Juvenile idiopathic inflammatory myositis: an update on pathophysiology and clinical care

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Abstract

The childhood-onset or juvenile idiopathic inflammatory myopathies are a heterogenous group of rare and serious autoimmune diseases of children and young people that predominantly affect the muscles and skin but can also involve other organs including the lungs, gut, joints, heart and central nervous system. Different myositis-specific autoantibodies have been identified that associate with different muscle biopsy features as well as with different clinical characteristics, prognoses and treatment responses. Thus, myositis-specific autoantibodies can be used to subset juvenile idiopathic inflammatory myopathies into sub-phenotypes; some of these sub-phenotypes parallel disease seen in adults whereas others are distinct from adult-onset idiopathic inflammatory myopathies. Although treatments and management have much improved over the past decade, evidence is still lacking for many of the current treatments and few validated prognostic biomarkers are available with which to predict response to treatment, comorbidities (such as calcinosis) or outcome. Emerging data on the pathogenesis of the juvenile idiopathic inflammatory myopathies are leading to proposals for new trials and tools for monitoring disease.

Introduction

The childhood-onset or juvenile idiopathic inflammatory myopathies (JIIMs) are a group of rare but serious conditions of children and young people that predominantly affect the muscles and skin but can also involve other organs including the lungs, gut, joints, heart and central nervous system. A newly defined EULAR–ACR system of classification[1] captures the most prevalent group of JIIM, namely juvenile dermatomyositis (JDM). However further refinement will be required for a classification that accurately captures the subtypes of JDM and delineates other forms of JIIM, including juvenile polymyositis, immune-mediated necrotizing myopathy (IMNM) in children or the overlap myositis syndromes. Unlike previous criteria, one advantage of the new EULAR–ACR criteria, according to an evaluation of these criteria in adult patients, is their ability to capture amyopathic dermatomyositis[2]. Although the EULAR–ACR classification criteria represent a new and superior standard, the Bohan and Peter criteria proposed in 1975[3] have still been used in some recent literature.

An important advancement in the past ten years years is a greater understanding of the disease phenotype on the basis of the myositis-specific autoantibody (MSA) profile. MSAs, present in approximately 60% of children with JIIM[4, 5], can help inform the disease course and risk of complications, such as interstitial lung disease (ILD) or calcinosis. MSA testing has helped to identify patients with IMNM, anti-synthetase syndrome or overlap syndromes who previously might have been classified as having juvenile polymyositis.

In terms of JIIM pathophysiology, vasculopathy and endothelial dysfunction are increasingly recognised as important elements, with number of circulating endothelial cells correlating with disease activity and nailfold abnormalities[6]. Type 1 interferon signature is a known key feature of JIIM (Table 2) but more work is needed to define the key drivers of this signature and the downstream effects that lead to immune dysregulation. Growing evidence supports involvement of mitochondrial dysfunction and endoplasmic reticulum (ER) stress. Greater understanding of pathogenesis might help identify important therapeutic targets, shown most recently by the promise of JAK-STAT inhibition in the treatment of JIIM-related muscle, skin and lung disease[7-11] . This approach needs to be explored further by clinical trials.

In this Review, we describe the key features of JDM and its subtypes, as well as juvenile-onset IMNM, juvenile polymyositis and the overlap syndromes. We also discuss the clinical phenotypes of JIIM in relation to the MSA profile, highlighting the main clinical associations, response to treatment and caveats of antibody testing (Table 1). We review advances in our knowledge of the pathogenesis of JIIM and assess how evidence over the last decade has contributed to the understanding and management of these

complex conditions, and what evidence is urgently needed to address the unmet needs in JIIM. Where data are available, we compare childhood-onset myositis and adult-onset myositis to highlight parallels or differences in antibody associations, genetics, clinical features, prognosis or outcomes. Detailed comparisons between adult and paediatric myositis have also been reviewed elsewhere[12, 13].

In the final section of this Review, we summarise current evidence in terms of JIIM treatment and highlight the need for head-to-head comparison studies to determine the best second-line treatment, options for recalcitrant disease and JIIM-related complications. A treatment algorithm for JIIM based on current available consensus is also presented, including the use of exercise therapy and psychological support as well as medications. Finally, we discuss some of the key challenges in the management of JIIM and how international collaboration helps to overcome these challenges and improve our understanding of this rare but important group of diseases .

Epidemiology

JIIM has a reported incidence of between 1.6-4 cases per million children per year[14] and an estimated prevalence of 2.5 cases per 100,000 children[14], but limited data are available. Although the mortality in JIIM has decreased considerably since the pre-steroid era and is often reported as being below 4% worldwide[15-17], mortality remains as high as 5-8% in some cohorts[18-20] . In a North American study, the mortality associated with juvenile connective tissue disease overlap phenotypes was higher (standardised mortality ratio (SMR) 66.9) than that associated with juvenile polymyositis (SMR 30.7) or JDM (SMR 8.3)[21]. Risk factors, identified by multivariant analyses, included older age or illness severity at disease onset, weight loss and delay to diagnosis.

As mortality rates have decreased over the years, more emphasis has been placed on evaluating long-term functional outcomes, morbidity and health-related quality of life. Notably, the risk of disease damage increases almost linearly for each year of disease[22], highlighting the importance of early disease control. Damage, usually mild, is most common in the cutaneous, endocrine, muscular or skeletal domains, with identified predictors of damage including high disease activity or severity of disease at onset, duration of active disease, the presence of early organ damage (within 6 month of diagnosis) and functional disability[19, 23, 24]. Functional impairment is usually mild, but reported in up to 41% of patients and can be associated with increased pain and decreased quality of life[16, 17, 19, 20, 23-25]. Children can be affected by impaired growth or delayed puberty, particularly if there is preceding growth failure or if the active phase of disease occurs during early puberty [26]. In a report of adults who had JDM and were surveyed at an average age of 20 years, 59% perceived that their myositis was still active and 65% were still taking immunosuppressive medication[27].

JIIM is also associated with long-term risks relating to cardiovascular, pulmonary or cerebrovascular disease [6, 28-31]

Clinical phenotypes

On the basis of clinical and histopathological findings, JIIM can be separated into various subtypes. JDM, the most common JIIM subtype, represents more than 80% of patients, followed by overlap myositis[14, 15, 19, 32]. In this section, we first review the clinico-serological subtypes of JDM before discussing the features of amyopathic JDM, anti-synthetase syndrome (ASyS), IMNM and overlap syndromes. In the absence of myositis, patients with characteristic skin rashes are considered to have amyopathic or clinically amyopathic JDM, but this phenotype is rare in children[33, 34],[35]. Juvenile polymyositis is a very rare subtype, characterised by severe muscle inflammation and characteristic but not pathognomonic histological, radiological and electromyographic findings[36]. Emerging data suggest that some patients previously diagnosed as having JDM or juvenile polymyositis instead fall within the IMNM[37], overlap myositis or anti-synthetase syndrome (ASyS) category[38], on the basis of their autoantibody profile (Table 1).

Juvenile dermatomyositis

JDM is defined by the presence of proximal symmetric myositis and characteristic cutaneous features and has a median age of diagnosis of 7.4 years[32]. Calcinosis has been reported in 20–47% of patients with JDM in different cohorts[16, 39]. Approximately 60% of patients with JDM are positive for a myositis specific antibody (MSA) (Table 1). Increasingly, expert consensus is that JDM can be divided into the following subtypes defined by the presence of a specific MSA: anti-Mi2 antibody-positive JDM, anti-nuclear matrix protein 2 (NXP2) antibody-positive JDM, anti-transcriptional intermediary factor 1 (TIF1) antibody-positive JDM, anti-melanoma differentiation-associated gene 5 (MDA5) antibody-positive JDM, anti-small ubiquitin-like modifier activating enzyme (SAE) antibody-positive JDM, and MSA-negative JDM[38](Table 1). Two MSA can co-exist in the same patient, but this is extremely rare, although some patients do have both an MSA and one or more myositis-associated autoantibody (MAA)[5] .

Anti-TIF1 antibody-positive JDM

Anti-TIF1 antibodies are the most common MSA in JIIM, with a reported frequency of between 17-35% (Table 1)[4, 5, 40]. These antibodies are most common in white children and those children with a younger age of disease onset[5] (median age of 7 years at disease onset in one North American study). The clinical phenotype of anti-TIF1 antibody-positive JDM includes mild muscle disease with relatively low creatinine kinase serum levels but with severe skin involvement including an increased risk of ulceration and lipodystrophy[4, 5, 41]. Other frequent skin manifestations include Gottron, malar rash, erythema, 'shawl-sign' rash, photosensitivity and cuticular overgrowth[5]. Dysphagia can also occur in these patients[4] . Some patients

have a chronic severe disease course, requiring the use of second-line or third-line treatment regimes, including cyclophosphamide or biologic drugs [4]. Although anti-TIF1 antibodies confer an increased risk of malignancy in patients with adult onset myositis [42, 43], this association has not been reported in individuals with childhood-onset myositis.

Anti-NXP2 antibody-positive JDM

Anti-NXP2 antibodies (initially known as anti-MJ antibodies) are present in approximately 15-25% of patients with JDM (Table 1) and are one of the most common MSAs in white populations[5, 44, 45]. Anti-NXP2 antibody-positive patients with JDM typically present at a young age, and have the highest incidence of calcinosis among the various JDM antibody subtypes, with age of onset itself found to be linearly associated with risk of calcinosis in a UK cohort[46]. Calcinosis is also associated with the presence of anti-NXP2 antibodies in adult-onset IIM [47]. Muscle disease can be severe in childhood-onset anti-NXP2 antibody-positive disease and can include muscle contractures, muscle atrophy and functional compromise[45]. Other features of anti-NXP2 antibody-positive disease include gastrointestinal involvement, risk of dysphagia, dysphonia and skin ulceration [4]. The disease can be difficult-to-treat, has a low probability of treatment discontinuation, does not always respond well to conventional treatment and can result in a poor long-term prognosis [48, 49].

