A Review of Inflammatory Idiopathic Myopathy focusing on Polymyositis

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Abstract

Inflammatory idiopathic myopathies are a group of autoimmune diseases affecting predominantly the proximal skeletal muscles, with raised muscle enzymes, with or without skin involvement and extramuscular organ involvement. Autoantibodies help to characterise patients into different clinical phenotypes. Successful treatment necessitates controlling inflammation early with corticosteroids and invariably requires additional immunosuppressive therapy.

This review focuses on the aetiology, pathogenesis, clinical presentation, investigations and management of patients presenting with inflammatory idiopathic myopathies, predominantly focusing on polymyositis and antisynthetase syndrome.

Inflammatory idiopathic myopathies (IIM) are a group of rare autoimmune diseases characterised by proximal skeletal muscle weakness, raise muscle enzymes (e.g. creatine kinase (CK)), and extramuscular organ involvement, most frequently the lungs, resulting in interstitial lung disease (ILD). Numerous autoantibodies are associated with the disease, many linked to different clinical phenotypes. This review focuses on the adult-onset IIM, polymyositis (PM), immune-mediated necrotising myopathy and dermatomyositis (DM) (inclusion body myositis is beyond the scope of this article).

PM predominantly presents with proximal symmetrical muscle weakness, while DM is characterised by skin and muscle involvement, both are associated with extramuscular features.

Epidemiology

The incidence of DM and PM combined is 6-10 per million [1] with a peak incidence of 60-69 years and 50-59 years in PM and DM respectively. The prevalence is approximately 2 and 8 per 100,000 from both single centre and multicentre data [1,2]. The combined female to male ratio is 2:1 [3], but when split by disease, DM it is 2.1:1 and in PM 1.6:1 [1].

In a UK study, 69.6% of patients were Caucasian, 13% Afro-Caribbean, 13% Asian and 4.3% other [4]. World-wide, however, there is a higher incidence of inflammatory myositis in black patients compared to white.

Diagnostic Criteria

The Bohan and Peter set out diagnostic criteria for PM and DM which remain widely used (Table 1) [3]. The revised diagnostic criteria by Targoff in 1997 includes the muscle specific antibodies [5] and maintains sensitivity of diagnosis, but improves specificity from 23% to 62% [6].

Aetiology

The aetiology of IIM is multifactorial and a combination of environmental and genetic risk factors.

Environmental risk factors

Infectious agents (e.g. Coxsackie virus B, cytomegalovirus and toxoplasmosis[7]), as well as foods, medication and vaccinations have been implicated in the development of IIM, although studies are often conflicting. Medications include D-Penicillamine, fibrates, 3-hydroxy-3methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, hydroxyurea, L-Tryptophan [causes an eosinophilia myalgia syndrome] and Ciguatera toxin. Vaccines linked with myositis are DTP (diphtheria-typhoid-pertussis), MMR (measles-mumps-rubella), BCG (Bacillus Calmette–Guérin), influenza, hepatitis A/B. Occupational exposure to silica and cyanoacrylate glue may also be associated with myositis, as is UV light, chimerism and graft vs host disease [7].

Genetic risk factors

Although no one gene has been identified as underlying cause of IIM, genetic risk factors are associated with IIM. These include HLA alleles found on chromosome 6 (most specifically HLA-DQA1*0501 and HLA-DRB1*0301 [8,9]). Polymorphisms in the tumour necrosis factor α (TNF-α) gene encoding region [9] are correlated with longer disease course and increased disease severity.

Pathology/pathogenesis

Both adaptive and innate immune pathways are implicated in the development of IIM. Although there are many similarities, PM and DM demonstrate distinct immunohistopathological phenotypes, suggesting the underlying pathogenesis may not be the same.

The immune-mediated necrotizing myopathies (IMNM) have very little inflammatory infiltrate on biopsy, necrosis is the predominant finding [10,11].

Innate immune mechanisms drive the pathology, including pro-inflammatory cytokines such as interleukin (IL)-1α, type 1 interferon (IFN) and TNF-α. IL-1α can persist in the absence of other

inflammatory infiltrates, suggesting it contributes to the persisting weakness even after the inflammation is controlled [12].

