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MEDICAL AFFAIRS

Scan to see argenx pipeline and enrolling trials

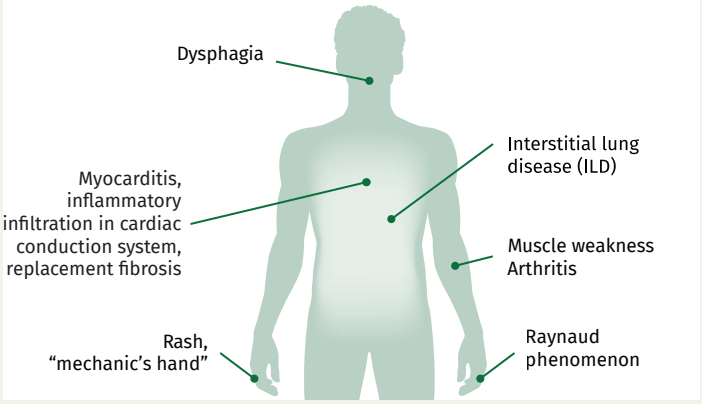
Idiopathic Inflammatory Myopathies (IIM or Myositis)

IIM (also known as myositis) is a group of rare autoimmune diseases characterized by inflammation and skeletal muscle weakness that sometimes involves the skin, joints, lungs, gastrointestinal tract, and heart[1]

Subtypes

Clinical manifestations and muscle histopathologic features of myositis vary between subtypes of the disease[2,3]

Common Clinical Manifestations of Myositis[3]



- **Dermatomyositis (DM):** Subacute onset of proximal, symmetric weakness with characteristics of skin rash in patients of any age[4]
- **Antisynthetase syndrome (ASyS):** Multisystem disease that is relatively homogeneous and does not always present with myositis[3,a]
- **Immune-mediated necrotizing myopathy (IMNM):** Acute or subacute onset of proximal, often severe weakness in adults[4,a]
- **Inclusion body myositis (IBM):** Slow onset of proximal and distal weakness, frequent falls, muscle atrophy in quadriceps and forearms; mild facial weakness in adults ≥50 years old[4]
- **Overlap myositis (OM):** Heterogeneous IIM subgroup with varying histological findings which can occur with other connective diseases (eg, SLE, systemic sclerosis, Sjögren's syndrome, or rheumatoid arthritis)[3]
- **Polymyositis (PM):** Subacute onset of proximal weakness in adults with other causes excluded.[4] Most patients previously diagnosed with PM are classified as having ASyS, IMNM, IBM, or OM[3,b]

[a]Newer subgroups, ASyS and IMNM, have been identified on the basis of MSAs.[3]
[b]Historically, PM was the overarching name for these disorders, but it is disputed as an entity within the spectrum and is considered a diagnosis by exclusion.[3,5]

Disease Burden

Myositis has a substantial impact on disability, especially by reducing physical functioning[6-8]

>60% experienced difficulty climbing a flight of stairs (prospective cross-sectional global survey)[7,c]

16% and **24%** of mortality is caused by infection and CV disease, respectively (retrospective analysis in Portugal)[6,d]

46% experienced ≥5 falls and **24%** experienced a bone fracture, of whom **33%** required surgery (prospective cross-sectional global survey)[7,c]

73% and **61%** experienced pulmonary and CV damage, respectively (retrospective analysis in Portugal)[6,d]

37% experienced joint pain for >5 years (prospective cross-sectional global survey)[7,c]

36% is the estimated prevalence of dyphagia (meta-analysis)[8,e]

- In a population-based cohort in Norway, patients with myositis were found to have an estimated 1.7- to 2.6-fold higher risk of death compared with the general population[9,f]

[c]Based on a global prospective cross-sectional patient-reported online survey developed by Myositis Support and Understanding and University of Texas-Southwestern (N=583; 71% female; 88% white or Caucasian; age range, 18-90).[7]
[d]Based on a retrospective analysis of patients with IIM (n=146 for damage analysis; n=25 for mortality analysis) followed in a tertiary hospital in Portugal between 1971 and December 2022 to characterize morbidities associated with myositis, including effects on QoL and mortality as assessed using the MDI and HAQ-DI.[6]
[e]Based on a meta-analysis of 109 studies including 10,382 patients with myositis identified from a MEDLINE search from inception to January 2020. Definitions and assessments of dysphagia differed between studies included in the meta-analysis.[8]
[f]In a population-based cohort of patients with myositis in Norway (N=326); main disease-related causes of death included cancer, interstitial lung disease/pulmonary hypertension, infection, and aspiration and dysphagia.[9]

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Proposed Role of IgG Autoantibodies in Myositis

Evidence suggests that several IIM subtypes, particularly DM, IMNM, and ASyS, are associated with IgG autoantibodies, myositis-specific autoantibodies (MSAs), and myositis-associated autoantibodies (MAAs)[2,3,10]