Anti-MDA5 antibody-positive JD

Patients with anti-MDA5 antibody-positive JDM typically have minimal or no muscle involvement [4, 50, 51]. The characteristic clinical phenotype includes frequent skin rashes, cutaneous ulceration and arthritis (affecting mainly the small joints of the hand and feet), in addition to constitutional symptoms (such as weight loss), oral ulceration and increased risk of interstitial lung disease (ILD) [4, 50, 52-54]. Patients with early ILD detected by computerised tomography or pulmonary function tests (PFT) are frequently asymptomatic[55] . Rapidly progressive ILD is a rare but potentially fatal complication of idiopathic inflammatory myopathy (IIM) in both children and adults with anti-MDA5 antibodies and reports suggest that this complication occurs more often in East Asian patients than in other populations [55-57] . Anti-MDA5 antibody-positive patients are more likely to receive shorter treatment with glucocorticoids than other JIIM autoantibody subtypes, although overall treatment duration and frequency of clinical remission in anti-MDA5 antibody-positive JDM is similar to that of other JDM subtypes[50].

Anti-Mi2 antibody-positive JDM

Anti-Mi2 antibodies are present in 4–10% of patients with JDM[4, 5]. Anti-Mi2 antibody-positive JDM is more common in Hispanic patients with an older disease onset (median age of disease onset of 11 years) than other JIIM autoantibody subtypes[5] . Children with anti-Mi2 antibody-positive JDM typically present with severe muscle disease and notable skin involvement, frequently referred to as 'classic JDM'[4, 5]. Common

skin rashes include those pathognomonic for JDM (such as heliotrope rash and Gottron papules), along with malar rash and periungual nailfold capillary abnormalities[5]. The severity of the myositis is reflected by high muscle biopsy scores of the patients [58]. Children with anti-Mi2 antibody-positive JDM are less likely to have ILD than patients with other JDM subtypes, but have a greater risk of dysphagia and oedema[4, 5]. Despite the severe presentation, anti-Mi2 antibody-positive patients respond well to conventional treatment and have a good chance of being off treatment at 2 years[48].

Amyopathic juvenile dermatomyositis

Amyopathic JDM can occur in some children but it is rare (<5% of patients with JIIM)[35, 59]. Anti-TIF1 antibodies, followed by anti-MDA5 antibodies, are the most common MSAs associated with this JIIM subtype[34]. Patients with amyopathic JDM tend to have a young age of disease onset and have less myalgia, arthritis, calcinosis, dysphagia or abdominal pain than other patients with JDM[34]. Skin manifestations include Gottron papules, heliotrope rash, malar rash, periungual capillary abnormalities and photosensitivity[34]. Some patients with anti-SAE antibodies can present initially with skin disease, with muscle involvement occurring at a later stage [4, 60]. In a case report, one patient had anti-SAE antibody-positive amyopathic JDM complicated by ILD[61]. In the absence of myositis, some experts believe that the presence of a MSA can support a diagnosis of JIIM[62, 63].

Anti-synthetase syndrome

Anti-synthetase syndrome is characterised by the presence of antibodies against aminoacyl tRNA synthetases (anti-ARS antibodies; also known as anti-synthetase antibodies) and a broad spectrum of clinical features. Eight anti-synthetase antibodies have so far been described in JIIM: anti-Jo1 (anti-histidyl-tRNA synthetase), anti-PL12 (anti-alanyl-tRNA synthetase), anti-PL7 (anti-threonyl-tRNA synthetase), anti-EJ (anti-glycyl tRNA synthetase), anti-KS (anti-asparagyl-tRNA synthetase), anti-OJ (anti-isoleucyl-tRNA synthetase), anti-Ha (anti-tyrosyl-tRNA synthetase) and anti-Zo (anti-phenylalanyl-tRNA synthetase) antibodies. Clinical manifestations of anti-synthetase syndrome, as documented in a North American study, include proximal muscle weakness (100%), arthritis (74%), mechanic's hand (32%), fever (63%), Raynaud phenomenon (32%) and ILD (63%)[5]. Anti-synthetase syndrome is rare in children and much knowledge is extrapolated from the disease in adults. Among adults with anti-synthetase syndrome, patients positive for anti-Jo1 antibodies are more likely to have myositis, whereas other patients, especially those with anti-PL12 antibodies, are more likely to have isolated ILD and therefore might only be under the care of a respiratory physician[64, 65].

Immune mediated necrotizing myopathy

IMNM is a rare and recently characterised subtype of JIIM that includes anti-signal recognition particle (SRP) antibody-positive myopathy, anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) antibody-

positive myopathy and antibody-negative IMNM[38, 66]. The hallmark muscle biopsy finding of IMNM is muscle fibre necrosis with the absence or minimal presence of lymphocytic infiltrate[66]. Children with IMNM characteristically present with severe muscle weakness and notably elevated serum levels of muscle enzymes. Anti-SRP antibody-positive patients can have dysphagia[67], and in rare instances can have cardiac involvement[66, 68]. Some patients can also present with skin and other extra-muscular manifestations, which can include arthralgia or Raynaud phenomenon, as well as ILD [66]. Children with anti-HMGCR antibodies typically present with severe proximal muscle weakness, and can have muscle atrophy, contractures and arthralgia[37, 66] . Although in adults the development of anti-HMGCR antibodies is frequently associated with exposure to statins, this association is absent in children with anti-HMGCR antibodie [37, 69]. Autoantibody negative INMN remains poorly characterized.

In children, anti-SRP or anti-HMGCR myopathy presenting with slowly progressive muscle weakness could be mistaken for muscular dystrophy[70]. A high index of suspicion with muscle biopsy, immunohistochemical or genetic testing might be appropriate. Patients with muscular dystrophy can share the same pattern of muscle weakness (with more proximal than distal involvement), elevation of muscle enzymes, oedema on MRI and myopathic features on biopsy, but can be distinguished from JIIM by a tendency to have more insidious disease onset, weakness in other muscle groups, calf muscle of generalised muscle hypertrophy, joint contractures, scapular winging, scoliosis, spinal rigidity, cardiomyopathy or macroglossia and the absence of a MSA[70].

Overlap myositis

Currently, no unifying internationally accepted definition of overlap myositis exists as different connective tissue diseases can have similar clinical features. An international survey of clinical opinion on criteria for JDM–scleroderma overlap, which occurs in 15-20% of patients with JDM according to some reports[71], proposed the use of the presence of two or more of the following criteria: Raynaud phenomenon, sclerodactyly and sclerodermatous skin changes in a child fulfilling criteria for JDM[72]. In a large US study of 1,718 patients with SLE (451 paediatric and 1,267 adult patients), 6.3% of the patients had concurrent myositis[73] whereas in a UK cohort of patients with JIIM, 2.5% of the patients were given a diagnosis of JDM–SLE overlap[15].

The most commonly detected autoantibodies in overlap syndromes are MAAs (Table 1), although these antibodies can also be found in other JIIM subtypes. One or more MAAs might co-occur with MSAs in the same patient[4, 12]. MAAs include anti-Ro52, anti-PM/Scl and anti-U1RNP antibodies[5, 74]. For example, in one cohort, MSAs were detected in 6/49 (12%) of patients with overlap CTD or MCTD, whereas MAAs were present in 25/49 (51%) of the patients[4]. Overlap syndromes are associated with an increased risk of extra-

muscular manifestations and a higher risk of mortality, in particular because of the higher risk of ILD, compared to other JIIM autoantibody subtypes highlighting the importance of a correct diagnosis and early treatment[32].

Myositis in other paediatric conditions

Other than primary myositis, myopathy or myositis can be a presenting feature in a number of different inflammatory conditions seen in childhood. Clinical presentation of myositis in childhood sarcoidosis is a rare but reported manifestation[75] . Thus, sarcoidosis or granulomatous myositis should be considered in patients presenting with myositis and hypercalcemia[75]. Myositis can also be present in childhood vasculitides, with reports of polyarteritis nodosa presenting as polymyositis [76] and deficiency of adenosine deaminase 2 (DADA2), a monogenic autoinflammatory disease, presenting with inflammatory myositis[77].

Advances in genetic testing have resulted in an increasing recognition of monogenic autoinflammatory diseases and testing for such diseases should be included in the differential diagnosis of patients with myositis [78]. Characteristic features of monogenic autoinflammatory diseases include onset at an early age, fever and systemic inflammation affecting the eyes, joints, skin and serosa, but any system can be involved. Monogenic interferonopathies, such as proteasome-associated autoinflammatory syndromes (PRAAS) and stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy syndrome (SAVI), can mimic JDM[78, 79]. Protracted febrile myalgia is a rare manifestation of Familial Mediterranean fever (FMF) characterized by prolonged severe and symmetric muscle pain, fever and elevated inflammatory markers, that can also mimic JIIM[80].

Pathophysiology

Although the triggers of disease in JIIM remain elusive, several studies over the past few years have implicated new or interconnected mechanisms in the skin, blood vessels and muscle (FIG 1), as discussed in this section.

Environmental risk factors

Although the exact cause of this heterogeneous group of diseases remain largely unknown, complex interactions between genetic and environmental factors, as well as immune and non-immune mechanisms, have a role in JIIM pathogenesis[81]. The contribution of several bacterial and viral pathogens have been studied, including streptococcal infections, picornavirus, enterovirus, mycoplasma, with inconclusive results[82-85]. Some patients have presented with Myositis following SARS-CoV-2 infection or vaccination against SARS-CoV-2[86, 87] , but such case reports await confirmation by larger epidemiological studies . Ultraviolet light intensity and exposure [88, 89] have been associated both with disease aetiology and severity[90]

in JIIM. Such exposures might be associated with specific clinico-serological subtypes: for example, in a large North American study, previous high exposure to ultraviolet light was associated with increased odds of having anti-TIF1 antibodies[89]. Other studied risk factors in JIIM include air pollution, maternal smoking and maternal occupation[91]. Some evidence suggests that certain immunisations, stressor events, heavy exercise prior to diagnosis and prolonged breastfeeding increase the risk of specific JIIM phenotypes[92] but the results need to be confirmed in bigger, multinational studies.