MHC class 1 antigens are upregulated in IIM in response to type 1 IFN, a finding not seen in normal muscle fibres [12]. This upregulation may make the muscle fibres targets for CD8+ cytotoxic T cells and contribute to muscle fibre destruction. This upregulation precedes the lymphocytic infiltrates into the muscle fibres on biopsy [13].

MHC class 1 antigen expression has a predominantly perifascicular accentuation in DM and antisynthetase syndrome (ASS), but has a more confluent distribution seen in PM [14,15].

DM characteristically demonstrates complement-mediated vasculopathy of the small vessels. Ischaemia and muscle damage are the result of deposition of C5b-9 membrane attack complexes around the microvasculature. Histologically, there are mononuclear inflammatory cell infiltrates (predominantly B cells and CD4+ T cells) within the muscle fibres, distributed in a perivascular and perfascicular distribution. There is usually evidence of degenerating and regenerating muscle fibres [16,17]. Ischaemic microangiopathy may give rise to perifascicular atrophy of the myofibrils. The presence of B cells and CD4+ T cells suggest a humorally mediated pathogenesis.

Biopsies from patients with PM characteristically exhibit CD8+ cytotoxic T cells surrounding non-necrotic muscle fibres [16,17]. This appearance results in muscle fibre necrosis and regeneration. The microvasculature remains intact, and the presence of B cells is extremely rare. These features suggest that the disease is cell mediated. The CD8+ T cells and macrophages clonally expand, and interact with the MHC class 1 expressing muscle fibres, driving the muscle fibre changes in the endomysium.

Autoantibodies are positive in up to 80% of patients with IIM [18,19], with ANA being the most common [24-60%]. Autoantibodies to extractable nuclear antigens (ENA) (including anti-Ro, anti-La, anti-Smith, anti-RNP and anti-Scl70) if present suggest an overlap condition with another

autoimmune rheumatic disease (ARD). Muscle specific antibodies (MSAs) include anti-SRP and anti-Jo-1 help confirm the diagnosis.

Antisynthetase antibodies

Antisynthestase syndrome (ASS) is characterised by antisynthetase antibodies, that bind directly to the aminoacyl transfer RNA synthetases, a group of enzymes that catalyse the binding of a specific amino acid to the cognate tRNA during protein synthesis. These antibodies are highly specific for IIM, and can be detected prior to disease onset. The antisythetase antibodies are the most commonly identified MSAs. They are found in 35-40% of patients with IIM [20] (Table 2) and have a distinct phenotype.

Necrotising myopathy is a subset of IIM, and is associated with a different group of antibodies, notably those binding the signal recognition particle (SRP). Their presence suggests an antibody-mediated mechanism, with a possible drug trigger, viruses, cancer, and other ARDs [10,21]. Statins are specifically known to cause a statin-induced necrotizing myopathy, especially in the presence of an antibody against HMG-CoA reductase. Biopsies demonstrate CD3 lymphocytes and CD68 macrophages around the necrotic and regenerating muscle fibres.

Clinical features

Muscle Weakness

The classical presentation of IIM is symmetrical, bilateral, proximal muscle weakness, and is the presenting symptoms in 84% of patients, while myalgia is seen in up to 75% of patients at presentation [1]. Up to 97% of patients have evidence of muscle weakness during the course of their disease [1]. Patients often report difficulty in combing hair or reaching for objects above their head with upper limb muscle involvement. Lower limb involvement typically presents with difficulty standing up from a chair, or walking up stairs.

Antisynthetase Syndrome (ASS)

Patients with ASS often have very specific features linked to the antibody present in their serum (Table 2). ILD is frequently found, as are inflammatory arthritis, fever, mechanics' hands and Raynaud's Phenomenon (RP) [22]. Anti-Jo-1 antibody is the most common AS antibody detected.

IMNM-specific phenotypes

Anti-SRP antibodies present with a rapidly progressive myopathy and noticeable dysphagia [23]. These patients are less responsive to immunosuppression and have a poorer long term outcome.

