5 antibodies in patients with DM. However, different risk factors, including the combined frequency of HLA-DRB1*01:01 and *04:05, have been associated with susceptibility to anti-MDA5 antibody-positive DM in the Japanese population.[23] In addition, an association between HLA-B*08:01 and an anti-Jo 1 antibody was found in a Caucasian cohort.[24] A genome-wide association study of IIM patients in an Asian population revealed a variant of *WDFY4* that was significantly associated with clinical amyopathic dermatomyositis (CADM, rs7919656; $OR = 3.87$; $P = 1.5 \times 10^{-8}$). This variant interacted with pattern recognition receptors and MDA5, and augmented NF-κB activation by these receptors.[25] Epigenetic modifications, including DNA methylation, histone modification, microRNA, and lncRNA activity, may also play a role in IIM pathogenesis.[26]

Immune mechanisms

Vascular injury, which may result from inappropriate complement activation, plays a central role in the pathogenesis of DM. Formation of membrane attack complexes deposited on the endothelial cell wall of the endomysial capillaries results in endothelial injury that leads to cutaneous lesions, vasculopathy, and perifascicular atrophy.[27] In addition, evidence that suggests that blood vessel exposure to interferons (IFNs) may lead to endothelial injury, ultimately responsible for the cutaneous and pulmonary lesions associated with this disease.[28,29] IFN pathways have been identified as key players in the pathophysiology of myositis.[30] In particular, analysis of the association between microRNA and mRNA initially revealed that the IFN network orchestrated primarily by activated monocytes/macrophages may be responsible for the occurrence of a cytokine storm in anti-MDA5-associated ILD.[31] Prolonged autoantibody production, such as anti-Jo1, anti-MDA5, and anti-ARS-induced $CD4^+$ Th1-cell proliferation, produces high levels of IFNγ,[32] which upregulate major histocompatibility complex (MHC) class I and enhance T-cell cytotoxicity. Antigen-specific $CD8^+$ cells bind directly to aberrantly expressed MHC class I molecules on the surface of muscle fibers through their T-cell receptors, forming the MHC-CD8 complex. Perforin granules released by auto-aggressive T cells mediate muscle fiber necrosis.[27,33]

Additionally, increased levels of IFNγ-induced chemokine (C-X-C motif) ligand (CXCL) 9 and CXCL10 induce the recruitment of intrapulmonary profibrotic M2 macrophages, which produce transforming growth factor-β (TGF-β) to directly promote pulmonary fibrosis.[34] Locally, macrophages and airway epithelial cells are the main sources of stromal cell-derived factor-1 (SDF-1), which induces the accumulation of intrapulmonary $CD4^+CXCR4^+$ T cells. These T cells in turn produce profibrotic agents, such as TGF-β, α-smooth muscle actin, and collagen I.[35] Cytokines released by the recruited $CD4^+CXCR4^+$ T cells promote the differentiation of profibrotic $CD8^+$ T cells and profibrotic M2 macrophages[28] (Figure 1). The pathogenic role of autoantibodies remains unclear; however, the anti-MDA5 antibody may potentially contribute to the pathogenesis of IIM-ILD, which may be involved in the dysregulation of the IFN pathway and tissue deposition.[36,37]

Risk factors for developing ILD in IIM patients

The prevalence of ILD in IIM patients ranges from 20% to 86%, depending on the composition of different subtypes of IIMs and the sensitivity of the screening technique.[1] Several patient characteristics have been associated with a higher risk of developing ILD in IIM patients (Table 1). ILD is more common in patients with antisynthetase syndrome (77.4%) and CADM (80.6%).[11,38] In addition, ethnicity[39] and older age of onset[40] are associated with ILD development. The most commonly presented symptoms are cough and dyspnea;[11] however, IIM-ILD may be associated with extrapulmonary manifestations

