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Corticosteroids in Myositis and Scleroderma

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Synopsis

Idiopathic inflammatory myopathies (IIM) involve inflammation of the muscles and are classified based on the patterns of presentation and immunohistopathologic features on skin and muscle biopsy into four categories: dermatomyositis, polymyositis, inclusion body myositis, and immune mediated necrotizing myopathy. The term “scleroderma” refers to fibrosis of the skin. Localized scleroderma (morphea) is skin-limited, while systemic sclerosis (SSc) is associated with vascular and internal organ involvement. Although there is a paucity of randomized clinical trials, treatment with systemic corticosteroids (CS) is the standard of care for IIM with muscle and organ involvement. The extra-cutaneous features of systemic sclerosis are frequently treated with CS, however high doses have been associated with scleroderma renal crisis in high-risk patients. CS monotherapy is neither recommended for the cutaneous manifestations of dermatomyositis nor scleroderma. While CS can be effective first line agents, their significant side effect profile encourages concomitant treatment with other immunosuppressive medications to enable timely tapering.

Keywords

Idiopathic Inflammatory Myopathies; Myositis; Systemic Sclerosis; Scleroderma; Morphea; Corticosteroids; Glucocorticoids

Idiopathic Inflammatory Myopathies

Background and Clinical Manifestations

Idiopathic inflammatory myopathies (IIM) are rare systemic diseases that involve muscle inflammation and manifest clinically as an insidious onset of weakness over weeks to months. IIMs are classified based on the patterns of presentation and immunohistopathologic

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features on skin and muscle biopsy into four major categories: dermatomyositis (DM), polymyositis (PM), inclusion body myositis (IBM), and immune mediated necrotizing myopathy (IMNM).¹

Diagnostic Evaluation

Elevated serum levels of muscle enzymes (aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), aldolase, and lactate dehydrogenase (LDH)) are present in at least 90% of patients with an IIM.² Although CK is the most sensitive and specific marker of muscle damage, patients can have elevated aldolase or other muscle enzymes without accompanying increases in CK levels.²

Further evaluation with electromyography (EMG), magnetic resonance imaging (MRI), and muscle biopsy, may be necessary to identify evidence of muscle inflammation.^{1,2} EMG activity depends on the degree of inflammation.² MRI can detect muscle necrosis, degeneration, and inflammation through increased signal intensity on short tau inversion recovery (STIR) imaging.^{2,3} T1-weighted images identify atrophy and chronic muscle damage while T2-weighted images can identify active inflammation.³ Muscle biopsies show inflammatory infiltrates, vascular involvement, and necrosis, depending on the subtype of IIM. Additional evaluation for extra-muscular involvement and cancer screening may be warranted depending on the subtype of IIM.¹

Classification Criteria for IIM

The most commonly used classification criteria for PM and DM was proposed by Bohan and Peter⁴ in 1975 and includes: 1) symmetric proximal muscle weakness; 2) elevated muscle enzyme levels; 3) a myopathic pattern on EMG; 4) muscle biopsy showing myofiber necrosis, regeneration, variation in fiber diameter, and an inflammatory exudate; 5) characteristic skin findings (DM). The American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) are currently validating updated classification criteria, which include weakness involving particular muscle groups, hallmark cutaneous manifestations, and specific muscle biopsy findings.⁵

Treatment Options

Systemic corticosteroids (CS) are the most commonly used medications for IIM with muscle involvement, either as monotherapy or in combination with other immunomodulatory agents.^{6,7,8} The significant side effect profile of CS, including myopathy, avascular necrosis of the bone, osteoporosis, hyperglycemia, infection and cataract formation, motivates a multi-therapy treatment plan with the goal to minimize CS dose.⁷

Polymyositis

Background and Clinical Manifestations

Polymyositis presents with bilateral, symmetric proximal muscle weakness that progresses over weeks to months.^{1,2} Neck flexor weakness, dysphagia, and dysphonia can occur from pharyngeal and laryngeal muscle involvement. Interstitial lung disease (ILD) can affect 5–46% of patients with PM and up to 70–100% of those with anti-synthetase syndrome.⁹ This

syndrome consists of fever, mechanic's hands, Raynaud phenomenon, myositis, ILD and arthritis, and is frequently associated with the anti-Jo-1 antibody.¹ Finally, patients with PM have a 2 fold increase in the incidence of malignancy compared to the general population within the first five years of disease onset.²