There is suggestion that antibodies against HMGCR are triggered by statin exposure [24], especially in HLA-DR11 carriers. Weakness can persist even after the medication is withdrawn. The antibody concentration correlates with serum CK [11].

Rash

A rash is one of the defining features of DM and is typically found in a photosensitive distribution. The characteristic manifestations of DM rashes include a violaceous discolouration around the eyes [heliotrope], predominantly the upper eyelids, often with associated periorbital oedema. Gottren's papules are found over the extensor surface of the metacarpophalangeal (MCP) joints or the interphalangeal (IP) joints and appear as symmetrical palpable erythematous lesions. The typical mechanics' hands present as hyperkeratosis, and painful fissuring of the skin at the tips and sides of the fingers. These are most typically found in the patients with ASS. Patients can also present with macula erythema either in the distribution of the lower anterior neck and upper anterior chest (the V sign), or in a shawl distribution (Shawl sign). Periungal erythema is more common in the juvenile DM cohort than adult. Capillaroscopy demonstrates abnormal tortuous nailfold capillaries.

Antibodies in DM are highlighted in Table 2.

Other clinical features

GI tract

Dysphagia is a presenting feature in about 25% of patients, but will eventually affecct 60% of patients [1]. Patients can also develop dysphonia and even aspiration pneumonia as a result of pharyngeal weakness, and upper oesophageal dysmotility [25].

Patients with anti-SRP are more likely to develop refractory dysphagia [26] compared to the other forms of myositis.

Respiratory

ILD is found in up to a third of patients with IIM, and 95% of patients with ASS [27,28]. This feature is most specifically seen in patients with anti PL-12, anti-KS and anti-OJ antibodies [20,29]. 70% of anti-Jo-1 patients have associated ILD. It can either present subclinically (through screening) or with dyspnoea on exertion and a non-productive cough. Muscular weakness contributes to symptoms with dysphagia predisposing to aspiration pneumonia, or respiratory muscle weakness. Nonspecific interstitial pneumonitis (NSIP) is the commonest finding on imaging, but usual interstitial pneumonitis (UIP) is also regularly identified. NSIP carries a better prognosis, being more responsive to immunosuppression.

Rapidly progressive ILD is seen in patients with anti MDA-5 antibodies [28], often with subclinical myopathy.

Patients with ILD are at a higher risk of developing pulmonary hypertension or cor pulmonale, and require regular screening with pulmonary function tests and echocardiograms.

Joints

Arthritis is a relatively common symptom in IIM, and can predate the muscle weakness by years. It is a presenting feature in 20-30% of patients [30,31]. Typically, it presents as a symmetrical polyarthritis mainly affecting the MCP joints, proximal IP joints, wrists and knees [32].

Inflammatory arthritis, is more common in patients with ASS, especially those with anti-Jo-1 antibodies (75%) [33]. About 55% of patients with anti-Jo-1 ASS associated arthritis develop a symmetrical polyarthritis without erosions [34], 25% an isolated arthralgia, and 15-19% develop a subluxing arthropathy mainly of the distal interphalangeal joint and IP joint of the thumb [typically nonerosive] [35]. Erosions are rare in ASS, unless patients are rheumatoid factor (RF) positive [33], or have anti-PL7 antibodies [34].

30% of patients with anti-Jo-1 ASS are anti-CCP (cyclic citrullinated peptide) positive, and 13.5% are also RF positive. Nearly all patients with anti-CCP antibodies and IIM develop arthritis [35] and have significantly more articular damage on plain radiograph compared to ASS patients without the antibodies (87% and 11% respectively) [35].

Raynaud's Phenomenon

RP affects 40%-60% of IIM patients, and more commonly in DM than PM (39% and 19% respectively [1]). There is a higher prevalence of RP in ASS patients[36,37]. About 50% of patients with anti-Jo-1 myositis also have RP [34], which can precede muscle weakness by a median of 13 months [IQR 12-48 months][38]. Capillaroscopy usually confirms nailfold abnormalities and thermography demonstrates slow rewarming [34].