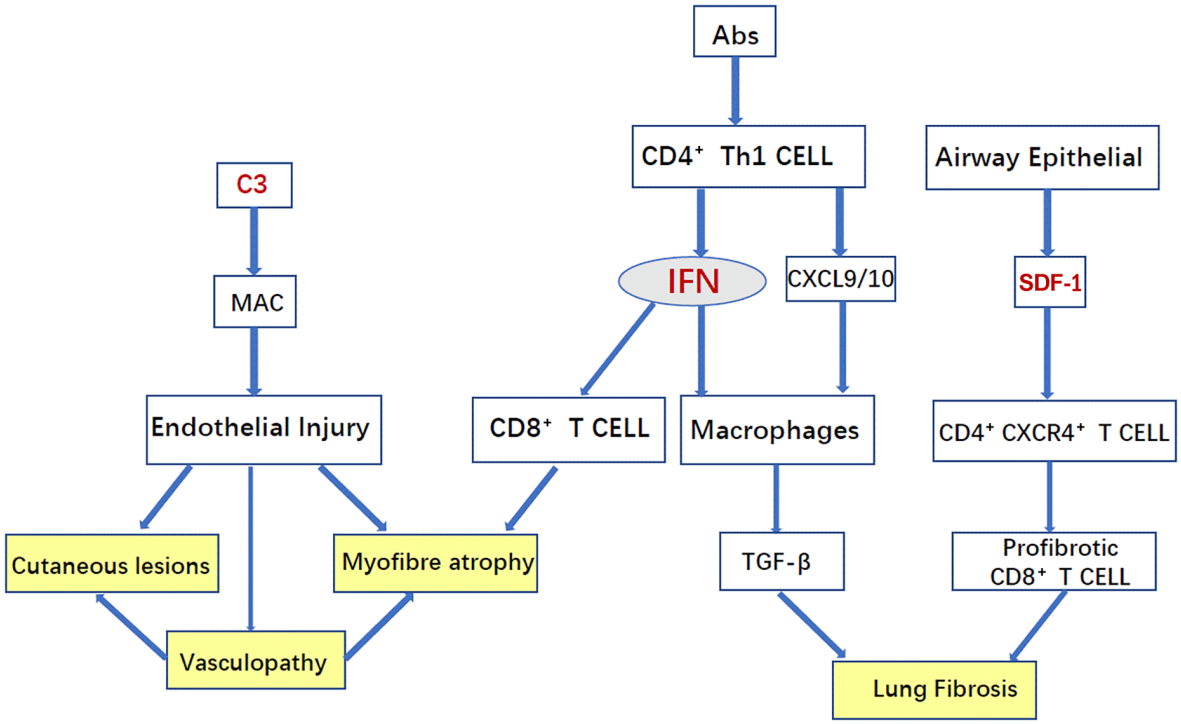

Figure 1: Proposed mechanisms in IIMs. Complement 3 activation is an early event leading to the formation of MACs, which is deposited on the endothelial cell wall of the endomysial capillaries. Endothelial injury caused by MACs leads to cutaneous lesions, vasculopathy, and perifascicular atrophy. Prolonged autoantibody production induced CD4⁺ Th1-cell proliferation produces high levels of IFNγ, which upregulate MHC class I and enhance T-cell cytotoxicity. Antigen-specific CD8⁺ cells bind directly to aberrantly expressed MHC class I molecules on the surface of muscle fibers and mediate muscle fiber necrosis. Increased levels of IFNγ-induced chemokines induce the recruitment of intrapulmonary profibrotic M2 macrophages, which produce transforming growth factor-β (TGF-β) to directly promote pulmonary fibrosis. Locally, macrophages and airway epithelial cells are the main sources of stromal cell-derived factor-1 (SDF-1), which induces the accumulation of intrapulmonary CD4⁺CXCR4⁺ T cells. Cytokines released by the recruited CD4⁺CXCR4⁺ T cells promote the differentiation of profibrotic CD8⁺ T cells and profibrotic M2 macrophages. IIMs: idiopathic inflammatory myopathies; C3: complement 3; MAC: membrane attack complexes; IFN: interferons; SDF-1: stromal cell-derived factor-1; TGF-β: transforming growth factor-β; MHC: major histocompatibility complex.

such as arthritis,[11] with or without mild myopathy,[11] facial rash,[11] and mechanic's hand.[40]