Genetics

In both adult and paediatric IIM, the strongest genetic association in white populations is within the 8.1 ancestral haplotype (AH8.1; also known as the *HLA A1-B8-DR3-DQ2* haplotype) of the major histocompatibility complex (MHC), first detected by GWAS analyses[93]. Subsequent studies using Immunochip data in well-characterised, larger cohorts have confirmed this association[94]. More recently in 2022, in a large international genetics study of JDM that used dense exome SNP genotyping, researchers revealed that the allele *HLA-DRB1*03:01* and amino acid position 37 within HLA-DRB1 are both strongly associated with JDM, and that this association was independent of position 74, a position associated with adult-onset dermatomyositis, enabling differentiation between juvenile and adult-onset disease[95]. Further analyses suggested that position 37 of HLA-DRB1 was independent of the AH8.1 ancestral haplotype and confirmed previous associations with AH8.1 and *HLA-DRB1*03:01*. Specific associations of the *HLA-DQB1*02* allele with disease differ between adult-onset and childhood-onset anti-TIF1 antibody-positive dermatomyostis[96]. Similarly, paediatric-onset anti-HMGCR antibody-positive myositis has a specific association with *HLA-DRB1*07:01*, whereas adult-onset anti-HMGCR antibody-positive myositis is associated with *HLA-DRB1*11:01*[37]. The R620W variant of *PTPN22* and a non-synonymous SNP (rs2304256) in TYK2 have also been associated with both adult and juvenile IIM as well as other autoimmune conditions[97]

Vasculopathy of JIIM

Vasculopathy and endothelial dysfunction are thought to have an important role in JDM and have been associated with systemic disease[98]. In a flow cytometry analysis, the number of circulating endothelial cells but not circulating endothelial progenitor cells were increased in the peripheral blood of patients with JDM compared with healthy individuals[99]; a study of 90 patients with JDM found that the number of circulating endothelial cells correlated with disease activity and nailfold abnormalities, and were increased in both patients with active JDM and patients with inactive JDM compared with healthy individuals[6]. In a separate study, patients with JDM who were positive for anti-TIF1 antibodies had lower nail fold end row loop counts (indicative of vasculopathy) at diagnosis and a prolonged duration of untreated disease, compared with other patients with JDM [100]. Endothelial soluble adhesion molecules, including soluble intercellular adhesion molecule 1 (sICAM1) and sICAM3, soluble vascular cell adhesion molecule 1 (sVCAM1), VCAM1, and E-

selectin, are key players in the adhesion and migration of leukocytes through the endothelium towards inflamed sites and are under investigation as biomarkers of vasculopathy in JIIM [6, 98, 101]. These molecules are mainly secreted by activated endothelial cells, highlighting the association of these molecules with vasculopathy in JDM. The soluble forms of these molecules maintain many of the functions and the structure of the cell-bound adhesion molecules and therefore are of interest as potential therapeutic targets.

The role of interferon and immune cells

A strong interferon type I signature has been extensively implicated as a characteristic feature of JII'[, including studies of patient blood, muscle and skin[79, 102-104]. Type II interferon has also been associated with JIIM[105] . Both type I and II interferons originate as viral interfering proteins; several type I interferons exist (including IFNα and IFNβ), all of which bind to the type I interferon receptor[106], whereas IFNγ is the only type II interferon and binds to the separate type II interferon receptor. Several different assays exist that assess the levels of interferon type I and II , the downstream targets and related biomarkers (Table 2).

In parallel to the interferon pathway, both innate and adaptive immune dysregulation are thought to contribute to JIIM. The presence of MSAs and their association with distinct clinical phenotypes (which differ between juvenile and adult-onset disease[52]) strongly implicate a role for B cells in disease. Notably, in an international trial of adult and juvenile IIM, B cell depletion appeared to have clinical benefit in patients with JDM, according to a sub-analysis [107]. In additional to clinical phenotypes, specific MSAs are also associated with pathology and patterns of inflammatory infiltrate in muscle biopsy samples[58]. In a study of $CXCR5^+$ T follicular helper (T_{FH}) cells in patients with JDM, the cells were skewed towards T helper 2 (T_H2) and T helper 17 (T_H17) cell subsets[108], which might drive B cells towards autoantibody production and a pro-inflammatory phenotype. A separate study confirmed skewing of the T cell compartment towards a T_H17 phenotype in juvenile, adolescent and adult patients with dermatomyositis[109]. Inflammatory T cells, B cells and tissue macrophages are all present in the inflamed muscle of patients with JDM [110-112]. An analysis of peripheral blood B cells in patients with JDM showed that a population of immature transitional B cells ($CD19^+CD24^{hi}CD38^{hi}$ cells) is expanded during active disease and correlates with disease activity[113]. Transcriptional and functional analyses have confirmed that these immature transitional B cells have an upregulated IFNα signature that is associated with an abnormal ratio of IL-6 to IL-10 production, suggesting that these cells are driven towards a pro-inflammatory phenotype that hinders the immunoregulatory properties of the cells [113].

The inflammatory T cell and B cell infiltrate within muscle biopsy samples (which is typically perivascular) correlates with interferon-driven MxA expression and drives the inflammatory domain score of a JDM muscle biopsy score [48, 102, 110].This muscle biopsy score has prognostic value in predicting treatment and

disease[48, 110]. Tissue macrophages in JDM muscle are highly pro-inflammatory and secrete both cytokines and pro-inflammatory molecules including calprotectin[111]. In an immunofluorescence analysis of muscle biopsy samples, the expression of IFNγ and HLA class II molecules were increased in patients with JDM not undergoing treatment compared with healthy individuals, and the type I and type II interferon scores were associated with muscle infiltration by endomysial and perimysial $CD3^+$ cells, as well as $CD68^+$ cells, and perifascicular atrophy of the muscle[105]. Transcriptomic analyses suggest that skin lesions of patients with JDM contain higher numbers of macrophages and $CD4^+$ memory T cells than non-lesional skin and share a similar gene expression pattern as skin lesions from patients with childhood-onset systemic lupus erythematosus (SLE)[114], including a prominent type I interferon signature. However, the factors most important in driving the type I interferon signature and immune cell dysregulation remain elusive. More work is needed to understand these mechanisms: high resolution techniques (such as single cell transcriptional analyses by RNA sequencing) for assessing skin, muscle and blood samples, as well as differential transcriptional expression in specific cell lineages, in parallel with functional studies in JDM, are ongoing and will generate important mechanistic insights into the interferon signature, its relation of other dysregulated pathways and how these processes are impacted by treatment or disease activity.

Neutrophils, NETs and mitochondrial dysfunction

Neutrophils, an essential component of the innate immune system, can produce neutrophil extracellular traps (NETs) that are comprised of DNA–histone complexes and other released proteins . The role of NETs is to help capture, degrade and kill pathogens (such as bacteria) [115]. Various studies implicate dysregulated neutrophil pathways, including NET formation, in JDM . For example, a muscle biopsy analysis found increased amounts of NET remnants in patients with JDM compared with healthy individuals , which was more evident in patients with calcinosis[116]. In a concurrent study, the level of circulating NET complexes was also higher in patients with JDM than in healthy individuals[117] and correlated with disease activity and the presence of anti-MDA5 antibodies, but conversely did not correlate with calcinosis[116, 117]. In one of these studies, NETs were shown to contain mitochondrial DNA (mtDNA)[116], which is notable as studies in SLE have shown that mitochondrial dysfunction leads to the extrusion of oxidised mtDNA in NETs, which in turn induces an type I interferon response[118]. Indeed, gene expression network analysis of muscle has implicated a role for mitochondrial dysfunction in JDM and a recent study demonstrated that highly abnormal mitochondrial function in monocytes from JDM patients, (including the presence of enlarged mitochondrial networks, or 'megamitochondria') leads to oxidsed mitochondrial DNA production and drives further type I IFN production[119, 120]. Furthermore, anti-mitochondrial autoantibodies are presence in the serum of some patients (1% (4/371) of patients in one enzyme-linked immunosorbent assay (ELISA)-based analysis)[121]. This growing body of evidence supports the involvement of mitochondrial dysfunction in JDM pathogenesis and in type I interferon-mediated inflammation.

ER stress

JDM is characterized by an increased expression of MHC class I molecules on muscle fibres, which is thought to be driven by both type I and type II interferon signalling [102, 122]. Accumulation of class I MHC proteins can result in ER stress and can lead to cell death[123]. ER stress might also synergise with factors secreted by infiltrating myeloid cells, such as myeloid related protein 8 (MRP8), MRP14 and other endogenous TLR ligands, to further damage the muscle [111]. For example, in one study, concentrations of MRP8 and MRP14 were significantly increased in the serum of patients with JDM compared with age-matched healthy controls ; further analysis suggested that these inflammatory proteins were secreted by $CD68^{+}$ myeloid cells and synergised with ER stress to promote the production of IL-6 and MCP1 in the muscle[111]. In a separate muscle biopsy analysis, the muscles of adults with IIM contained higher levels of proteins involved in the ER stress-induced-autophagy pathway (such as the ER chaperone protein glucose-regulated protein 78 (GRP78)) than muscles of individuals lacking any myopathic features , which correlated with levels of autophagy, muscle damage and disease activity [124]. These studies demonstrate that ER stress might have an important role in JIIM pathogenesis.

Diagnosis

The diagnosis of JIIM requires careful evaluation of a number of clinical features, supported by a combination of laboratory, radiological and histopathological investigations. A Single Hub and access point for Paediatric Rheumatology in Europe (SHARE) initiative-based consensus guideline has set out recommendations for the diagnosis of JIIM, including investigations to differentiate JIIM from other causes of muscle weakness, to confirm a diagnosis of JIIM and to determine the presence of organ involvement[125]. A similar process has been followed by the Paediatric Rheumatology Association of Japan and the Japan College of Rheumatology to produce a clinical practice guideline, recognising that the frequency of complications and drug use differs between Europe, the United States and Japan[126 127]. Diagnostic testing has been discussed in detail elsewhere[85], and therefore a full description of diagnostic work up will not be repeated here, but may include formal evaluation of muscle strength, detailed cutaneous assessment, testing muscle enzymes and other blood tests and performing pulmonary function tests, electrocardiogram (ECG), echocardiogram, and radiological investigations. Changes in practice over the last decade particularly relating to the role of MRI, muscle biopsy and MSAs will briefly be described[85, 125].

Magnetic Resonance Imaging (MRI) is now favoured as a diagnostic tool, but muscle biopsy also remains important, particularly in the absence of skin rash or when presentation is atypical[125]. When performed, use of a standardised JDM biopsy score is helpful in quantifying the severity of histopathological abnormalities, and together with MSA status, might help predict the disease course[48, 110, 125].