Constitutional symptoms

Constitutional symptoms, mainly weight loss [50%), and fevers (55%) [39]precede the diagnosis of dermatomyositis in nearly 50% of patients [39], and are reported in up to 72% of anti Jo-1 ASS [40]. Fever is more likely at the onset of the disease, or with disease relapse [32], than at other times.

Cardiac

Cardiac abnormalities are extremely rare in IIM. These include conduction defects, congestive cardiac failure, pericarditis, and valvular heart disease [41]. Mortality is often secondary to right heart failure in the context of ILD.

Cardiac involvement is more frequently seen in anti-SRP patients compared to other phenotypes [23]. Asymptomatic arrhythmias have rarely been reported in DM [42].

Overlap conditions

Myositis can be found in combination with other ARDs.

Anti-Ku antibodies are found in 55% of patients with PM/SSC (systemic sclerosis) overlap syndrome, and 20-30% of patients with IIM in total[20].

Nearly 50% of overlap myositis-systemic sclerosis patients[20], have antibodies to anti-PM-Scl 75 and anti-PM-Scl 100. These patients tend to have both lung and oesophageal involvement.

Other antibodies include Anti-Ro (10-20% of IIM), and anti-La (5%) and anti-U1RNP (20-30%) which are more often found in systemic lupus erythematosus (SLE) (up to 4% of SLE patients have concomitant myositis), and Sjogren's syndrome[18].

Important differential diagnoses

Non-inflammatory myopathies must be excluded. They include muscular dystrophy of late onset, limb-girdle dystrophy with adult onset, and myotonic dystrophy type 2.

Mitochondial myopathies can present with proximal muscle weakness and a raised CK, and emphasise the need for a muscle biopsy in order to differentiate between these diagnoses.

Drug induced myopathies (e.g. D-Penicillamine, Interferon) remain in the differential. HMG-CoA-reductase inhibitors (commonly known as statins), are one of the commonest medications to cause myalgia with a normal CK as a side effect (affecting 1-10% of patients) [43]. Rhabdomyolysis is

devastating but rare, affecting less than 0.1% of patients. Statin-related myopathy is more commonly seen in those that are hypothyroid, patients on multiple medications (especially inhibitors of the cytochrome p450 group of enzymes), and those that abuse alcohol. Upon stopping a statin, symptoms can persist for up to 6 months.

Endocrine myopathy including hypo or hyperthyroidism, and hyperparathyroidism can present with proximal weakness.

Muscular dystrophy is a group of progressive myopathic disorders caused by genetic defects. Although biopsies taken from these patients may initially show endomysial inflammatory cell infiltrate, this tends to be limited to areas adjacent to necrotic muscle fibres, unlike PM [44].

Metabolic myopathies are inherited myopathies associated with abnormalities in carbohydrate and lipid metabolism. These include conditions such as carnitine deficiency and myoadenylate deaminase deficiency. Patients present with episodes of acute muscle pain and tenderness, with or without association myoglobinuria, often triggered by exertion. This can lead to chronic weakness with repeated episodes [44].

Infectious myopathies are often triggered by an acute viral illness such as coxsackie virus or influenza virus. Human immunodeficiency virus (HIV) can also be associated with weakness either as a presenting feature or at late stages in the disease. Patients present with muscle tenderness and elevated muscle enzymes which is hard to distinguish from PM, but the biopsy tends to have fewer inflammatory infiltrates [44].

Investigations

Bloods

Initial laboratory tests include full blood count, inflammatory profile including erythrocyte sedimentation rate, C-reactive protein, thyroid-stimulating hormone and free thyroxine 4,

electrolytes (sodium, potassium, creatinine, magnesium, calcium, phosphate, magnesium), lactate dehydrogenase, liver function tests (aspartate aminotransferase, alanine aminotransferase) and CK. Immunoglobulins and protein electrophoresis are useful, as well as a full viral screen including HIV, hepatitis B and hepatitis C serology. Autoantibodies including ANA, ENA and muscle specific antibodies (MSA) should be checked.

Whereas the majority of patients with IIM present with a raised CK, those with IMNM may have CK levels more than 10 times the upper limit of normal.