- In patients with myositis, IgG autoantibodies are internalized within muscle cells, localize to the target autoantigen, and disrupt the autoantigen protein function[11]
- Patients with PM and DM may have elevated IgG levels compared with healthy controls[12]
- Passive transfer of IgG purified from the plasma of patients with IMNM can induce muscle weakness, necrosis, and muscle fiber regeneration in a mouse model[1,13]

MSAs

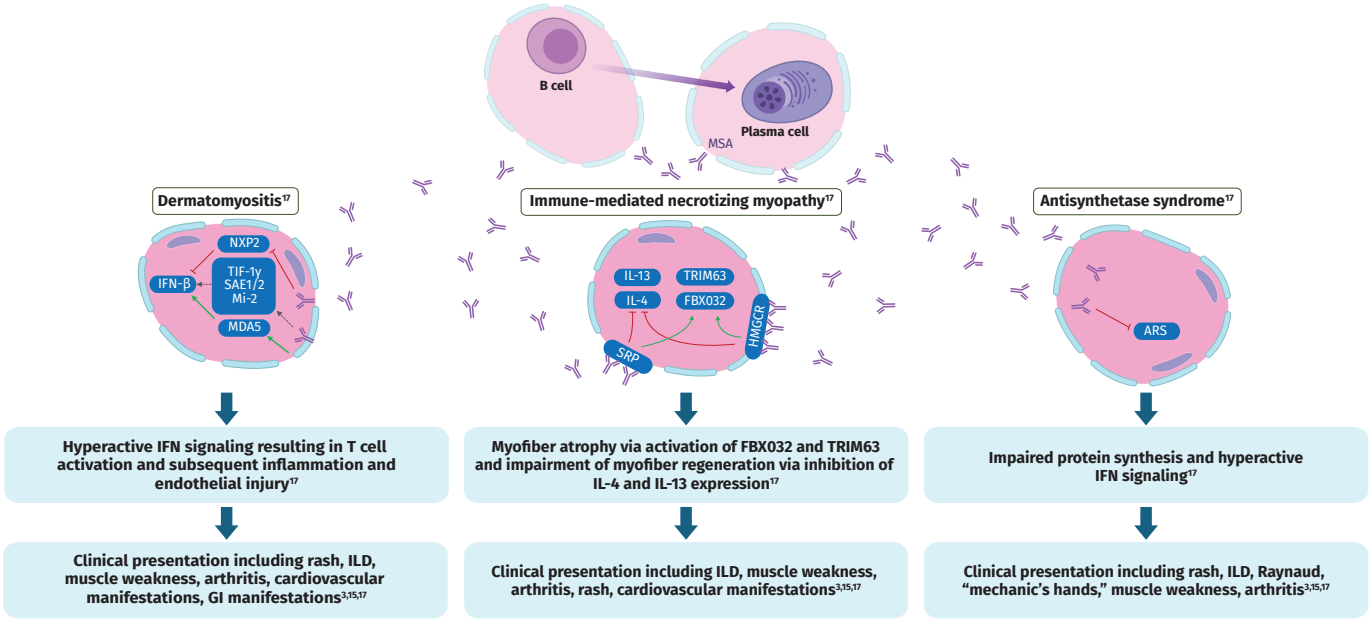
- MSAs are exclusively found in patients with myositis and have been demonstrated to correlate with distinct clinical phenotypes[3,15]
  - However, some patients with myositis show no detectable MSAs and are considered seronegative, including 34% of patients with IMNM[16]

MAAs

- While MSAs are specific to myositis and linked to distinct clinical phenotypes, MAAs are less specific, often found in overlap connective tissue diseases (eg, SLE, systemic sclerosis, Sjögrens syndrome)[2,14]
- MAAs may correlate with clinical features (eg, "mechanic's hand," ILD, dysphagia severity) and represent important diagnostic markers[14]

Proposed Pathophysiology Across Myositis Subtypes[17,g]

MSAs may modulate immune pathways, leading to distinct clinical phenotypes across subtypes[17]



[g]Green arrows indicate activation, red arrows indicate inhibition, broken arrows suggest hypothesized functions, and the purple arrow illustrates B cell differentiation.

Abbreviations: ARS, aminoacyl-tRNA synthetase; CV, cardiovascular; FBX032, F-box only protein 32; GI, gastrointestinal; HAQ-DI, Health Assessment Questionnaire-Disability Index; HMGCR, 3-hydroxy-3-methylglutaryl-coenzyme A reductase; IFN, interferon; IL, interleukin; IgG, immunoglobulin G; MDA5, melanoma differentiation-associated protein 5; MDI, Myositis Damage Index; Mi-2, nucleosome-remodeling deacetylase complex; NXP2, nuclear matrix protein 2; QoL, quality of life; SAE1/2, small ubiquitin-like modifier activating enzyme; SLE, systemic lupus erythematosus; SRP, signal recognition particle; TIF-1, transcription intermediary factor 1; TRIM63, tripartite motif containing 63.

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