A major advance over the last decadehas been the routine use of MSAs to aid the diagnosis of JIIM, to help define or predict disease phenotype and to develop a more personalised approach to management[64, 128, 129] (although the absence of a MSA does not rule out JIIM[5, 128, 130]). A recent survey of members of the International Myositis Assessment and Clinical Studies (IMACS) group found that over 80% of participants reported that MSA testing increased their confidence in the diagnosis and information that they gave to patients on prognosis[128]. However, more than 90% of respondents expressed the need for more education on the interpretation of antibody results[128]. The MSA–MAA profile might influence the investigative screening or treatment decisions by indicating the risk of a chronic disease course or specific complications such as ILD or calcinosis (Table 1). Results of MSA–MAA testing can vary depending on which technique is used, with some techniques not reliably detecting certain MSAs, as described in Table 1. Measurement by immunoprecipitation is considered the gold standard, but is expensive and time consuming and additional testing is required to differentiate between the presence of anti-NXP2 antibodies and anti-MDA5 antibodies[131]. Other techniques used in practice include line blot, dot blot, commercial multiplex assays, ELISAs and gel precipitation. Line blot is a cheap and rapid to perform technique, but false positives can occur, and this technique does not reliably detect anti-TIF1[130]antibodies, which is the most common MSA in JIIM[130-132]. ELISA is a reliable test for detecting anti-TIF1 antibodies and produces a fast and quantitative result, but multiple assays might be required to test for all MSAs. Some MSAs are cytoplasmic and therefore MSAs can still be present when an antinuclear antibody (ANA) test result is negative. The staining pattern seen on human epithelial type 2 (HEp-2) cells can be used, along with the clinical phenotype, to help ascertain if the results of MSA testing are correct[131]. False positive results should be considered if more than one MSA is reported as positive, or if the MSA result does not fit with the HEp-2 staining pattern or expected clinical phenotype. Repeating a test using the same technique is rarely useful and in ambiguous cases a different testing technique or specialist laboratory is preferable. Further details on the expected HEp2 cells staining pattern and challenges with MSA testing are summarized in Table 1.

Management

The treatment of JIIM needs to consider the disease severity of the patient, including the presence of systemic and/or organ involvement and the disease phenotype. As well as these features, the MSA–MAA profile can inform the management and treatment of the patient, given the associations of specific MSAs and MAAs with clinical phenotypes, prognosis and risks of complications (FIG 2). Treatment decisions are best made in a specialist paediatric centre by a multi-disciplinary team, owing to the rarity and heterogenicity of the diseases[125, 133]. Consensus guidelines provide a framework for healthcare professionals on the basis of the best possible evidence available[125, 133]. A 2022 evidence-based British Society for Rheumatology guideline for childhood and adult-onset myositis, and a previous European consensus

recommendation for JIIM, emphasise the need for a safe and effective exercise programme and attention to psychological wellbeing in addition to drug therapies for the management of JIIM[125, 133]. The Childhood Arthritis and Rheumatology research Alliance (CARRA) guideline provide Consensus Treatment Plans (CTPs) for different severity levels of juvenile myositis[134-136]. Treatments for JIIM have been well described in reviews elsewhere[85, 129, 137, 138]. A suggested treatment algorithm based on the best available current evidence and integrating current recommendations from the various guidelines is shown in FIG 3. The following section outlines drug and non-medication aspects of management of juvenile myositis.

Medication

A combination of high dose corticosteroid in combination with methotrexate (15-20mg/m^2, maximum 40mg/week) is the first-line induction treatment for most cases of JIIM[125, 133, 139]. Methotrexate is favoured over ciclosporin owing to having a more favourable adverse effect profile; however, both medications, when used with prednisolone, were superior to prednisolone alone in a multi-centre randomised trial of 139 patients with new-onset JDM [140]. Clinicians have the choice of oral prednisolone (1-2mg/kg/day with ceiling doses applied, typically capping at 60mg/day) or intravenous methylprednisolone (10-30mg/kg/day, maximum of 1g/day)[125, 133, 134, 139]. Intravenous administration might result in an increased therapeutic effect and less toxicity compared with oral corticosteroid and should be considered especially when there are concerns about gastrointestinal absorption[125, 133]. Intravenous methylprednisolone might have the additional benefit of reducing skin disease more rapidly than oral prednisolone[141].

Evidence is lacking to determine the best second-line treatment when the combination of corticosteroids and methotrexate does not adequately control disease or patients are intolerant to methotrexate. Head-to-head comparison studies are needed. In the absence of current evidence, CARRA have developed a series of consensus treatment plans to limit treatment variation among patients and enable comparative effectiveness studies from registry data[134-136, 142]. Some evidence, in the form of case series involving small to moderate numbers of patients, supports the use of mycophenolate mofetil (MMF) for the treatment of skin or muscle disease [143-146]. Evidence for the use of azathioprine comes from historical studies that included small numbers of patients, and although this drug can be used as an adjunctive treatment, it has become less favoured over the last two decades for the treatment of IIM in paediatric practice[147, 148]. Some evidence is available on the use of tacrolimus to treat JIIM but is limited by the small number of patients involved[149-151]. Adult data suggest that tacrolimus or ciclosporin alongside corticosteroids should be considered for patients with myositis-associated ILD, and although these data are often extrapolated to JIIM, insufficient data is available to form evidence-based recommendations for this complication in childhood-onset disease[133]. Date from case series of adult and paediatric patients suggest that cyclophosphamide or rituximab could be considered when ILD is present and should be used early,

potentially as part of an induction regime[133]. Although no standardised treatment guidelines are available on the management of ILD in adult patients with IIM, a summary of evidence and treatment approach has been presented in a review and, in the absence of evidence in JIIM, might provide useful guidance in the treatment approaches for childhood-onset disease[152]. In this review, the authors suggests that corticosteroids are used as the initial treatment for acute disease followed by MMF or azathioprine as first-line steroid-sparing agents. Tacrolimus is suggested as an appropriate second-line steroid sparing agent for patients with disease that is refractory to MMF or azathioprine, or for select patients with severe disease. Cyclophosphamide is proposed as a third-line steroid sparing agent. IVIG or rituximab are advocated as appropriate adjunctive agents in combination with traditional steroid-sparing agents for patients with refractory disease[152].

Intravenous immunoglobulin (IVIG) might be a helpful adjunct for severe or refractory skin disease, muscle inflammation or dysphagia[133]. In a randomised placebo controlled 16-week trial of IVIG in adult patients with dermatomyositis (the ProDERM trial), a higher proportion of patients in the IVIG treatment group reached the primary outcome of total improvement score (a composite measure of disease activity) of at least 20 (indicating at least minimal improvement) than in the placebo control group ($p<0.001$)[153] . Although evidence in adult-onset disease includes randomised trials, evidence in JIIM is mostly limited to cohort studies or case series[154-159]. Interpreting observational evidence is challenging owing to the use of concomitant therapies, the variable doses or treatment courses of IVIG used and the small numbers of patients involved. In one notable study, the researchers applied bias reduction methods to assess the efficacy of IVIG in a retrospective cohort of 78 patients with JDM, demonstrating that IVIG was efficacious in controlling severe or refractory disease, particularly in those patients who had steroid-resistant disease[158] . Other immunomodulating drugs have also been reported to improve symptoms of dysphagia or improve objective measures of swallowing function[133]. Cyclophosphamide tends to be reserved for more severe or refractory disease in view of the toxicity of this drug, but might be considered in cases of major organ involvement, including ILD or ulcerative skin disease[125, 133, 157, 158, 160, 161]. Despite lack of evidence from randomized controlled trials, the use of IVIG or cyclophosphamide is supported by case reports, case series and analysis by marginal structural modelling (MSM)[157-160].

Evidence related to the treatment of skin manifestations in JIIM is limited, but IVIG or rituximab can be used to treat skin manifestations refractory to corticosteroid and DMARDs [133, 157, 158]. In the ProDERM trial, IVIG was efficacious in improving skin disease activity in patients with adult-onset dermatomyositis, as measured by the modified Cutaneous Dermatomyositis Disease Severity and Activity Index (CDASI)[153]. Despite the relative lack of evidence for use of hydroxychloroquine in JIIM, limited to case series with small numbers of patients, this drug is often used as an adjunctive treatment for skin disease and arthritis[162-164].

519 Hydroxychloroquine is included in the CARRA Consensus Treatment Plan for skin predominant disease[142].
520 However, in a prospective study of 184 children with JDM treated at a single children's hospital, although
521 hydroxychloroquine was often administered to those patients with higher skin activity scores, the drug did
522 not lead to any statistically significant improvement in skin rash by the end of the observation period[141].
523 Topical tacrolimus (0.1%) or topical corticosteroids might help localised skin disease, particularly for
524 symptomatic redness or itching[125].
525
526 The use of biologics in JIIM has been summarized elsewhere in a systematic review[165]. Rituximab treatment
527 for refractory muscle or skin disease is supported by one randomised controlled trial and various case series
528 or cohort studies [107, 166-170]. In the Rituximab in Myositis (RIM) randomised controlled trial, despite failure to
529 meet the primary or secondary endpoints, 83% of the patients met the definition of improvement[107]. Data
530 were reported in aggregate but post-hoc analyses suggested that patients with JIIM were more likely to
531 respond to treatment than those patients with adult-onset myositis[133, 166]. The presence of anti-Mi2
532 antibodies, anti-synthetase antibodies or other undefined autoantibodies were other predictors of a
533 beneficial response, but anti-Mi2 antibodies and anti-synthetase antibodies are less common in JIIM than
534 in adult disease [165, 166, 168]. In this trial, rituximab treatment also led to improvement in cutaneous disease
535 [168]. Evidence in adult-onset myositis (that is, data from retrospective and prospective studies rather than
536 randomised controlled trial data) suggests that rituximab might be helpful in IIM-related ILD, but more data
537 are needed in JIIM[64, 133, 152].
538
539 Data from case series and cohort studies suggest that TNF blockade by infliximab or adalimumab can be
540 helpful for refractory muscle or skin disease, including calcinosis [165, 171-175]. In an open-label 12-week trial of
541 the TNF inhibitor etanercept, the drug showed no appreciable benefit in nine patients with refractory
542 JDM[174], whereas etanercept had a steroid-sparing effect in a randomised double-blind placebo controlled
543 52-week trial involving 16 patients with adult-onset IIM [176]. In rare instances, TNF inhibitors have been
544 reported to induce myositis or cause disease flares in adult patients with IIM [177, 178]. Although TNF inhibitors,
545 particularly adalimumab or infliximab, might be helpful in some patients with JIIM, evidence from a systemic
546 review suggest that treatment with these drugs does not lead to complete remission and better treatments
547 are needed [165]. Abatacept has demonstrated efficacy in a randomised controlled trial in adult onset
548 myositis[179] and in an open label therapeutic trial in JIIM[180]. Abatacept might be helpful for the treatment of
549 resistant disease, including calcinosis[179, 181, 182].
550
551 JAK–STAT inhibitors (often now known as JAKi) target the interferon pathway and show clear promise in the
552 treatment of IIM-related muscle, skin and lung disease[7, 64, 183]. A number of reports have highlighted the
553 potential safety and efficacy of JAKi (including tofacitinib and baricitinib) in treatment-resistant adult