Testing for the presence of MSAs and myositis-associated autoantibodies (MAAs) completes the clinical evaluation of IIMs. Patients who test positive for anti-ARS antibodies frequently present with ILD,[11,39,41] particularly anti-Jo1,[11,40,41] anti-PL7,[42] anti-PL12,[42] and anti-OJ[11] antibodies. The clinical spectrum of anti-ARS autoantibodies includes fever, mechanic's hand, arthritis, myositis, Raynaud's phenomenon, and ILD. In a retrospective multicentric study,[42] bivariate, multiple correspondence, cluster, and survival analyses were performed to characterize the clinical phenotype of patients with antisynthetase syndrome. ILD was more prevalent in patients with anti-PL7 and anti-PL12 than in those with anti-Jo1 antibodies (80% and 88% *vs.* 67%, respectively; $P = 0.014$). Patients with anti-PL12 or anti-PL7 antibodies exhibited diseases that were more restricted to the lungs. A meta-analysis[43] that enrolled 27 cohort studies described the clinical spectrum associated with ARS autoantibodies; patients with non-anti-Jo1 ARS were reported to more likely present with ILD than those with anti-Jo1 autoantibodies. Anti-MDA5 antibody, originally identified in CADM, is associated with poor prognosis due to the high prevalence of RP-ILD.[28] ILD occurs in 82% to 100% of patients with anti-MDA5 DM in Chinese population.[10,44,45] Importantly, MAAs such as anti-Ro52 antibodies could predict the development of ILD.[11,40]

To date, multiple biomarkers for ILD have been identified. Serum markers such as ferritin,[46] interleukin (IL)-18,[46] Krebs von den Lungen-6,[47–49] and surfactant Protein-D[48] are also believed to be associated with ILD. Macrophage activation was observed in anti-MDA5 DM, and Zuo *et al.* reported that the infiltration of CD163-positive macrophages into alveolar spaces was significantly higher in the RP-ILD group of DM patients.[50] Levels of macrophage activation markers, such as soluble CD163 (sCD163)[51] and sCD206,[52] are elevated in patients with ILD, especially in those with RP-ILD. A meta-analysis and systematic review suggested that YKL-40, a member of the mammalian chitinase-like protein family, may be a useful biomarker for the diagnosis and prognosis prediction of

Table 1: Predictors associated with the presence of interstitial lung disease in idiopathic inflammatory myopathies

Items	Predictive factor	First author
Demographic	Black ethnicity	Chua *et al.*[39]
IIM subtypes	ARS	Vojinovic *et al.*[11]
	CADM	Gan *et al.*[38]
Clinical manifestations or complications	Older age of onset	Huang *et al.*[40]
	Mechanic's hand	Huang *et al.*[40]
	Polyarthritis	Vojinovic *et al.*[11]
	Dyspnea	Vojinovic *et al.*[11]
	Facial rash	Vojinovic *et al.*[11]
	Without myositis	Vojinovic *et al.*[11]
Laboratory tests	Lower CPK levels	Vojinovic *et al.*[11]
MAAs or MSAs	Antisynthetase antibody	Vojinovic *et al.*[11]
		Chua *et al.*[39]
		Li *et al.*[41]
	Anti-Jo1	Vojinovic *et al.*[11]
		Huang *et al.*[40]
		Li *et al.*[41]
	Anti-OJ	Vojinovic *et al.*[11]
	Anti-PL7	Hervier *et al.*[42]
	Anti-PL12	Hervier *et al.*[42]
	Anti-Ro52	Vojinovic *et al.*[11]
		Huang *et al.*[40]
	Anti-MDA5 antibody	Li *et al.*[10]
		Cao *et al.*[44]
		Chen *et al.*[45]
Biomarkers	Ferritin	Gono *et al.*[46]
	IL-18	Gono *et al.*[46]
	KL-6	Takanashi *et al.*[47]
		Ohnishi *et al.*[48]
		Wang *et al.*[49]
	Surfactant protein-D	Ohnishi *et al.*[48]
	Serum sCD163 levels	Zuo *et al.*[50]
		Enomoto *et al.*[51]
	Median sCD206 levels	Shen *et al.*[52]
	Serum YKL-40 levels	Jiang *et al.*[12]
		Hozumi *et al.*[13]
		Tong *et al.*[53]
	Serum CYFRA21-1 levels	Gan *et al.*[38]
	$CD4^+CXCR4^+$ T cells%	Wang *et al.*[35]
Pulmonary function tests	FVC%	Chua *et al.*[39]
	DL_{CO}%	Chua *et al.*[39]
Imaging	Extent of ILD on HRCT	Fathi *et al.*[54]
	Lung ultrasound B lines	Wang *et al.*[49]