Diagnostic Evaluation

Up to a 50-fold increase in CK can be observed in active PM.³ More than half of patients with PM present with myositis-associated (MAA) or specific antibodies (MSA) (Table 1).^{10,11} EMG of affected muscles shows short-duration, low-amplitude, polyphasic motor unit potentials.² Muscles with active inflammation exhibit "irritable myopathy" with spontaneous activity (positive sharp waves and fibrillation potentials) and/or complex repetitive discharges.² MRI may show edema and increased signal in the muscles on T2-weighted imaging. Finally, characteristic muscle biopsy findings of PM include scattered necrotic and regenerating myofibers of variable size; perivascular and endomysial inflammatory infiltrates of MHC-I/CD8+ complexes; and macrophages without microvascular involvement.^{3, 6}

Treatment

Corticosteroids—Although no randomized controlled trials using CS have been conducted, studies have demonstrated decreased muscle inflammation with CS use,^{12,13} and 60–80% of patients show improvement in muscle strength.^{1,6,7} Initial treatment usually consists of oral prednisone (0.5–1.5mg/kg/day), with IV treatments (500–1000mg/day for 3–5 days) reserved for severe cutaneous disease or muscle weakness, dysphagia, respiratory muscle involvement, and ILD.^{1,8,9} One RCT comparing monthly oral pulse dexamethasone (six cycles of 40mg/day for four consecutive days at 28-day intervals) with daily prednisolone (70 to 90mg/day) for 28 days followed by a slow taper, did not demonstrate improved efficacy with pulse dosing, but did show fewer adverse effects.¹⁴ High dose (60–80 mg/day) CS treatment is usually continued for 2–4 weeks with slow tapers extending 3–6 months.^{1,6} In patients with severe disease and ILD, or in patients with co-morbidities such as osteoporosis and diabetes combination therapy with another immunosuppressant is initiated immediately.⁹

Corticosteroid Sparing Options—Another immunosuppressive drug is typically started concurrently with CS to enable timely tapering of the CS (Table 2).¹ Azathioprine (AZA) in combination with prednisone has been shown to result in less functional disability and lower CS dosing at 3 years compared with prednisone monotherapy.¹ When AZA/CS combination therapy was compared to methotrexate (MTX)/CS, both had similar efficacy, but MTX was better tolerated.⁸ Additionally, cyclosporine has been shown to be as effective as MTX for myositis, with favorable outcomes for treatment of ILD.^{1,9} Mycophenolate mofetil (MMF) has also shown efficacy and tolerability, and is generally considered the CS-sparing drug of choice when PM is complicated by ILD.^{1,9} A growing body of evidence supports the use of intravenous immunoglobulin (IVIG) for more severe disease presentations, including dysphagia, respiratory muscle involvement, and refractory cases.¹ Cyclophosphamide (CYC) may be required for recalcitrant cases and patients with significant cardiac or pulmonary disease.^{1,9} Finally, data from the Rituximab in Myositis Trial, the largest

randomized placebo controlled myositis trial to date, demonstrated that 83% of patients treated with rituximab experienced disease improvement and required less CS.¹⁵

Dermatomyositis

Background and Clinical Manifestations

DM has pathognomonic cutaneous features including heliotrope rash, periorbital edema, Gottron's papules, Gottron's sign, shawl sign, holster sign, mechanic's hands, malar erythema and nailfold capillary changes (Figure 1).¹ Euwer and Sontheimer¹⁶ described the variable presentations of DM as symptomatic myositis with evidence of muscle inflammation on laboratory, EMG, and biopsy evaluation; a hypomyopathic presentation with asymptomatic muscle inflammation; and an amyopathic variant without muscle symptoms or muscle inflammation for at least 6 months after cutaneous symptoms arise. Similar to PM, extramuscular involvement can occur in DM, with ILD affecting 21–78% of patients.⁹ DM patients (in particular those with amyopathic DM and certain autoantibodies (Table 3)) have a 3–6 fold increased risk for malignancy in comparison to the general population.²