Anti-HMGCoA reductase antibodies have been found to correlate strongly with disease activity and CK, and a decrease in antibody titre is associated with improved arm strength and CK levels [11].

Muscle biopsy

This remains the gold standard for confirming the diagnosis of IIM, distinguishing from a necrotising and inflammatory biopsy, and excluding a non-inflammatory myopathy.

The biopsy findings of PM and DM have already been discussed. On biopsy, patients with ASS demonstrate prominent perimysial inflammation with fragmentation and perifascicular myopathic changes [45].

Patients with anti-SRP antibodies demonstrate characteristic biopsy changes of muscle fibre necrosis and endomysial fibrosis with little inflammatory infiltrate visible [23,26].

Skin biopsies are occasionally utilised to confirm DM, especially when the muscle biopsy is indeterminate.

Neurophysiology

Electromyography (EMG) is a useful means of distinguishing a myopathy from a neuropathy. It is abnormal in around 90% of patients presenting with IIM [4].

EMG findings include polyphasic motor unit action potentials of short duration and low amplitude, coupled with increased insertional and spontaneous activity with fibrillation potentials, sharp waves, and occasionally repetitive discharges.

Muscle imaging

Magnetic resonance imaging (MRI) is increasingly used as the imaging modality of choice for confirming IIM. It aids in choosing sites of maximal inflammation for biopsy, and to monitor treatment response. It is also a sensitive means of differentiating acute inflammation from muscle atrophy and chronic muscle damage.

Diagnosing ILD

Given the multisystem nature of IIM, a baseline chest radiograph and pulmonary function tests are important at the time of diagnosis.

Pulmonary function tests can also give an idea of the extent of weakness, especially if there are reduced inspiratory pressures, or poor effort due to respiratory muscle weakness. This weakness will put the patient at risk of aspiration pneumonia. Reduced diffusing capacity suggests a fibrotic process. High resolution Computed tomography [CT] is then utilised in order to confirm NSIP with ground-glass opacities without honeycombing (the most common abnormality noted in lung disease in IIM).

Cancer screening

Up to 25% of patients with DM develop a malignancy within 0-5 years of disease onset, whereas this association is only 10-15% in patients with PM [46]. The risk factors include male gender, older age at disease onset, extensive skin or muscle involvement, elevated inflammatory markers, and negative ANA and MSAs or positive for anti TIF1ɣ (accounts for over 50% of adult patients with cancer-associated DM [47]). The risk is reduced in those with ASS or overlap syndrome. The most

frequent IIM associated malignancy are breast and ovary in women, lung and prostate in men, as well as pancreatic, gastric, colorectal, bladder cancer and non-Hodgkin lymphoma [46].

There are no clear guidelines of how or when to screen patients for malignancy. Our practice is a focus on the patient's history (especially a history or weight loss and constitutional symptoms) since the last clinic appointment, and to have a low threshold for a chest radiograph and abdominal ultrasound, or if clinical suspicion is high- positron emission tomography scan.

Treatment/Management

The main aims of treatment are to suppress inflammation, improve muscle power and prevent chronic damage to muscles and extramuscular organs. However there is a lack of robust data to guide treatment. Most studies are based on observational data, or on small randomised control trials. Our centre's treatment algorithm is shown in Box 1.

Glucocorticoids remain the mainstay of treatment in IIM [48]. Initial dosing is approximately 0.5 mg/kg of prednisolone, but the many side effects of steroids encourage a reducing regime over the first two months. Disease relapse with rapid reduction of prednisolone [49] results in the need for steroid-sparing agents. Severe weakness unresponsive to oral prednisolone requires intravenous methylprednisolone at a dose of 500mg to 1g daily for 3 days, prior to switching to an oral dose of prednisolone. These patients may require a slower steroid reduction.

Methotrexate and azathioprine are often used as first line disease modifying agents (DMARDS). A Cochrane review found insufficient evidence of improved efficacy using one DMARD [methotrexate, azathioprine or cyclosporine] in combination with corticosteroids in preference to another. Methotrexate showed similar improvement in both DM and PM in composites score of muscle endurance and function. This was not statistically different from azathioprine in a head to head trial [50].