myositis [184], [7]. In JIIM, JAKi (including baricitinib, tofacitinib and ruxolitinib) have shown promise in various case reports and case series, predominantly involving patients with refractory muscle or skin disease that is unresponsive to alternative immunosuppressive treatment(s)[8-10, 185-187] . These studies have been carefully reviewed in a systematic review elsewhere which describes 48 publications reporting 145 unique patients (including 61 cases of JIIM) with refractory disease at baseline and demonstrated that treatment with JAKi led to improvement in a wide range of manifestations including skin, muscle and ILD.[7]. As well as providing evidence on the clinical efficacy of JAKi, these studies suggest that JAK inhibitors can modulate the disease at an immunopathogenic level, as demonstrated by the downregulation of interferon biomarkers, the type I interferon signature and STAT1 phosphorylation in T cells and monocytes to similar levels as that in healthy individuals[8-11, 186]. These encouraging results suggest that JAK inhibition could be an effective, targeted treatment for JDM, and highlight the importance of confirming these findings in clinical trials [7, 183, 188].

An important challenge in JIIM is the treatment of calcinosis. Some evidence is available on the use of DMARDs, medications that affect calcium and phosphorus metabolism, mechanical therapies and adjunctive therapies in the treatment of calcinosis in JIIM, as reviewed elsewhere[189-191]. However, the available evidence is limited and largely based on case reports or case series, cohort studies or limited controlled studies. A major unmet need exists for an improved understanding of calcinosis pathogenesis, for standardised tools to measure calcinosis and for efficacious treatment of this burdensome complication[189, 190]. Consensus guidelines advocate for early aggressive treatment at disease onset to decrease the long-term risk of calcinosis, as well as consideration of an early increase in treatment of ongoing disease activity and intensifying immunosuppressive therapy in the presence of calcinosis[125, 133]. Other than associations with some MSAs, as described above, evidence on risk factors for calcinosis is limited, but a single centre retrospective study of 172 patients identified nailfold capillary abnormalities at baseline as a risk factor for calcinosis in univariate and multivariate analysis[192]. Some data are available on the histopathological and chemical composition of calcinosis, genetic and inflammatory markers in IIM-associated calcinosis and potential biomarkers of this complication, which have been reviewed in further detail elsewhere[193].

Exercise

Cardiorespiratory fitness can be impaired in patients with JIIM during both inactive and active disease and in patient with both monocyclic and polycyclic disease courses owing to factors such as cardiovascular deconditioning and reduced thoracic compliance[194-198]. Studies, including a randomised controlled trial in children and adolescents with JDM, have demonstrated the safety and efficacy of exercise training programmes, including the positive effects of these programmes on health-related quality of life[199-201].

Hence, the management of JIIM should include a safe and appropriate exercise programme that is led and monitored by a specialist physiotherapist and/or occupational therapist[125, 133].

Some data is available on the efficacy of interventions to reduce fatigue in paediatric conditions such as JIIM, including land or aquatic-based exercise, medications and psychological interventions, which have been evaluated in a systematic review elsewhere[202]. Efficacy of current interventions to reduce fatigue could not be established due to insufficient evidence. Fatigue is multi-dimensional and is not necessarily always correlated with disease activity and is instead strongly associated with biological, lifestyle, psychological and social factors[202]. Further multidimensional intervention studies are needed to identify the best management of this troublesome symptom.

Psychological support

JIIM has a notable impact on the emotional health of young people and their families[203, 204] Mental health issues, most commonly anxiety and depression, are reported frequently by children and young people with JIIM[204, 205]. Psychological wellbeing, psychiatric comorbidities and health-related quality of life should be assessed using age-appropriate tools[133]. Access to mental health provision, ideally embedded within paediatric rheumatology services so that young people feel that counsellors understand their disease, is paramount[204-206]. Factors that impact negatively on the health-related quality of life of patients, including pain, muscle weakness, functional impairment or physical disability, poor sleep and fatigue, should be managed appropriately[25, 133, 207, 208].

Assessment of disease activity and treatment response

Disease activity should be measured in a quantifiable way in both clinical practice and clinical research studies to determine changes in disease activity over time and response to treatment. Tools to measure disease activity have been comprehensively reviewed by others[129, 209]. The International Myositis and Clinical Studies (IMACS) group and Paediatric Rheumatology International Trials Organisation (PRINTO) have developed core sets to measure disease activity and damage, predominantly for use in research studies or clinical trials[129, 209]. The ability to robustly define response to therapy is crucial for conducting clinical trials and has been addressed by the development of ACR–EULAR response criteria[210, 211]. To define the optimal set of items collected in clinical practice to enable entry into research registries and comparison of data over time, an international collaboration has defined a consensus core dataset that is in use by several major registry studies[15, 212-214]. Consensus recommendations advise the routine use of measures such as the manual muscle testing in eight muscle groups (MMT-8) tool and the childhood myositis assessment scale (CMAS) to assess muscle strength and function[125]. Age-specific considerations need to be taken into account when using tools that measure muscle strength, function and quality of life[133]. For example, for the CMAS,

results for head-lift, leg lift and sit up manoeuvres are dependent on the age of the patient and very young children should not be expected to achieve a score of 52, even when disease is inactive[215, 216]. A shortened version of the MMT-8 tool that tests four (MMT-4) or six (MMT-6) muscle groups and a hybrid version that includes all 8 items of the MMT-8 tool and 3 items from the CMAS have demonstrated good measurement properties and might be more suitable than MMT-8 or CMAS for routine clinical use[217, 218]. More work is needed to define and reach consensus on the optimal tools for assessment of skin disease activity and measurement of quality of life in JDM[129, 214]. Several tools are currently available including the cutaneous assessment tool (CAT), disease activity score (DAS) and myositis intention to treat activity index (MITAX), each of which correlate with the physicians skin visual analogue scale (VAS)[219]; furthermore, the cutaneous disease area and severity index (CDASI) has been extensively used in studies of adult dermatomyositis and might be equally valuable for use in JDM[129, 209, 220].

The importance of patient reported outcome measures in outcome assessment within trials and in the clinic is becoming increasingly recognised. A study that included patients with JDM suggested that three tools from the patient reported outcomes measurement information system (PROMIS) are an improvement over the previously widely-used childhood health assessment questionnaire (CHAQ) for capturing patient reported outcomes [221]. PROMIS tools can be administered as fixed short forms or via computerised adaptive testing, the latter of which results in less pronounced floor and/or ceiling effects than fixed short forms[222].

Conclusions

Our understanding and management of juvenile onset myositis has changed considerably in the past two decades, but numerous challenges remain (Box 1) and much work is still needed. A deeper appreciation of the underlying mechanisms that initiate and perpetuate inflammation of the blood vessels, muscles, skin and other organs, and how inflammatory mechanisms intersect with other aetiological pathways in JIIM, is needed. New insights are becoming available from studies at a single cell level of gene expression, function and metabolic profiles. Further studies into the mechanisms of important patient-reported symptoms, such as fatigue, are also much needed. A vital aim is so ensure that novel data on underlying mechanisms are shared collaboratively and made accessible to drive the design of biomarker studies and enable validation studies and meta-analyses. The highly collaborative nature of myositis research, both basic and clinical, has enabled major progress thus far, and will support such platforms through which to generate evidence for new treatments, despite the rarity of JIIM (Box 1).

This strongly collaborative community, across paediatric, adolescent and adult myositis research is reflected in the first 'age-inclusive' trial in myositis (the RIM trial)[107]; such a design enables faster results for children and young people, rather than waiting for a 'child specific' trial for drugs that have been granted a licence

in adults. Progress has also been made using longitudinal observational data to support so called 'trial in silico ' analyses[223]; this approach will become more possible through widespread use of an agreed common clinical dataset[214], which is embedded in clinical care and large research registries[15, 212, 213]. Translation of this core dataset for use in adolescent and adult care could facilitate evidence generation on long-term outcomes, which is currently lacking. Current long-term outcome data clearly indicate increased risks of cardiovascular or pulmonary disease in patients with IIMs compared with the general population. In the future, the integration of biomarker and pathogenesis data with long-term outcome data of those treated in the modern era will be critical for informing our patients and their families about comorbidities, outcomes and the chances of sustained remission.

Ultimately, a combination of better understanding of disease mechanisms, biomarkers that accurately track disease activity, including subclinical disease, and definitions of outcomes that include the patient perspective will be needed to deliver a personalised approach to managing myositis in children, young people and the adults they become.

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Acknowledgements

The authors would like to thank the members of the UK JDM Cohort and Biomarker Study (JDCBS) and the patients and families who contribute to it. The JDCBS is currently funded by grants from the Great Ormond Street Children's Charity, Cure JM, Myositis UK, Versus Arthritis and Remission Charity.

Competing interests

All authors declare that the UK JDM Cohort and Biomarker Study (JDCBS) is currently funded by grants from the Great Ormond Street Hospital (GOSH) Children's Charity, the National Institute for Health Research (NIHR) Biomedical Research Centre at GOSH, Cure JM, Myositis UK, Versus Arthritis and Remission Charity. L.R.W. declares that she is a consultant for Pfizer Inc (with consulting fees going wholly to the University College London). The other authors all declare no competing interests. The other authors all declare no competing interests.

Contributions

All authors researched data for the article, contributed substantially to discussion of the content, wrote the article and reviewed and/or edited the manuscript before submission.