Diagnostic Evaluation

Muscle enzyme levels can be normal or elevated up to 50-fold in DM.⁶ EMG and MRI findings in active myositis are similar to those seen in PM. Features differentiating DM from PM on muscle biopsy include CD4+ T-cell and B-cell infiltrates in perimysial, perifascicular, and vascular areas causing microangiopathic ischemia.¹ Skin biopsies in patients with DM show an interface dermatitis, perivascular lymphocytic infiltrate, epidermal atrophy, basement membrane thickening, increased dermal mucin and vascular ectasia, which may be indistinguishable from findings in cutaneous lupus.⁸ The discovery and phenotypic characterization of novel DM-specific autoantibodies has improved diagnostic and prognostic capabilities, as more than 80% of patients are positive for one of these antibodies, which tend to be mutually exclusive (Table 3).^{10,17}

Treatment

Corticosteroids—In cases of DM with muscle and organ involvement, CS are the first line of treatment, with an algorithm similar to PM. However, cutaneous manifestations are often not as responsive to CS as is muscle disease, and skin lesions can flare after discontinuation of CS.^{7,8} Steroid induced myopathy may be confusing as patients develop, rather than present with, symmetric muscle weakness; however, there is no evidence of muscle inflammation, and termination of CS results in improvement in strength.¹⁸ The American Academy of Dermatology¹⁹ recommends topical corticosteroids (tCS) under occlusion for patients with limited skin involvement. Lower potency tCS (hydrocortisone 2.5%, desonide 0.05%) are advised for the face, axillae, and groin to decrease the risk for skin atrophy.⁷

Corticosteroid Sparing Options—Photo-protective clothing, sunscreen with sun protection factor (SPF)>50, and sun avoidance are vital since cutaneous DM may be worsened by UVA/UVB irradiation⁷. Topical calcineurin inhibitors can be used on areas

with thinner skin.^{7,8} Hydroxychloroquine (HCQ) can be effective for cutaneous DM⁷ however, up to 25% of DM patients can develop a rash to HCQ (unpublished data). In a randomized controlled trial, Dalakas et al.²⁰ showed efficacy of IVIG for both skin and muscle inflammation in DM patients. Case series have demonstrated some benefit from MTX, MMF, and AZA for skin and muscle disease.^{1,7,8,9} MMF, CYC, cyclosporine, and rituximab have been used for DM-associated ILD.^{1,7,9}

Inclusion Body Myositis

Background and Clinical Manifestations

IBM is characterized by the insidious onset of weakness in an asymmetric distribution, involving both proximal and distal extremities.²¹ The Griggs diagnostic criteria for IBM include: 1) age >45; 2) symptom duration > 12 months; 3) CK <15-fold the upper limit of normal; 4) pronounced weakness of the long finger flexors and/or knee extensors; 5) histology with vacuolization and/or protein accumulation.²² IBM presents in association with other connective tissues diseases (CTD) in 15% of patients; however, unlike PM and DM, it is not associated with an increased risk of ILD or malignancy.²³

Diagnostic Evaluation

Myositis-specific and myositis-associated antibodies are not typically observed in IBM; however, antibodies to cytosolic 5'-nucleotidase 1A (anti-Mup44/cN1A antibodies) have been identified in up to 30% of patients.²¹ EMG findings are similar to those in PM/DM, but some patients demonstrate a mixed neurogenic and myopathic pattern.²⁴ MRI shows atrophy and signal abnormalities in affected muscle groups.²³ Classic findings on muscle biopsy include CD8+ T-cell infiltration of non-necrotic myofibers; accumulation of abnormal protein aggregates; and the presence of rimmed vacuoles.²¹

Treatment

Corticosteroids—An effective treatment for IBM has yet to be identified. CS can lower muscle enzymes, but do not affect symptoms or disease progression.²¹ One study showed decreased inflammatory infiltrates, but increased amyloid deposition on muscle biopsy after CS treatment, concerning for disease acceleration.²⁴ Treatment with CS may be more effective for IBM patients with an associated CTD.