IIM: idiopathic inflammatory myopathy; ARS: anti-aminoacyl-tRNA synthetase; CADM: clinical amyopathic dermatomyositis; CPK: creatine phosphokinase; MAAs: myositis-associated autoantibodies; MSAs: myositis-specific autoantibodies; MDA5: melanoma differentiation-associated gene 5; IL-18: interleukin 18; KL-6: Krebs von den Lungen 6; sCD163: soluble CD163; sCD206: soluble CD206; YKL-40: chtinase-3-like-1 protein; CYFRA21-1: cytokeratin-19 fragment; FVC%: percent-predicted forced vital capacity; DL_{CO}%: percent-predicted diffusing capacity of the lung for carbon monoxide; ILD: interstitial lung disease; HRCT: high-resolution computed tomography.

ILD.[12,13,53] Tumor-associated antigens were observed in IIM-ILD; further investigation revealed that the higher serum level of cytokeratin-19 fragment (CYFRA21-1) was a risk factor for ILD.[38] Peripheral $CD4^+CXCR4^+$ T cells, which promote pulmonary fibroblast proliferation via IL-21, are potential biomarkers associated with the severity and prognosis of IIM-ILD.[35]

In the past decade, chest high-resolution computed tomography (HRCT) and pulmonary function tests (PFTs) have been fundamental for ILD diagnosis and follow-up. As in previous reports,[54] linear opacities, consolidations, ground-glass opacities, and peribronchovascular thickening were the most common HRCT abnormalities revealed during initial imaging. A drop in the percent-predicted diffusing capacity of the lung for carbon monoxide (DL_{CO}%) or forced vital capacity (FVC%) occurred within a year of ILD onset in IIM patients in a British cohort, and progressive lung damage occurred in patients with IIM-ILD, heralded by decline in lung function at one year.[39] Lung ultrasound B lines, used as radiation-free markers, have shown a significant correlation with serum KL-6 levels, HRCT, and PFTs in patients with IIM-ILD.[49]

Risk factors for developing RP-ILD in IIM patients

RP-ILD is usually fatal in patients with IIM who succumb within a few weeks or months.[4,55] Therefore, predictive parameters for the onset of RP-ILD are critical for the early treatment of patients with IIM (Table 2). Multiple studies have explored several baseline parameters associated with RP-ILD in patients with IIM; age over 57 years at disease onset,[10] CADM subtype,[4,38,56] fever,[57] C-reactive protein (CRP)[57] level, periungual erythema,[10,57] and ferritin[5] level were all reported as predictive factors for disease onset and poor prognosis. RP-ILD occurs in 39% to 79% of patients with anti-MDA5 DM in Chinese populations.[28] A meta-analysis revealed that anti-MDA5 antibodies can be considered a valuable tool for identifying a high risk of developing RP-ILD in IIM patients, regardless of ethnic origin.[45] A retrospective study in MDA5-DM-ILD patients revealed that lower OI at baseline and lower zone consolidation were associated with a higher risk of acute or subacute interstitial pneumonia (A/SIP).[58] Previous studies revealed that elevated on-admission disease activity[4], lower DL_{CO}%,[4,59] and history of pulmonary tuberculosis[56] were independent risk factors for RP-ILD in IIM patients. However, bacterial and fungal infections, the most common pulmonary infections in patients with IIM-ILD, were not significantly correlated with the development of RP-ILD.