If azathioprine is chosen as first line, then thiopurine methyltransferase levels should be checked prior to screen for enzyme deficiency. Those that are deficient have an increased chance of myelosuppression. The dose used is 2-2.5 mg/kg [51]. Azathioprine and Methotrexate can also be used in combination where either agent alone has not proved effective [52].

Mycophenolate mofetil (MMF) is increasingly being chosen as an effective treatment for myositis, in both severe DM and PM. Improvement in skin disease, and muscle strength are seen in patients who have not responded to conventional treatment [53,54]. Small studies have suggested MMF also benefits pulmonary function tests in patients with DM and ILD [55].

Cyclophosphamide may be useful in patients with ILD and severe myopathy [56,57]. Up to 70% of patients with ILD improve both symptomatically and when measured on their FVC (by at least 15% from baseline)[56]. The intravenous form is favoured due to fewer side effects, and typically 500 to 750 mg is given in monthly doses over 6 months.

There is limited supporting evidence for intravenous immunoglobulin (IVIg) in both refractory PM and DM to conventional DMARDS [58,59]. However it is expensive and usually provides only short lived benefit. Cherin et al showed 75% response rate in muscle power, and 90% biochemical improvement [59]. It is typically administered at a dose of 2g/kg usually spread over three days on a monthly basis for three months, provided a response to the treatment is seen.

Rituximab has been shown to be effective in patients with refractory disease, as defined by failure to control disease on at least one immunosuppressive agent for a duration of at least 3 months. A recent review 78.3% of patients refractory to conventional treatment responded to rituximab [60] (when assessing muscle power, lung function and skin manifestations). MSAs (especially anti-Mi-2 antibodies and anti-Jo-1 antibodies) were associated with a 3 x higher chance of improvement compared to patients without any autoantibodies, when treated with rituximab [61]. The long term data also suggests that long-term remission for >12 months can be achieved. Fasano et al [60]

highlighted the beneficial effect of Rituximab specifically in patients with ILD, the CTD-ILD patients responding optimally [62].

In one study only 52% of patients (n= 151) with DM and significant skin disease responded to Rituximab and the relapse rate was high (48.6%)[60]. The heliotrope rash, erythroderma, Gottron sign and violaceous poikiloderma were most responsive to rituximab [63,64]. Paraneoplastic skin lesions did not generally improve.

Cyclosporine and Tacrolimus have a role in the treatment of IIM with ILD [65]. There is also some evidence that cyclosporine may induce partial regression of calcinosis [66].

Anti-TNF agents seem to be of little benefit. Furthermore studies consistently demonstrate the association of Anti-TNF agents with the onset of other auto-immune diseases including cutaneous vasculitis, lupus-like syndrome, SLE, and interstitial lung disease [67,68].

It is vital to reinforce the necessity to avoid UV rays, and to promote the use of at least factor 50 sunblock. Topical corticosteroids, hydroxychloroquine and topical tacrolimus (0.1%) [69] are often used to control the cutaneous manifestations.

Although calcinosis is extremely rare in the adult population, it remains a challenge to treat. Small improvements are anecdotally reported with diltiazem, colchicine, cyclosporine and bisphosphonates.

Monitoring response

The International Myositis Assessment and Clinical Studies Group have suggested core measures to monitor inflammatory myositis. These include Global activity, muscle strength, physical function, laboratory assessment and extramuscular disease.

It is critical to distinguish active disease (requiring further immunosuppression) from permanent damage or another concomitant condition. Scoring systems are means of helping to assess improvement, stability or deterioration in symptoms.

ACR/EULAR have developed a set of criteria to monitor response based on 6 core set measures [physician, patient, and extramuscular global activity, muscle strength, Health Assessment Questionnaire, and muscle enzyme levels], with a total improvement score classifying patients into minimal, moderate and major improvement groups [70]. Although mainly designed for trials, they can also help guide therapeutic response, and need for intervention.

Physiotherapy is mainly advised in the acute phase to maintain full range of joint movement. It is encouraged as patients start to recover, and full remission is not required for active therapy.