Corticosteroid Sparing Options—Case series with AZA, MTX, and MMF have not shown durable improvement in strength in IBM patients.^{23, 24} IVIG can decrease CK levels, but without symptomatic improvement.²⁴

Necrotizing Myopathies

Background and Clinical Presentation

Necrotizing myopathies (NM) present as acute or subacute symmetric, proximal muscle weakness, and are associated with necrosis without significant inflammation on muscle biopsy.²⁵ NM can be classified as non-immune mediated (NIMNM), triggered by medications or toxins, and immune mediated (IMNM), triggered by CTDs, viruses, cancers

and statin medications in the setting of positive serology.^{1,25} In NIMNM, patients experience symptom resolution in several weeks to months after discontinuation of the offending agent.¹ If symptoms persist despite discontinuation of the offending agent, IMNM should be considered.²⁵ To be classified as IMNM, patients must fulfill clinical criteria of adult DM or PM; have MSA; have no clinical features of IBM; and have characteristic histological findings on muscle biopsy.²⁶

Diagnostic Evaluation

In statin-induced cases, variable CK elevations can be seen.¹ 60% of patients with antibodies against 3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR) have had prior exposure to statins, suggesting the medication is an immunologic trigger.²⁷ Those who were never exposed had an indistinguishable clinical myopathy, evoking a pathomechanistic role of these antibodies in IMNM. Interestingly, 25–37% of patients with other IIMs have anti-HMGCR antibodies.²⁷ Anti-signal recognition particle (anti-SRP) antibodies are also found in up to 15% of cases of IMNM and are associated with more severe disease.²⁵ Typical histopathologic findings of IMNM include myofiber necrosis, membrane attack complex (MAC) deposition in small vessels, variable class 1 major histocompatibility complex (MHC-1) expression, and regeneration of muscle fibers without significant inflammation.²⁵ NIMNM appears similarly on biopsy, however the immunohistochemical abnormalities are often absent.²⁵ EMG can show irritable myopathy similar to other IIMs and MRI exhibits muscle edema, atrophy, or fatty replacement.²⁵

Treatment

Corticosteroids—If discontinuation of potentially offending agents does not lead to symptomatic improvement over several weeks and biopsy suggests IMNM, high dose oral prednisone (40–100mg/day) or pulse IV methylprednisolone (1g/day for 3–5 days) is initiated.²⁵ Grable-Esposito et al. reported that 60% of patients with statin induced anti-HMGCR+ IMNM required long-term immunosuppression for symptom control.²⁸

Corticosteroid Sparing Options—Similar to other IIMs, small studies suggest that other immunosuppressants, in conjunction with, or in lieu of CS, have shown benefit in refractory IMNM cases.²⁵

Scleroderma - Localized Scleroderma (Morphea) and Systemic Sclerosis

The term ‘scleroderma’ refers to fibrosis of the skin. Localized scleroderma (morphea) is skin-limited, while systemic sclerosis (SSc) is associated with vascular and internal organ involvement.²⁹ Unlike SSc, morphea is not typically associated with Raynaud’s phenomenon (RP), nailfold capillary changes, or the presence of SSc-specific autoantibodies (Table 4).^{30,31}

Localized Scleroderma (Morphea)

Background and Clinical Manifestations

In contrast to SSc, morphea is less symmetric, better demarcated, and typically spares the hands.³² Linear, pansclerotic, and generalized variants are most frequently associated with extra-cutaneous complications (Table 5).^{33,34} Morphea lesions have an initial inflammatory stage characterized by erythematous patches or plaques. Over time, the center becomes less erythematous, and the borders develop a violaceous appearance. Most lesions become inactive over 3–5 years, gradually softening and leaving behind patches or plaques with post-inflammatory hyperpigmentation.³³ Linear morphea tends to have a more chronic course. Reactivation may occur in all subtypes, with one study showing reactivation at the same site in 3.7% of patients after >6 months off of medication.³⁵

Diagnostic Evaluation

Clinical evaluation is the gold standard for morphea diagnosis and assessment. Although ANA is the most commonly reported positive autoantibody, this is typically low titer and not considered part of the diagnostic work-up.³⁰ Other autoantibodies that have been associated with morphea include anti-single-stranded DNA antibodies, anti-histone antibodies, and anti-topoisomerase II- α antibodies.³⁴ In early stage disease, skin biopsies show perivascular lymphocytes in the reticular dermis.³³ In late stages, inflammation disappears and collagen bundles of the reticular dermis become thickened in association with atrophic eccrine glands and a dearth of blood vessels.³³

Treatment

Corticosteroids—It is important to differentiate active from inactive morphea lesions, as the latter are unlikely to respond to treatment with immunosuppression.³⁴ Active disease may be indicated by growth or spread of lesions; appearance of new lesions; or clinical signs of inflammation, such as a violaceous or lilac border.