Key points

- Juvenile idiopathic inflammatory myopathies (JIIMs) can differ from adult-onset myopathies in terms of the pathogenesis, autoantibody profile, disease phenotype and treatment response, but these difference need to be further defined
- The myositis-specific autoantibody (MSA) and myositis-associated autoantibody (MAA) profile of a patient can help determine the disease phenotype and likely outcome of the patient, including their risk of disease complications
- More research is needed to provide an evidence-based approach to the management of refractory JIIM, major organ involvement and myositis-related complications or comorbidities.
- New therapeutic targets have been strongly implicated in JIIM by pathogenesis studies, most notably, the type I interferon pathway; clinical trials are urgently needed but innovative designs are required.
- Further research is needed to identify specific dysregulated pathways in addition to type I interferon and how these pathways relate to the MSA or MAA clinical subtypes.
- A better understanding is needed of the long-term outcomes of patients with JIIM into adulthood, including the factors that are important to patients and their families

Related links

- Juvenile dermatomyositis cohort biomarker study and repository: https://juveniledermatomyositis.org.uk/study-tools/
- British Society for Rheumatology: https://rheumatology.org.uk
- Childhood Arthritis and Rheumatology Research Alliance: https://carragroup.org
- International Myositis Assessment & Clinical Studies Group: https://www.niehs.nig.gov/research/resoures/imacs
- The International Myositis Society: https://imyos.org
- Paediatric Rheumatology International Trials Organisation: https://printo.it

LEGENDS

Fig. 1 | Factors implicated in the pathogenesis of juvenile myositis

The pathogenesis of juvenile idiopathic inflammatory myopathy (JIIM) involves a complex interplay between genetic and environmental factors, leading to immunological, vascular and metabolic dysfunction. a) Environmental triggers of JIIM might include ultraviolet (UV) radiation, pollution and microbial infections. b) Genetic loci in the MHC and non-MHC regions are implicated in disease susceptibility and development. c) Type I interferon signalling is thought to have a central role in the pathological changes seen in various tissues. d) Immune dysregulation within in the skin, muscle and blood vessels, as well as in other tissues (not shown), is thought to contribute to disease. Within the muscle, the over expression of MHC proteins, a hallmark feature thought to be driven by interferons, contributes to endoplasmic reticulum (ER) stress leading to an inflammatory cascade via the nuclear factor kappa B (NFκB) pathway. Autoreactive B cells are present, as demonstrated by the production of myositis specific antibodies (MSA), and regulatory B (B_{reg}) have a pro-inflammatory phenotype (including producing elevated levels of IL-6). Circulating inflammatory mediators include Galectin-9 and CXCL10, which correlate with disease activity. Abnormalities in the small blood vessels are reflected by a high number of circulating endothelial cells, which correlates with disease activity; muscle capillary loss and complement deposition on capillaries also frequently occur. T cell dysfunction includes a skewing of the T cell compartment towards a T helper 17 (T_H17) cell phenotype, including within the follicular T (T_{FH}) cell population Both neutrophil extracellular trap (NET) formation and mitochondria dysfunction occur in JDM and might be part of a pathological loop that drives interferon production. Overall, the pathogenesis of JIIM involves a complex interplay between innate and adaptive immunity that affects muscle, skin, and vascular tissues to drive ongoing inflammation and tissue damage.

Fig. 2 | Clinical features and autoantibody profile in JIIM indicative of severe disease and/or need for treatment escalation. Owing to the rarity and heterogeneity of juvenile idiopathy inflammatory myopathy (JIIM), children and young people should be managed by a multi-disciplinary team in a specialist centre. To predict the severity of the disease and the potential need for treatment escalation, many factors are considered, as illustrated, including the presence or absence of severe muscle weakness, dysphagia, ulcerative skin disease or major organ involvement. The myositis-specific autoantibody (MSA) and/or myositis-associated autoantibody (MAA) profile might predict the risk of JIIM-related complications, including major organ involvement. Some features associated with specific MSAs or MAAs are shown, but specific complications are not exclusive to patients with these MSA–MAA profiles and not all patients with a particular MSA–MAA profile will demonstrate these complications. ILD, interstitial lung disease; GI, gastrointestinal; MMT-8, manual muscle testing in eight muscle groups; CMAS, childhood myositis assessment scale.

Fig. 3 | Treatment algorithm for JIIM on the basis of current available evidence.

A treatment algorithm for juvenile idiopathic inflammatory myopathy (JIIM) shown is that is based on evidence-informed consensus recommendations in UK and Europe[125, 133]. Treatments need to be individualised and include consideration of the patient age, preferences for oral or parenteral administration of medications, severity of disease and response to treatment. No single approach will be right for every patient and clinicians need to use best judgement on the basis of evidence available. In most cases, with the exception of randomised controlled trials evaluating methotrexate versus ciclosporin, rituximab or exercise in myositis, evidence is limited to case series or cohort studies. More research is needed to compare the efficacy of second-line or third-line treatment options and determine the best treatment approach for myositis-related complications such as ILD or calcinosis. More evidence is also needed to determine the best treatment for refractory disease, which can be defined as myositis that responds inadequately to at least two immunosuppressant or immunomodulatory drugs given in their full dose for a minimum of 3 months, hindering weaning of corticosteroid. Patients with JIIM should have regular reviews that include measurement of muscle strength, assessment of skin disease and extra-muscular manifestations. Adherence to medication should be checked if patients fail to respond to medication as expected. Treatment should be escalated if patients fail to respond adequately to treatment or are intolerant to the treatment. Exercise therapy and psychological support are important aspects to the management of JIIM in addition to medication.

IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; JAK, janus kinase

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1419 Table 1: Main clinical associations of myositis-specific and myositis-associated autoantibodies in children

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Auto-antibody	Frequency in JIIM	Main clinical associations	Specific issues related to antibody testing[a]	Key differences between childhood-onset and adult-onset disease	Refs
Anti-TIF1 antibodies	17–35%; highest prevalence in white populations and younger age groups [Median age of onset 7 yrs (3.8-10.4 yrs) in a North American cohort.	Worse cutaneous disease than other JIIM MSA subgroups, including cutaneous ulceration, photosensitivity and lipodystrophy. Some patients can have an amyopathic phenotype, or extensive erythema, including the V sign, shawl sign or holster sign, and periungual nailfold changes. Disease often chronic or polycyclic. Patients more likely to receive second or third line treatment than other JIIM autoantibody subtypes.	ELISA more sensitive than immuno-precipitation (IP) for anti-TIF1. Poor sensitivity with line immune-assays (LIA) or dot immune-assays (DIA) means false negative or false positive results can occur. Levels of anti-TIF1 antibodies reported to decrease with rituximab therapy and correlate with disease activity IIF pattern (on HEp2 cells): Nuclear fine speckled.	Association with malignancy in adult-onset IIM not seen in children. Anti-TIF1 antibodies are more common in childhood-onset disease than adult-onset disease. Children less likely to develop the V-sign than adults.	4, 5, 41, 63, 64, 129-131, 138, 224
Anti-NXP2 (initially called anti-MJ) antibodies	15–25%; highest prevalence in white populations and younger age groups [Median age of onset of 5.8 yrs (3.9-10.2 years) in a	Main features include calcinosis, prominent muscle weakness, dysphagia and dysphonia. Some patients have joint contractures. Disease course often severe, with persistent disease activity and remission at 2 years less likely	Sensitivity of LIA is suboptimal for anti-NXP2. If measured by IP, additional testing required, such as Western blot (immunoblot), to differentiate between anti-NXP2 and anti-MDA5 antibodies, which produce similar IP patterns (the presence of a 140kDa	Association with cancer in adult-onset IIM not seen in children. Anti-NXP2 antibodies are more common in childhood-onset disease than in adult-onset disease	4, 5, 41, 63, 64, 129, 131, 138

	North American cohort.	compared to other JIIM autoantibody sub-types.	band). Commercial ELISA not yet available for anti-NXP2. IIF pattern: Nuclear fine speckled or multiple dots.		
Anti-MDA5 antibodies	6–38%; Highest prevalence in Japanese cohorts. Median age of onset of 8.7 yrs (6-13.2 years) in a North American cohort.	Mild muscle disease, including clinically amyopathic phenotype (more common in adult-onset disease than childhood-onset disease). Patients might have constitutional symptoms and weight loss. Higher risk of cutaneous and oral ulceration, arthritis and ILD than other JIIM autoantibody subtypes and increased risk of rapidly progressive ILD (particularly Japanese, Korean and Chinese patients). Disease frequently requires intensive immunosuppressive therapy.	Can be detected by IP-immunoblot or ELISA Levels of anti-MDA5 antibodies, as quantified by ELISA, reported to correlate with risk of ILD and cutaneous disease in Japanese cohorts and might be helpful in determining response to treatment. IIF pattern: Negative or cytoplasmic.	Similar disease phenotype.	4, 50, 57, 63, 64, 129, 131, 138
Anti-Mi2 antibodies	4–10%; Highest prevalence in patients of Hispanic ethnicity and older age groups [median age of onset of	Known as 'Classical JDM'. Marked muscle disease in the early disease stages that responds well to conventional treatment. -Higher chance of being off treatment after 2 years than other JIIM autoantibody subtypes	Reliably detected by LIA and IP. Anti-Mi2 antibodies reported to decrease following rituximab therapy and correlate with disease activity. IIF pattern: Nuclear fine speckled.	Similar phenotype across ages but children less likely to have a V-sign or shawl sign and have an increased risk of muscle weakness and dysphagia compared with	4, 5, 41, 63, 64, 129-131, 138, 224, 225