Various studies have been conducted to identify serum biomarkers for predicting RP-ILD in IIM patients, including macrophage activation markers, T-cell immunoglobulin receptors, and tumor-associated antigens. Indeed, previous studies have reported the importance of macrophage activation in DM-ILD pathophysiology. Higher sCD163[51] levels were observed in patients with RP-ILD, with a worse prognosis. sCD206[52] and serum neopterin levels[60] were found to be independent prognostic factors for RP-ILD in patients with DM. Increased serum galectin-9 (Gal-9) levels have been reported in patients with IIM, especially in the RP-ILD group. Thus, Gal-9 is considered an easily detectable biomarker for DM disease activity, and possibly for RP-ILD severity.[61] Other serum biomarkers, such as YKL-40[12] and CYFRA21-1,[58] were identified as useful indicators for the occurrence of RP-ILD and correlated with the severity of ILD and poor prognosis.

With the development of medical imaging techniques, HRCT has become essential for RP-ILD diagnosis and follow-up. Lower zone consolidation during HRCT has been reported to be associated with the onset of RP-ILD in IIM patients.[58] ^{18}F-Fluorodeoxyglucose (F-FDG) positron emission tomography (PET)/computed tomography (CT) has proven to be a valuable hybrid technique (combining nuclear and CT imaging) for detecting interstitial lesions in IIM patients. Our previous study also indicated that higher ^{18}F-FDG uptake by the interstitial lesions observed in the PET/CT images of IIM patients was significantly associated with RP-ILD and unfavorable outcome.[59,62] Moreover, it seems reductive and inefficient to use a single clinical factor to predict RP-ILD in heterogeneous diseases. A holistic approach should be used to provide a better predictive model for RP-ILD based on multiple clinical, immunological, and radiographic factors. A multiparametric RRP model,[57] including fever, periungual erythema, elevated CRP level, and presence of anti-MDA5 antibody and anti-Ro-52 antibody, showed promising predictive accuracy for the incidence of RP-ILD. A "DLM" model[59] was established by including DL_{CO}%, bilateral lung mean standard uptake value, and abnormal mediastinal lymph node to predict RP-ILD with a cutoff value of ≥ 2 and an area under the curve (AUC) value of 0.905.

Predictors for unfavorable outcome in IIM-ILD

IIM-ILD is a major cause of death, with an estimated excess mortality rate of approximately 40%.[3,63] Thus, it is crucial to optimize disease management based on prognostic factors to improve the clinical outcomes (Table 3). Previous studies have identified several predictors of unfavorable outcomes in IIM-ILD, including old age[5,64] skin ulcers,[65] DM/CADM subtypes,[41,60] disease activity index,[4] lower arterial partial pressure of O_2,[5] A/SIP,[64] and RP-ILD.[60,66] Serious infection[67,68] was also identified as a risk factor for early death in patients with IIM-ILD. The association between mortality and serious infection was informative, despite IIM-ILD patients

Table 2: Predictors associated with rapidly progressive interstitial lung disease in idiopathic inflammatory myopathies

Items	Predictive factor	First author
Demographic	Age ≥ 57 years at disease onset	Li *et al*.[10]
IIM subtypes	CADM	Liang *et al*.[4]
		Gan *et al*.[38]
		Wong *et al*.[56]
Clinical manifestations or complications	Fever	Li *et al*.[57]
	Periungual erythema	Li *et al*.[10]
		Li *et al*.[57]
	Lower OI	Gui *et al*.[58]
	MYOACT	Li *et al*.[57]
	History of TB	Wong *et al*.[56]
On-admission laboratory findings	Serum ferritin levels	Motegi *et al*.[5]
	Elevated CRP levels	Li *et al*.[57]
MAAs or MSAs	Anti-MDA5 antibody	Nombel *et al*.[28]
		Chen *et al*.[45]
Biomarkers	Median sCD163 levels	Enomoto *et al*.[51]
	Median sCD206 levels	Shen *et al*.[52]
	Serum Gal-9 levels	Peng *et al*.[60]
	Serum YKL-40 levels	Jiang *et al*.[12]
	Serum CYFRA21-1 levels	Gui *et al*.[58]
	Serum neopterin levels	Liang *et al*.[61]
Pulmonary function tests	DL_{CO}%	Liang *et al*.[4]
		Liang *et al*.[59]
Imaging	Lower zone consolidation in HRCT	Gui *et al*.[58]
	Bilateral lung SUV_{mean}	Liang *et al*.[59]
	Bilateral lung SUV_{max}	Cao *et al*.[62]
	Mediastinal lymph node SUV_{mean}	Liang *et al*.[59]
Integrated data model	DLM model	Liang *et al*.[59]
	RRP model	Li *et al*.[57]