Morphea lesions that are not associated with systemic complications are best treated with topical therapy. Class 1–2 high potency tCS applied twice daily are commonly used;^{34–36} however, there have been no studies evaluating their efficacy other than one case series showing improvement with topical calcipotriol and betamethasone.³⁷ Intra-lesional triamcinolone (5 mg/mL monthly for 3 months) can be used, especially for the treatment of linear morphea of the en coup de sabre variant.³⁵

CS may be indicated in cases of morphea associated with risk for functional impairment or systemic complications (Table 5).³⁸ Methylprednisolone 1 g/day for adults and 30 mg/kg/day (for a maximum of 500 mg/day) for children may be administered IV over 3 consecutive days per month for at least 3 months.³⁹ Oral CS dosing is more variable and may be dosed in the form of prednisone 0.5–2 mg/kg/day, with a maximum of 50–60 mg daily, tapered to 0.25–0.5 mg/kg/day maintenance over at least 2 months.^{35,40,41} Prednisone monotherapy may be associated with increased rates of relapse;⁴² thus, combination treatment with other modalities, usually methotrexate, is recommended.³⁹

Corticosteroid Sparing Options—For patients without severe disfigurement or systemic complications, non-CS treatments include topical tacrolimus or calcipotriene (+/– tCS) under occlusion (Table 6).^{39,43} Topical imiquimod may be helpful.^{39,43} Phototherapy, including psoralen UVA and narrow band UVB, may be useful for widespread active lesions both as monotherapy and as adjunctive treatment.^{39,43}

For patients at risk for significant cosmetic or functional impairment, combination therapy with IV or oral CS and MTX is recommended,^{35,39,41,43} with MMF as second line CS-sparing therapy.^{39,43} Variable success has been reported with cyclosporine, abatacept, penicillin, D-penicillamine, photophoresis, bosentan, infliximab, hydroxychloroquine, and imatinib.^{39,43,44}

Systemic Sclerosis

Background and Clinical Presentation

In 2013 ACR/EULAR revised the classification criteria for SSc to include skin thickening of the fingers or hands, puffy fingers, digital pits and ulcers, telangiectasias, abnormal nailfold capillaries, pulmonary arterial hypertension (PAH), ILD, RP, and SSc related autoantibodies.⁴⁶ The majority of patients with SSc experience RP and have nailfold capillary changes, but the extent of cutaneous fibrosis and the pattern of internal organ involvement is highly variable, correlating to some degree with autoantibody profile.³⁴ Patients with limited cutaneous disease (lcSSc) characteristically have skin thickening distal to the elbows and knees with or without facial involvement; however, up to 9% of patients remain *sine* sclerosis (systemic sclerosis *sine* scleroderma).^{34,45} Patients with diffuse cutaneous disease (dcSSc) develop skin thickening proximal to the elbows and knees, that may also involve the trunk.³⁴

Organ manifestations in SSc vary depending on cutaneous and autoantibody subtypes (Table 4).³¹ Myositis and synovitis are twice as common in patients with dcSSc versus lcSSc. Clinically significant ILD with pulmonary fibrosis is reported in up to 53% of patients with dcSSc and 35% of patients with lcSSc.⁴⁷ PAH has a similar occurrence rate between the two subsets and affects 7–12% of patients with SSc overall.⁴⁷ Gastrointestinal manifestations including dysphagia and gastroesophageal reflux occur in 70–80% of SSc patients, and gastric antral vascular ectasia occurs in up to 22% of patients.⁴⁷ Cardiac involvement occurs in 10–30% of patients.⁴⁷ Scleroderma renal crisis (SRC) presenting with progressive renal failure and microangiopathy occurs in 7–17% of patients with dcSSc and 2–9% of patients with lcSSc.⁴⁸

Diagnostic Evaluation

Basic laboratory evaluation and muscle enzymes should be performed on all patients with SSc. Evaluation for SSc-specific antibodies is warranted for diagnostic and prognostic information regarding internal organ involvement (Table 4).³¹ Pulmonary function testing and transthoracic echocardiography should be performed at baseline and annually to screen for pulmonary involvement. High-resolution computed tomography is useful for assessing

extent and progression of ILD. Right heart catheterization is necessary to confirm the presence of PAH.