Prognosis and Future prospects

Due to the delayed presentation of the non-Jo-1 PM, currently there is increased pulmonary morbidity and mortality in this cohort of patients compared to the anti-Jo-1 patients [71].

In our centre, over a 37 year period, 36.1% of patients had a monophasic disease course, 34% a relapsing and remitting, and 29.9% were defined as chronic persistent. 24.7% of patients died most commonly from infection (29.2%). Cumulative survival at 5 years was 94.6%, and at 10 years 82.2% [72].

Potential biomarkers to monitor disease activity are emerging. In DM these include IL6 and type 1 IFN genes. IL 6 regulates innate and adaptive immune responses, and has both B and T cell activity [73,74]. There is also evidence that Type 1 IFN has a role in DM, through activation of T cells, including NK cells and an influence on dendritic cell maturation. Thus anti IL^ therapy might be a possible treatment.

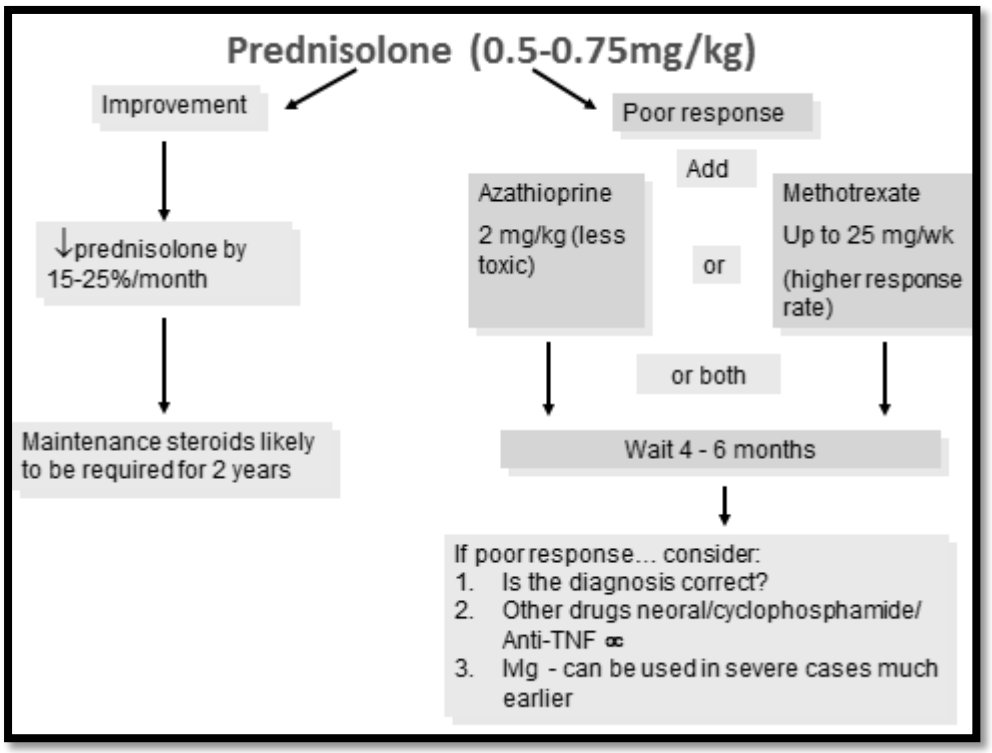
Table 1: Bohan and Peter diagnostic criteria for polymyositis [PM] and dermatomyositis [DM]

Item	Description		
1	symmetrical weakness of limb-girdle muscles and anterior neck flexors		
2	Muscle biopsy evidence typical of myositis		
3	Elevation of serum skeletal muscle enzymes, particularly CK		
4	Typical EMG features of myositis		
5	Typical DM rash, including heliotrope and Gottron's papules		
For the diagnosis of PM		For the diagnosis of DM	
Definite	All of items 1-4	Definite	Item 5 plus 3 of items 1-4
Probable	3 of items 1-4	Probable	Item 5 plus 2 of items 1-4
Possible	2 of items 1-4	Possible	Item 5 plus 1 of items 1-4