IIM: idiopathic inflammatory myopathy; CADM: clinical amyopathic dermatomyositis; OI: oxygen index; MYOACT: myositis disease activity assessment visual analogue scales; TB: tuberculosis; CRP: C-reactive protein; MAAs: myositis-associated autoantibodies; MSAs: myositis-specific autoantibodies; MDA5: melanoma differentiation-associated gene 5; sCD163: soluble CD163; sCD206: soluble CD206; Gal-9: galectin-9; YKL-40: chtinase-3-like-1 protein; CYFRA21-1: cytokeratin-19 fragment; DL_{CO}%: percent-predicted diffusing capacity of the lung for carbon monoxide; HRCT: high-resolution computed tomography; SUV: standardized uptake value; DLM model: a multiparametric score contained DL_{CO}%, lung and mediastinum; RRP model: a multiparametric model including fever, periungual erythema, elevated CRP level, and presence of anti-MDA5 antibody and anti-Ro-52 antibody.

receiving high-dose glucocorticoids only for relatively short periods. On-admission laboratory findings included serum ferritin,[8,60,66,69] lactate dehydrogenase,[66] anti-Ro 52 antibody,[70] anti-MDA5 antibody,[41,66] and anti-MDA5 antibody titers.[8,60,66]

Furthermore, biomarkers are not only correlated with clinical features but also closely involved in IIM-ILD pathophysiology. Serum biomarkers for predicting unfavorable outcomes have been verified in several studies, including alveolar surfactants (KL-6 and SP-D),[8,69,71] inflammatory marker YKL-40,[12,13] macrophage activation marker sCD163,[51] neopterin,[60] and chitotriosidase.[69] Other biomarkers, such as CYFRA21[58] and matrix metalloproteinase 7,[72] were also associated with unfavorable outcomes in IIM-ILD. Crosstalk between T cells ($CD3^+$ T cells[12] or $CD4^+CXCR4^+$ T cells[35]) and other lung-resident cells involved in the inflammatory and fibrotic context of IIM-ILD was independently associated with poor prognosis.

PFTs and HRCT can assess the degree of pulmonary function impairment and the extent of disease involvement and should be performed repetitively over time. Lower values of DL_{CO}%[13] and FVC%,[64] lower ground-glass opacity/attenuation (GGO/GGA)[64] and consolidation/GGA,[73] and extent of radiological abnormality[64] have all been demonstrated to predict poor prognosis for IIM-ILD.

Table 3: Predictors of unfavorable outcome in idiopathic inflammatory myopathies associated interstitial lung disease