Treatment

Treatment of SSc is guided by cutaneous and organ specific involvement, and as such, we will review treatment by organ system, with particular attention to those that may benefit from CS. CS are not used in the treatment of gastrointestinal and vascular manifestations of SSc, including Raynaud's phenomenon, digital ulcers, and PAH, and therefore management of these symptoms will not be discussed below.

Skin—Mild skin disease, limited to the face and fingers, does not warrant systemic therapy.⁴⁹ For more severe skin disease, treatment with corticosteroid sparing agents has demonstrated improvement.⁴⁹ About a quarter of patients with SSc develop calcinosis.⁵⁰

Corticosteroids: Due to lack of efficacy and risk for inducing SRC, particularly in patients with early dcSSc or with RNA-polymerase III antibodies, CS are not recommended for cutaneous SSc.⁵¹ Nevertheless, a recent survey reported that 31% of patients with lcSSc and 49% of patients with dcSSc received CS for treatment of various manifestations.⁵² Case reports have shown some benefit from intra-lesional steroids for calcinosis.⁵⁰

Corticosteroid Sparing Options: MTX and MMF have been shown to be effective for skin disease in small studies.⁴⁹ For diffuse, rapidly progressive disease, IVIG, CYC, and rituximab are alternative options.⁴⁹ Hematopoietic stem cell transplantation can be considered in patients with rapidly progressive skin disease.⁴⁹

Musculoskeletal—Musculoskeletal involvement in SSc includes painful tendon friction rubs; development of contractures related to tight skin over the joints; or overlap features with inflammatory myopathies and/or arthritis.⁴⁹

Corticosteroids: CS are most commonly used as treatment for the inflammatory components of SSc such as arthritis and myositis. Low doses (10–15mg daily) of prednisone may improve pain control and quality of life.⁴⁹ High dose CS may be necessary to control active myositis, but should be avoided if possible in patients at high risk for SRC.

Corticosteroid Sparing Options: Treatment of myositis in SSc patients is similar to that for patients with idiopathic inflammatory myopathies (IIM). HCQ, MTX, or leflunomide may be helpful for inflammatory arthritis.^{29,49} Small studies have shown benefit with TNF inhibitors, IVIG, abatacept, and tocilizumab for SSc-associated arthritis.²⁹

Interstitial Lung Disease—ILD is confirmed by ground glass opacities or fibrotic changes on HRCT and is associated with depressed forced vital capacity on PFTs.^{29,49} The most prevalent pattern of SSc-ILD is non-specific interstitial pneumonia (NSIP), seen in up to 78% of cases, followed by usual interstitial pneumonia (UIP) in 25–40% of cases.^{53,54}

Corticosteroids: SSc-ILD is treated with low dose CS (up to 15mg oral prednisone daily) usually in conjunction with other immunosuppressants,⁵⁴ particularly in patients with NSIP and significant ground-glass opacification.

Corticosteroid Sparing Options: The use of CYC has evidence-based support for the treatment of SSc-ILD and is recommended based on a placebo-controlled trial that showed improvement in pulmonary function, dyspnea, and quality of life.⁵⁵ Given the toxicity associated with CYC, most experts, upon completion of the course of CYC, continue maintenance immunosuppression with MMF, and a multicenter trial is underway comparing CYC with MMF as first line therapy in SSc-ILD.

Scleroderma Renal Crisis—SRC is defined as rapidly progressive renal failure with or without arterial hypertension.⁴⁹ It is associated with dcSSc and anti-RNA polymerase III antibodies. CS treatment (oral prednisone 15mg daily or higher) during the first 4 years of disease can trigger SRC, often without accompanying hypertension.⁵¹ Although first line treatment of SRC is ACE inhibitor therapy, studies have shown worse outcomes when ACE inhibitors are used prophylactically.⁵¹ There is no role for CS in the treatment of SRC.

Summary

Immunosuppressive therapies remain the mainstay of treatment for idiopathic inflammatory myopathies and some manifestations of scleroderma, although randomized controlled trials are limited and most recommendations are guided by clinical practice. Despite an increasing number of available immunosuppressive agents, CS continue to be a first line treatment for IIMs and some manifestations of scleroderma, especially synovitis, myositis, and ILD. Nonetheless, given the sequelae of long-term CS use, prompt tapering and use of other immunosuppressants for maintenance therapy is recommended.