	10.7 yrs (range 6.7-14.9 yrs) in a North American cohort.	Can follow a polycyclic course. Associated with pharyngeal weakness or dysphagia, oedema and cutaneous features. Decreased risk of ILD and lower mortality than that of other JIIM autoantibody subtypes.		adults. Anti-Mi2 antibodies associated with cancer in adults, but not in children	
Anti-SAE antibodies	0.3–9.1%	Predominant cutaneous involvement. Amyopathic at onset. Might be associated with dysphagia. ILD has been reported in a single case report of an anti-SAE antibody-positive patients with JDM.	Identified by IP in most cases but comparison to a reference serum sample might be necessary for confirmation. IIF pattern: Nuclear fine speckled	Anti-SAE antibody is rarely detected in JIIM and hence the clinical phenotype and response to treatment is difficult to define. Anti-SAE antibody association with malignancy reported for adult-onset disease only.	[4, 41, 64, 129, 131, 138]
Anti-aminoacyl-tRNA synthetase (anti-ARS) antibodies, also known as anti-synthetase antibodies	2–5%; Highest prevalence in patients of Black ethnicity and older age of onset [median age of onset of 12.3 yrs (range 7.1-15 yrs) in a North American cohort.	Anti-ARS antibodies are associated with an increased likelihood of having a juvenile connective tissue myopathy phenotype. Patients anti-ARS antibodies frequently have a chronic continuous disease course and a need for additional immunosuppressive therapy. Antibody-positivity is also	LIA, IP or ELISA commonly used to detect anti-Jo1 antibodies. Line blot might not detect rare anti-ARS antibodies (for example, anti-OJ antibodies). Anti-Jo1 antibodies reported to decrease following rituximab therapy and correlate with disease activity IIF pattern: Negative or cytoplasmic.	Similar phenotype in juvenile and adult-onset disease although this subtype is much less frequent in childhood than in adulthood. Important features such as Raynaud phenomenon, mechanics hands and ILD seem to	[4, 5, 38, 64, 129, 131, 138, 224, 225]

		associated with high rates of ILD and increased mortality. Some patients might present to respiratory services with isolated ILD. Anti-synthetase syndrome describes combination of symptoms including myositis, ILD, Raynaud phenomenon, fever, arthritis and mechanics hands. The presence of anti-ARS antibodies can be associated with lipodystrophy. Different anti-ARS antibodies are associated with muscle predominant or skin predominant disease. Non-Jo-1 anti-ARS antibodies (e.g., anti-PL7 and anti-PL12) are associated with severe lung involvement.		occur at a lower frequency in childhood-onset disease than in adult-onset disease.	
Anti-SRP antibodies	1.6-4%; highest prevalence in Black populations and older age of onset; [median age of onset of 14.6 yrs (range 11.6-16.1 yrs)	IMNM, characterized by necrosis of muscle fibres with no or minimal inflammation on muscle biopsy. Patients can have high serum levels of creatinine kinase. Disease ~~is~~ often chronic (and treatment-resistant) and might benefit from treatment with rituximab	Often screened for by ELISA or LIA. Commercially available kits only test for the 54KDa subunit of SRP, hence false negative results can occur. Anti-SRP antibody levels are unchanged following rituximab therapy but correlate with levels of	Less common in childhood-onset disease than in adult-onset disease, but similar phenotype. Children might be less likely to have palpitations and are less likely to	[4, 5, 41, 64, 66, 68, 129, 131, 138, 224]

	in a North American cohort.	in addition to corticosteroids and disease modifying drugs, as well as physiotherapy. Patients with anti-SRP antibodies more likely have severe muscle weakness and extra-muscular manifestations than patients with anti-HMGCR antibodies. Anti-SRP antibodies are also associated with risk of dysphagia, joint contractures, ILD, or cardiac involvement. Non-specific cutaneous features can be seen (<10%).	muscle enzymes. IIF pattern: Cytoplasmic.	die than adult-onset anti-SRP antibody-positive IIM. Children have been reported to have increased distal weakness, muscle atrophy and falling episodes than adult-onset disease. Younger age groups may have a worse prognosis but mortality lower in childhood-onset disease compared with adult-onset.	
Anti-HMGCR antibodies	1.1%	IMNM, characterized by severe proximal muscle weakness, joint contractures, high serum creatinine kinase levels and muscle fiber necrosis with no or minimal inflammation on muscle biopsy. Patients with these antibodies often have a poor response to medication and a chronic disease course. Patients also more likely to receive second or third line therapy, including biologics, than other JIIM autoantibody subgroups but might not benefit	Usually screened for using ELISAs but false positives can occur with this assay (with a false positive rate of up to 0.7%). A positive result can be confirmed by IP. IIF pattern: Negative.	Less common in JIIIM than in adult-onset IIM but similar phenotype to adult-onset disease. Unlike disease in adults, disease in children is not associated with previous exposure to statin medication. Children and young adults (typically statin naïve) can have a worse prognosis	4, 5, 37, 41, 64, 66, 68-70, 129, 138, 226

		from rituximab therapy. IVIG can be beneficial for some patients. Physiotherapy is important as part of treatment regime. Patients with anti-HMGCR antibodies are less likely to have extra-muscular manifestations than patients with anti-SRP antibodies, but can have cutaneous disease. Anti-HMGCR antibodies are also associated with dysphagia.		than older age groups. Cutaneous disease reported more frequently in childhood-onset disease than in adult-onset disease.	
Anti-Ro52 antibodies	6–14%	The presence of anti-Ro-52 antibodies is associated with a myositis overlap phenotype, as well as an increased risk of ILD. The disease course is frequently chronic, with an increased number of medications and a lower chance of remission than with other JIIM autoantibody subtypes	Detected by ELISA and not IP. IIF pattern: Negative or cytoplasmic.	Less common in JIIM than in adult-onset IIM.	[64, 74, 129, 138]
Anti-PM/Scl antibodies	3–5%	Anti-PM/Scl antibodies are associated with overlap syndromes, most commonly overall with scleroderma. These antibodies are also associated with an increased risk of	Can be screened for using IIF and identified by different immunoassays. IIF pattern: Nucleolar, homogenous.	Less common in JIIM than in adult-onset IIM.	[4, 41, 64, 131, 138]

		calcinosis and lipoatrophy.			
Anti-U1-RNP antibodies	4–5.6%	Anti-U1-RNP antibodies are associated with polymyositis or a polymyositis overlap phenotype, scleroderma overlap and mixed connective tissue disease. These antibodies are also detected in patients with SLE. Muscle weakness is less likely in patients with anti-U1-RNP antibodies than in other JIIM autoantibody subgroups.	Might not be detected by commercial line blots (such as the EUROIMMUN line blot). Test for these antibodies using an antinuclear antibody line blot. IIF pattern: Nuclear speckled.	Less common in JIIM than in adult-onset IIM.	[4, 64, 131, 138]
Other myositis-associated autoantibodies	Anti-Ku, anti-Scl70, anti Ro-60, anti U3-RNP and anti-mitochondrial antibodies are more likely to be identified in older patients than younger patients and are associated with polymyositis, a polymyositis phenotype or scleroderma overlap.			Less common in JIIM than in adult-onset IIM.	[4, 64, 131, 138]

IIF, Indirect immunofluorescence [relates to immunofluorescence pattern on Hep2 cells in this context]; IIM; idiopathic inflammatory myopathy; ILD, interstitial lung disease; IMNM, immune mediated necrotising myopathy; JIIM, juvenile idiopathic inflammatory myopathy; MAA, myositis-associated antibodies; MSA, myositis-specific antibodies; SLE, systemic lupus erythematosus; LIA, line immune-assay; DIA, dot immune assay.

[a] A clinician's guide to MSA and MAA testing is available at the Juvenile Dermatomyositis Cohort Biomarker Study (JDCBS) and Repository.

[b] Anti-aminoacyl-tRNA synthetase antibodies include anti-Jo1 (anti-histidyl-tRNA synthetase), anti-PL7 (anti-threonyl-tRNA synthetase), anti-PL12 (anti-alanyl-tRNA synthetase), anti-EJ (anti-glycyl tRNA synthetase), anti-KS (anti-asparagyl-tRNA synthetase), anti-OJ (anti-isoleucyl-tRNA synthetase), anti-Ha (anti-tyrosyl-tRNA synthetase) and anti-Zo (anti-phenylalanyl-tRNA synthetase) antibodies.

1436 Table 2 | Studies demonstrating the type I interferon signature in JIIM

1437

Methods	Sample	Findings	Refs
Type I interferon protein			
Single-molecule array (Simoa) IFNα assay (digital ELISA technology)	Plasma and serum	Higher IFNα levels in patients with JDM (n=43) than in healthy individuals (n=20).	[103]
Interferon-stimulated gene transcripts and interferon scores			
qPCR	Whole blood (PAXgene tubes)	75% of 101 measurements in 59 patients with JIIM showed upregulation of ISG transcripts (*IFI27, IFI44L, IFIT1, ISG15, RSAD2* and *SIGLEC1)* above a pre-determined cut-off point .	[227]
NanoString Technologies™	Whole blood (PAXgene tubes)	A 28-gene ISG-score in patients with active JDM (n=57) correlated with muscle and joint disease.	[79]
RNAseq	PBMCs	Patients with new-onset JDM (n=21) had a higher ISG score (5 gene score: *MX1, IFI44, IFI44L, LY6E, IFIT3*) than patients with muscular dystrophy (n=7), healthy individuals (n=6 children, n=9 adults), or patients with JDM in remission (n=10) .	[228]
qPCR	Muscle	IFNα and/or IFNβ-inducible genes, IFNγ and IFNγ-inducible gene expression were higher in patients with JDM (n=27) than in patients with muscular dystrophy (n=24) or healthy individuals (n=4) .	[105]
Microarray qPCR	Skin	Skin lesions in patients with JDM had a strong interferon signature (including the expression of *CXCL10, CXCL9* and *IFI44L*) and the interferon signalling pathway	[114]

		was identified as an important canonical pathway	
RNAseq	PBMCs	PBMCs from untreated patients with JDM (n=11) had a strong type I interferon signature that was associated with disease activity scores.	[104]
	Muscle and skin	The transcriptomic profile of the muscle and skin of patients with JDM (n=4) included enrichment in the type I interferon signature	
RNAseq	B cells	Enrichment of the IFNα response pathway. Upregulation of TLR7 and IRF7 expresion in patients with JDM prior to treatment (n=10) compared with in patients with JDM following treatment (n=9).	[113]
Gene expression meta-analysis	Muscle and skin	Meta-analyses was performed on six publicly available microarray data sets for muscle (that included data from 71 patients with dermatomyositis and 36 controls and skin (from 77 patients with dermatomyositis and 22 controls). 94 genes were upregulated in JDM across both tissues, which included genes involved in type I and II interferon signalling and MHC class I pathways.	[229]
Interferon-driven proteins			
Multiplex immunoassay	Plasma	The expression of galectin-9, CXCL10 (also known as IP-10) and TNF receptor 2 (TNFR2) were increased in patients with active JDM (n=25) compared with healthy children (n=14) or children with nonautoimmune muscle disease (n=8)	[230]
	Serum	Galectin-9 and CXCL10 outperformed creatinine kinase in distinguishing	[231]

		between patients with active JDM with patients with JDM in remission, and these markers were sensitive and reliable markers for disease activity in JDM in 3 cohorts (n=120).	
	Serum	Analysis of 2 independent JDM cohorts (n=30, n=29) showed that JDM patients with high serum levels of CXCL9, CXCL10, TNFR2 and galectin-9 may be more likely to respond poorly to standard treatment than those with low levels and these chemokines correlated with disease activity and measures of vasculopathy	[232]
Multiarray detection system, ELISA	Serum	The expression of IFNα, IFNλ1 and IFNγ, MCP1, CXCL10 (IP10), TNFR2 and Galectin-9 were higher in patients with JDM (n=90) than in healthy control subjects (n=70). The expression of IFNλ1, MCP1 , IP-10 and galectin were increased in active disease compared with disease in remission, and these markers correlated with disease activity and measures of vasculopathy	[6]
Flow cytometry	Blood monocytes	Patients with new-onset JDM (n=21) and a high expresion of Siglec-1 were at increased risk of intensification therapy 3 months after diagnosis compared with healthy controls (n= 6 children, n=9 adults) and JDM follow-up (n=10)].	[228]
Immunohisto-chemistry	Muscle	The expression of myxovirus-resistance protein (MxA) was identified in >50% of samples from patients with JDM and was associated with greater muscle weakness	[102]