Items	Predictive factor	First author
Demographic	Old age	Motegi *et al.*[5]
		Kamiya *et al.*[64]
IIM subtypes	DM	Li *et al.*[41]
	CADM	Li *et al.*[41]
		Peng *et al.*[60]
Clinical manifestations or complications	Skin ulcer	Yamasaki *et al.*[65]
	Lower PaO_2	Motegi *et al.*[5]
	A/SIP	Kamiya *et al.*[64]
	MYOACT score	Liang *et al.*[4]
		Peng *et al.*[60]
	RP-ILD	Lian *et al.*[66]
	Serious infection	Cao *et al.*[67]
		Sugiyama *et al.*[68]
On-admission laboratory findings	Ferritin	Wu *et al.*[8]
		Peng *et al.*[60]
		Lian *et al.*[66]
		Fujisawa *et al.*[69]
	LDH	Lian *et al.*[66]
MAAs or MSAs	Anti-Ro 52 antibody	Xu *et al.*[70]
	Anti-MDA5 antibody	Li *et al.*[41]
		Lian *et al.*[66]
	Anti-MDA5 antibody titers	Motegi *et al.*[5]
		Peng *et al.*[60]
		Lian *et al.*[66]
Biomarkers	Serum KL-6 levels	Wu *et al.*[8]
	Serum surfactant protein-D levels	Kaieda *et al.*[71]
	Serum sCD163 levels	Enomoto *et al.*[51]
	Serum YKL-40 levels	Jiang *et al.*[12]
		Hozumi *et al.*[13]
	Serum CYFRA21 levels	Gui *et al.*[58]
	Serum chitotriosidase levels ≥ 23.5 ng/ml	Fujisawa *et al.*[69]
	Serum MMP-7 levels > 5.08 ng/ml	Nakatsuka *et al.*[72]
	Serum neopterin > 22.1 nmol/l	Peng *et al.*[60]
	Peripheral $CD3^+$ T-cell counts	Jiang *et al.*[12]
	$CD4^+$ $CXCR4^+$ T cells%	Wang *et al.*[35]
Pulmonary function tests	Lower value DL_{CO}%	Hozumi *et al.*[13]
	Lower value of FVC%	Kamiya *et al.*[64]
Imaging	GGO/GGA	Kamiya *et al.*[64]
	Lower consolidation/GGA pattern	Tanizawa *et al.*[73]
	Extent of radiological abnormality	Kamiya *et al.*[64]
	Semiquantitative assessment in HRCT	Lian *et al.*[66]
Integrated data model	GAP-ILD model	Cao *et al.*[67]
	FLAIR risk score model	Lian *et al.*[66]
	MCK model	Gono *et al.*[74]

IIM: idiopathic inflammatory myopathy; DM: dermatomyositis; CADM: clinical amyopathic dermatomyositis; A/SIP: acute or subacute interstitial pneumonia; RP-ILD: rapid progressive interstitial lung disease; LDH: lactate dehydrogenase; MAAs: myositis-associated autoantibodies; MSAs: myositis-specific autoantibodies; MDA5: melanoma differentiation-associated gene 5; sCD163: soluble CD163; YKL-40: chtinase-3-like-1 protein; CYFRA21-1: cytokeratin-19 fragment; MMP: matrix metalloproteinase; DL_{CO}%: percent-predicted diffusing capacity of the lung for carbon monoxide; FVC%: percent-predicted forced vital capacity; GGO: ground-glass opacity; GGA: ground-glass attenuation; HRCT: high-resolution computed tomography; GAP-ILD: ILD-gender age and physiology.

The semiquantitative assessment of lesions in HRCT has also been shown to be relevant to the outcome.[66]

Predictive models based on a combination of several independent biomarkers for the diagnosis of unfavorable outcomes of IIM-ILD have been validated in recent studies. The GAP-ILD (ILD-gender age and physiology) model performed well in predicting the risk of mortality among patients with IIM-ILD.[67] A combined risk score (the FLAIR score), which includes ferritin, LDH (lactate dehydrogenase), and anti-MDA5 antibody levels, HRCT imaging score, and rapid progressive ILD (RP-ILD), could help to predict survival in patients with ADM-ILD and recommend further risk-based treatment.[66] Furthermore, the MCK model using CRP and KL-6 levels combined with anti-MDA5 antibody level was replicated in a validation cohort and was demonstrated to be useful for predicting prognosis in patients with IIM-ILD.[74] In a retrospective study, a decrease in serum surfactant protein-A and/or KL-6 levels was associated with improved lung function in patients with ILD.[75]