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Key Points

- Treatment with corticosteroids is the standard of care for idiopathic inflammatory myopathies with muscle and organ involvement.
- Extra-cutaneous features of scleroderma occasionally warrant treatment with corticosteroids, however high doses have been associated with the development of scleroderma renal crisis in high-risk patients.
- Corticosteroid monotherapy is not recommended for cutaneous manifestations of dermatomyositis and scleroderma.
- The significant side effect profile of corticosteroids encourages concomitant treatment with other immunosuppressive medications to enable timely tapering.

Figure 1.
Gottron's papules and periungual changes seen in dermatomyositis

Table 1**Myositis Associated and Myositis Specific Autoantibodies**

Myositis Associated Autoantibodies				
Antibody	Antigen	Frequency	Disease Associations	Clinical Associations
Anti-56kDa	Ribonucleoprotein component	up to 90%	Overlap syndromes	
Anti-U1RNP	U1 small nuclear ribonucleoprotein	12%	Myositis-SLE Myositis-SSc	Erosive arthritis, alopecia, ILD, oral ulcer, rarely renal disease
Anti-Ro/SSA	RNA-protein particle	10–30%	Overlap syndromes	Sicca symptoms
Anti-La/SSB	RNA-protein particle	10%	Overlap syndromes	Sicca symptoms
Anti-PM-Scl	Nucleolar protein complex	8%	50–60% have Myositis-SSc overlap	RP, myositis, calcinosis
Anti-U3_RNP	U3 small nuclear ribonucleoprotein	5%	Myositis-SLE Myositis-SSc	
Anti-Ku	DNA-binding proteins	<1%	Myositis-SSc Myositis-SLE	Severe ILD, mild myopathy
Myositis Specific Autoantibodies				
<i>Anti-Synthetases</i>		25–30%	PM/DM	<i>Anti-Synthetase syndrome-(myositis, ILD, arthritis, RP, “mechanic’s hands”, fever), acute onset in Spring, poor prognosis</i>
Anti-Jo-1	His-tRNA synthetase	25%		
Anti-PL-7	Thr-tRNA synthetase	3%		
Anti-PL-12	Ala-tRNA synthetase	3%		
Anti-OJ	Ile-tRNA synthetase	1%		
Anti-EJ	Gly-tRNA synthetase	1%		
Anti-KS	Asp-tRNA synthetase	1%		
Anti-Ha	Tyrl-tRNA synthetase	1%		
Anti-Zo	Phe-tRNA synthetase	1%		
Anti-Mup44/cN1A	Cytosolic 5'-nucleotidase 1A	30%	IBM>PM/DM/IMNM	
Anti-HMGCR/Anti-200/100	3-Hydroxy-3-methylglutaryl-CoA reductase	3–8%	NM IMNM	Acute/subacute presentation, associated with statin use, necrotizing myopathy
Anti-SRP	Signal recognition particle proteins	3–6%	PM>DM NM IMNM	Acute onset in fall, cardiac involvement, poor prognosis, necrotizing myopathy
Anti-KJ	Translation factor	<1%	PM ILD	

Myositis Associated Autoantibodies				
Antibody	Antigen	Frequency	Disease Associations	Clinical Associations
Anti-Fer	Elongation factor 1-Alpha	<1%	PM/DM	
Anti-Mas	Small RNA	<1%	PM/DM	

Table 2

Corticosteroid Sparing Immunosuppressant Treatment Options for Myositis

Therapy	Route	Dose
Azathioprine	PO	2–3mg/kg/day divided bid
Methotrexate	PO	15–25mg/week; single or divided dosing; 1 day/week dosing
	SQ/IM	20–40mg/week; 1 day/week dosing
Cyclosporine	PO	4–6mg/kg/day divided twice daily
Tacrolimus	PO	0.1–0.2mg/kg/day divided twice daily
Mycophenolate Mofetil	PO	2–3g/day divided twice daily
Cyclophosphamide	PO	1–2mg/kg/day
	IV	0.5–1g/m ² every 4 weeks
Rituximab	IV	750mg/m ² (up to 1g), repeat in 2 weeks; course repeated every 6–9 months
IVIG	IV	2g/kg divided over 2–5 days every 4 weeks