1438

ELISA: enzyme-linked immunosorbent assay; MSA, myositis-specific autoantibodies; ISG, interferon-stimulated gene; JDM: juvenile dermatomyositis; JIIIM, juvenile idiopathic inflammatory myopathy; PBMCs: peripheral blood mononuclear cells; qPCR: quantitative polymerase chain reaction; MHC: major histocompatibility complex.

Box 1: Challenges in the management of JIIM

JIIM as a group are rare conditions

Challenges

- Randomised controlled trials (RCTs) are challenging
- Within JIIM, rare sub-phenotypes or patients with severe disease are often excluded from clinical trials
- Children and adolescents are often excluded from clinical trials of idiopathic inflammatory myopathies

Mitigated by:

- International collaboration through PRINTO and IMACS has led to successful RCTs and other important research studies
- All clinical trials are advised to have a paediatric investigational protocol

Evidence is lacking

[bH2] Challenges

- Head-to-head comparison studies are needed to determine the best second-line treatment for JIIM
- A paucity of evidence-based data is available for patients with refractory disease.
- Evidence is lacking to determine the best treatments for skin disease, calcinosis or disease involving vital organs.
- An unmet need exists to better understand the pathogenesis of calcinosis and define standardized assessment tools.
- The division of trials into 'adult' and paediatric trials- artificially dichotomises the evidence base]

Mitigated by:

- Evaluation of disease course through practice and registry data, including the use of CARRA-developed consensus treatment plans.
- Collection of data and biospecimens within disease registries and the development of a consensus core dataset to enable uniform data collection and comparison across groups
- Development of evidence informed consensus guidelines, such as SHARE and/or BSR guidance on the management of IIM

- Collaborative working of the PReS JDM working party, CARRA JDM working group, IMACS and iMYoS.

Lost opportunity for long-term data collection

Challenges:

- Continuity of long-term data in research registries might be lost when young people transition to adult services
- Ensuring continuity of data across the life course is crucial to better understand the long-term risks of disease, such as the impact of disease on cardiovascular risk, fertility, mental health, education level and employment.

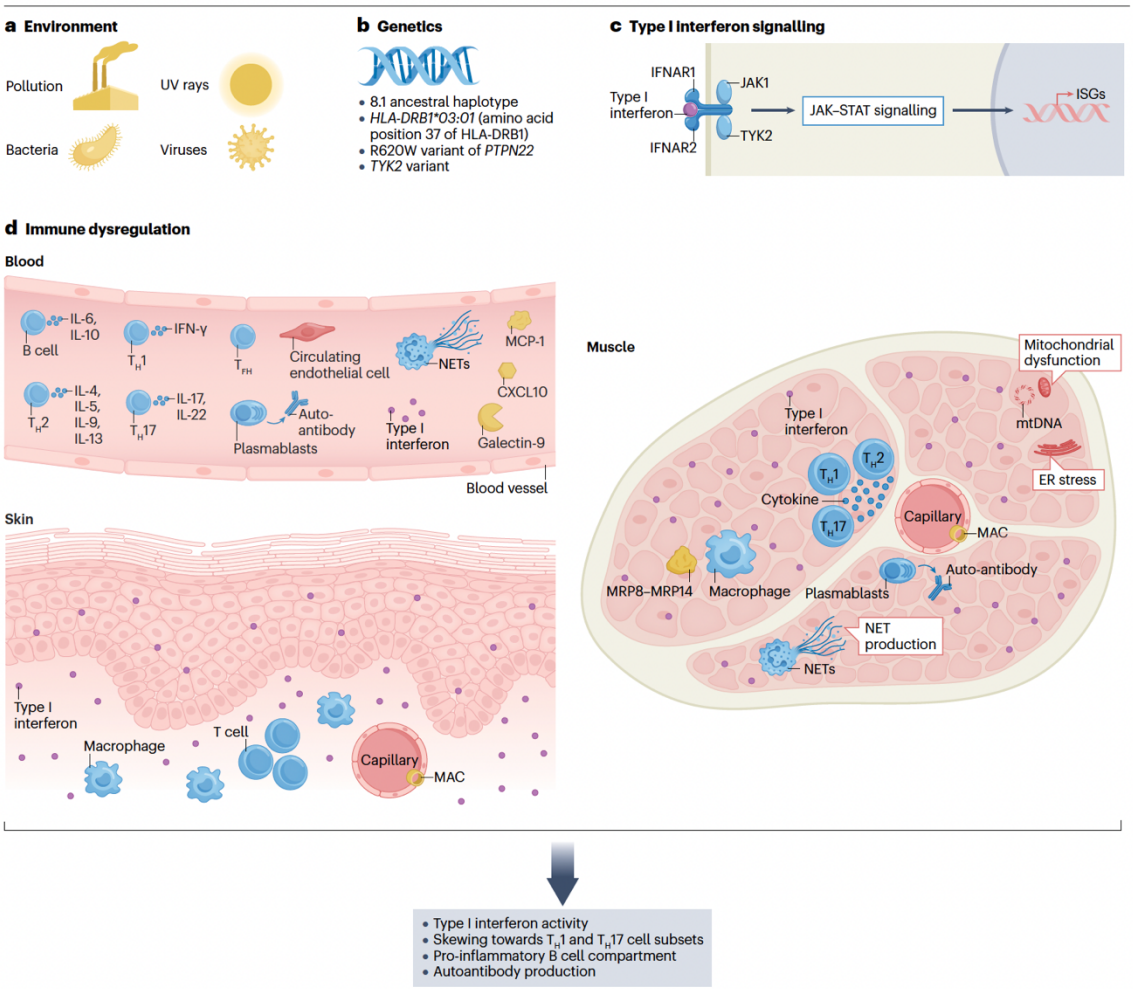
[bH2] Mitigated by:

- Research registries such as MYONET (formally Euromyositis) and some country-specific registries enable data collection across paediatric and adult registries.
- Attempts have been made to develop strategies to enable data sharing (while protecting data ownership and governance) but need to be developed further.

ToC statement

This Review provides an overview on the clinical features and subtypes, pathophysiology and management of juvenile idiopathic inflammatory myopathies, including updates in our understanding of this heterogenous group of diseases that might change clinical practice in the near future.

Figure 1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Pollution
UV rays
Bacteria
Viruses
b Genetics
• 8.1 ancestral haplotype
• HLA-DRB1*03:01 (amino acid position 37 of HLA-DRB1)
• R620W variant of PTPN22
• TYK2 variant
c Type I interferon signalling
IFNAR1
Type I interferon
IFNAR2
JAK1
TYK2
JAK–STAT signalling
ISGs
d Immune dysregulation
Blood
B cell
IL-6, IL-10
IFN-γ
TH1
TFH
Circulating endothelial cell
NETs
MCP-1
CXCL10
TH2
IL-4, IL-5, IL-9, IL-13
TH17
IL-17, IL-22
Auto-antibody
Plasmablasts
Type I interferon
Galectin-9
Blood vessel
Skin
Type I interferon
Macrophage
T cell
Capillary
MAC
Muscle
Mitochondrial dysfunction
mtDNA
ER stress
Type I interferon
TH1
TH2
Cytokine
TH17
Capillary
MAC
Auto-antibody
MRP8–MRP14
Macrophage
Plasmablasts
NET production
NETs
• Type I interferon activity
• Skewing towards TH1 and TH17 cell subsets
• Pro-inflammatory B cell compartment
• Autoantibody production

Figure 2

Fig 2

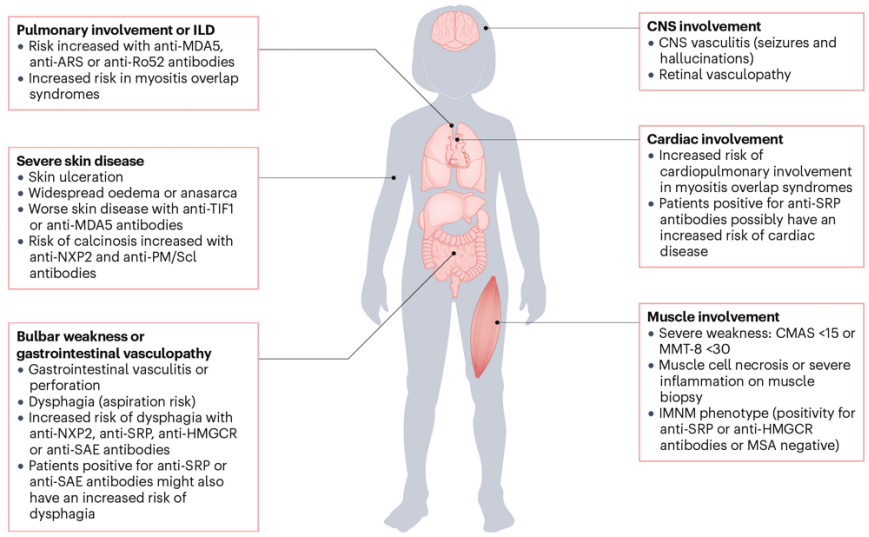

Figure 3

Fig 3