Implications of therapy

Based on the mechanism of IIM-ILD, inhibition of both T-cell activation and cytokines, such as IFNs, is considered valuable approaches for the treatment of IIM-ILD. Combination immunosuppressive therapies are widely used. For instance, steroid administration is the first-line therapy in the acute presentations of ILD, which include new-onset disease or a flare-up of chronic ILD.[2] Pulse-dose steroids (500 mg to 1 g/day for 3 days) are typically used in IIM patients with RP-ILD or diffuse alveolar damage. Second-line treatment includes mycophenolate mofetil, Azathioprine, cyclophosphamide (CYC), or calcineurin inhibitors, such as cyclosporine and tacrolimus, can be used empirically for glucocorticoid sparing. In a long-term retrospective study, both mycophenolate mofetil and azathioprine were associated with a lower prednisone dose and improved FVC% predicted.[76] In evidence (134 studies)-based recommendations for the treatment of anti-MDA5 positive DM-RP-ILD, the initial use of combined immunosuppressive therapy with high-dose glucocorticoids and calcineurin antagonists with or without CYC is the first choice.[77] In a prospective study, intravenously pulsed CYC in combination with prednisone and cyclosporine A was investigated in cases of DM-related RP-ILD. Half of the patients survived and had a favorable outcome for more than 2 years, although the remaining patients died of respiratory failure within 3 months.[55] CYC is frequently administered to patients with severe or refractory myositis-related ILD.[78] A systematic review of 12 studies on refractory IIMs and IIM-ILD concluded that CYC improved both muscle strength and PFTs; 58% (34/59) of the patients showed an improvement of > 10% in their FVC%, 64% (27/42) showed an improvement of > 10% in their DL_{CO}%, and 67% (35/52) showed significant improvement in their HRCT scores.[79] However, limited evidence exists regarding the therapeutic potential of biologics in the treatment of IIM-ILD. In patients with IIM-ILD who do not respond to combination therapy, clinicians can prescribe alternatives, such as rituximab or tofacitinib, for current therapy. Several studies have reported PFT improvement in patients with ARS-ILD using rituximab, a monoclonal antibody that depletes B-cell proliferation.[80–82] A case series described the use of rituximab in patients with severe acute ILD or in patients where CYC administration or combination therapies failed. More than half of the patients showed different degrees of improvement in PFTs, and pulmonary HRCT was observed in more than half of the patients.[83]

Considering the importance of the IFN signaling pathway in IIM-ILD, inhibitors of Janus kinases (JAKi) are promising treatment options.[84] One study has reported that tofacitinib was successfully used in patients with amyopathic DM-ILD patients.[85] Several studies have reported the efficacy of tofacitinib in patients refractory to standard treatment.[86,87] The therapeutic value of JAKi in repressing muscle injury as well as complications of ILD should be validated. In addition, T-cell activation may play a role in the pathogenesis of IIM-ILD. Abatacept, which prevents T-cell activation by binding to CD80 and CD86 on antigen presenting cells, may be a potential treatment. A phase II randomized clinical trial involving 20 patients (9 DM and 11 PM) reported that nearly half of the patients exhibited improvement in disease activity upon abatacept administration.[88] The effectiveness of this immunomodulator in pulmonary involvement of IIMs has not been validated, and this should be explored in future. Intravenous immunoglobulin is becoming an important adjunctive treatment option in patients with IIM with refractory, severe, or rapidly progressive ILD.[89] The use of antifibrotic agents in connective tissue-related ILDs has been a focus of scientists in recent years. In a previous open-label trial, the effect of pirfenidone was similar to that of conventional immunosuppressives alone, in terms of improved outcomes. However, the subanalysis indicated that pirfenidone may be beneficial for patients with subacute CADM-ILD (disease duration of 3–6 months).[8] Furthermore, nintedanib was initially found to improve survival and reduce the incidence of RP-ILD in patients with IIM-ILD in a pilot propensity score matching analysis.[90] Plasmapheresis and extracorporeal respiratory membrane lung should be considered rescue options in life-threatening situations. Lung transplantation is the last alternative for treatment of terminal ILD, with very few published case reports showing success in patients with IIM-ILD.[91]

CONCLUSION

The lung is the most common extramuscular organ involved in IIMs, and increasing awareness of clinical characteristics, progression, and mortality associated with IIM-ILD is essential among physicians. Systematic screening of MSAs, serum biomarkers, PFTs, and HRCT is beneficial for the evaluation of disease progression and prognosis. Better identification of patients at risk for RP-ILD or with unfavorable outcomes will be beneficial for the adjustment of immunosuppressive therapy.

Conflict of Interest

None declared.

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