Table 3**Dermatomyositis Predominant – Myositis Specific Autoantibodies**

Antibody	Antigen	Frequency (%)	Clinical Associations
Anti-MDA-5/CADM140/IFIH1	Melanoma differentiation associated protein 5	15–30 (in Asian populations)	Mild or no muscle disease, rapidly progressive ILD in Asian populations, poor prognosis, cutaneous ulcers, alopecia, arthritis
Antip155/140/TRI M33/TIF-1- γ	Translational intermediary factor 1- γ	20–40	Cancer in adults (60–80%), widespread/severe skin disease, less ILD
Anti-Mi-2	Nuclear helicase	10–30	Classic skin and muscle disease, good prognosis, low ILD/Cancer
Anti-SAE-1/2	SUMO-1 activating enzyme	8	Disease progresses from skin to muscle, dysphagia, good prognosis
Anti-NXP2/MJ	Nuclear matrix protein 2	10–25	Calcinosis, cancer in males

Table 4

Systemic Sclerosis Associated Autoantibodies

Antibody	Frequency (%)	Typical Disease Subtype	Clinical Associations
Anticentromere	20–38	lcSSc	PAH, digital ulcers, calcinosis
Antitopoisomerase I	15–42	dcSSc	ILD, cardiac involvement, digital ulcers
Anti-RNA polymerase III	5–31	dcSSc	SRC, tendon friction rubs, synovitis, myositis, joint contractures, malignancy, GAVE
Anti-U1-RNP	2–14	Overlap	RP, puffy fingers, arthritis, myositis, PAH
Anti-Th/To	1–13	lcSSc	ILD, pulmonary hypertension
Anti-PM-Scl	4–11	MyositislcSSc	RP, arthritis, myositis, calcinosis
Anti-U3-RNP (fibrillarin)	4–10	dcSSc	African Americans, cardiac involvement, ILD, PAH
Anti-hUBF (NOR 90)	<5	lcSSc	Mild organ involvement
Anti-U11/U12RNP	3	lcSSc	RP, GI involvement, severe ILD
Anti-Ku	2–4	MyositislcSSc	Myositis, arthritis, joint contractures, ILD, dysphagia

Table 5**Subtypes and Clinical Associations of Morphea**

Classification	Included subtypes	Definition	Clinical Pearls	Potential complications
Plaque	Superficial (morphea en plaque, guttate, keloidal) Deep (morphea profunda, subcutaneous morphea)	Areas of induration limited to epidermis and dermis Areas of induration including the subcutaneous tissue (may include fascia and muscle); overlying skin may not be involved	Often develop plaques in areas of pressure, such as the waistline, bra line “Bound down” or “pseudo-cellulite” appearance	
Generalized		Four or more plaques >3 cm in size, involving 2 or more anatomical areas (head-neck, each extremity, anterior trunk, posterior trunk)	Spare the face and hands	Myalgia, arthralgia, fatigue
Linear	Linear morphea of the extremities En coup de sabre Progressive facial hemiatrophy (Parry-Romberg syndrome)	Linear induration involving the dermis and subcutaneous tissue (may involve underlying muscle and bone) Linear induration involving the dermis of the face and scalp (may involve underlying muscle, bone, and central nervous system) Loss of dermis, subcutaneous tissue, muscle and bone of the unilateral face		Joint contractures, limb length discrepancy, muscle atrophy, muscle cramps, ulcers Facial disfigurement, central nervous system/ocular involvement, seizure Facial disfigurement, central nervous system/ocular involvement, seizure
Pansclerotic		Circumferential involvement of limbs involving epidermis, dermis, subcutaneous tissue, muscle, and bone; may affect other areas of the body with full depth sclerosis		Joint contractures, muscle atrophy, nonhealing ulcers, squamous cell carcinoma
Mixed		Combination of 2 or more subtypes of morphea		Arthralgia, decreased range of motion, limb contracture, myalgia

Table 6

Evidence-based treatment algorithm for morphea

	First line	Second line
Uncomplicated morphea	Tacrolimus; Calcipotriene +/- betamethasone dipropionate;Phototherapy (if large body surface area)	Topical imiquimod; Methotrexate and systemic corticosteroids (if progressing and treatment refractory)
If involving face, crossing joints, or risk of functional impairment	Methotrexate and systemic corticosteroids	Mycophenolate mofetil