Table 2: Table to summarise prevalence of autoantibodies and clinical phenotypes seen in IIM [18,75]

Myositis Specific Antibodies		**Target Autoantigens**	**Clinical Phenotype**	**Frequency in adult Idiopathic inflammatory myositis (%)**	**Prognosis**
Anti-synthetase syndrome (Anti-aminoacyl-tRNA synthetases	Anti Jo-1	Histidyl	Characterised by myositis, mechanics hands, Gottron's papules, non-erosive subluxing arthritis (especially anti Jo-1 and anti PL-7), fever, RP (predominantly anti-PL-12 and anti-Zo) and ILD. PL-7 tendts to present with a lower CK and milder muscle disease. Anti-PL-12, Anti-OJ, and Anti- KS are especially prone to ILD	11-20	
	Anti-PL-7	Threonyl		<5%	
	Anti-PL-12	Alanyl			
	Anti-EJ	Glycyl			
	Anti-OJ	Isoleucyl			
	Anti-KS	Asparaginyl			
	Anti-Ha	Tyrosyl			
	Anti-Zo	Phylalanyl			
Acute Necrotising Myopathy	Anti-SRP	Ribonucleoprotein complex (6 polypeptides and 7SL RNA)	Severe muscle weakness with associated very high CK (up to 25 000). Higher risk of refractory dysphagia	4-6 %	Often steroid responsive, but can be refractory to treatment, and usually require long-term immunosuppression
	Anti-HMG-CR	HMG CoA reductase	Weakness associated with statin use, and weakness persists despite discontinuation of medication. CK usually 2000 -35 000	6-9 %	
Adult Dermatomyositis	Anti-Mi-2	Nucleosome remodelling histone deacetylase complex	Cutaneous disease, milder muscle disease with lower CK than other IIM subsets	5-10% (10-30% adult DM)	Low risk malignancy and good response to treatment. Low mortality rate
	Anti-TIF1-ɣ (Anti-155/140)	Transcriptional intermediary factor 1-ɣ	Severe cutaneous disease. Strong affiliation with malignancy.	13-21 % (23-30% of all DM)	Reduced risk ILD, RP, arthritis
	Anti-NXP-2	Nuclear matrix protein 2 (p140)	More commonly seen in JDM with associated calcinosis. Adults develop cutaneous disease, systemic features and ILD	3 %	
Amyopathic Dermatomyosits	Anti-SAE	Small ubiquitin-like modifier activating enzyme	Severe skin disease precedes onset of muscle and dysphagia	5% overall (8% of DM)	Good prognosis, low risk of ILD
	Anti-MDA5	Melanoma-differentiation associated gene 5	Amyopathic DM. severe skin disease with skin ulceration, palmar papules, panniculitis. Rapidly progressive ILD, often with pneumomediastinum	Overall prevalence unknown. Accounts for 20-30% of patients from Asian with DM	Poor prognosis given rapidly progressive ILD
Myositis-Associated antibodies	Anti-PM-Scl	Nucleolar protein complex	SSc overlap, Raynaud's phenomenon, ILD	9-10% (accounts 50% of myositis-scleroderma overlap syndrome	
	Anti-U1 RNP	U1 small nuclear RNP	Undifferentiated CTD	10%	
	Anti-Ku	DNA-PK regulatory subunit	SSc overlap, ILD	20-30%	
	Anti-Ro	Y1-Y5 RNP	Sjogren's overlap, often associated with Jo-1	10-20%	
	Anti-La	RNA polymerase III termination factor	Sjogren's overlap	5%	

Box 1


Prednisolone (0.5-0.75mg/kg)
Improvement
Poor response
↓prednisolone by 15-25%/month
Add
Azathioprine
2 mg/kg (less toxic)
or
Methotrexate
Up to 25 mg/wk
(higher response rate)
or both
Maintenance steroids likely to be required for 2 years
Wait 4 - 6 months
If poor response... consider:
1. Is the diagnosis correct?
2. Other drugs neoral/cyclophosphamide/ Anti-TNF ∞
3. Ivig - can be used in severe cases much earlier

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