Review

Juvenile dermatomyositis. Where are we now?

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ABSTRACT
Juvenile onset idiopathic inflammatory myopathy (IIM) has many similarities and distinct differences from adult-onset disease. This review will focus on recent developments in understanding and treatment of juvenile dermatomyositis (JDM), the most common disease sub-type of IIM in childhood. JDM is a systemic immune mediated vasculopathy, increasingly recognised as a group of distinct phenotypes with variable presentation and outlook. This overview will describe long-term outlook and disease course including health-related quality of life and emerging treatments.

Introduction
The childhood idiopathic inflammatory myopathies (IIM) are rare, serious chronic conditions of childhood, of which the most common is juvenile dermatomyositis (JDM). Recent reviews have comprehensively described clinical serological and morphological features of JDM as well as potential triggers for JDM, disease pathogenesis and immunopathogenic implications of vasculopathy, signs of systemic disease activity based on affected tissues or organs, diagnostic testing, biomarkers and monitoring tools, and treatment options (1-9). This overview will focus on long-term outcome and emerging treatments and provide an update on recent evidence for biomarkers which may track disease activity or be used to stratify patients. JDM has a pronounced type I interferon signature and new treatment approaches will take advantage of this, but more evidence is needed for the safety and efficacy profiles. With increased knowledge of pathogenesis, work is ongoing to define and validate reliable biomarkers that can be used in clinical practice to robustly monitor response to treatment.

Classification of IIM
Diagnostic criteria for IIM published by Bohan and Peter over 40 years ago are still commonly used, despite attempts to update these criteria to incorporate immunological/ histopathological advances and recognising that several of the criteria rely on diagnostic tests not routinely performed in children by all centres (10-12). The sensitivity and specificity of the Bohan and Peter criteria against appropriate disease confounders had not been validated until recently, when performance of existing criteria was tested in adult and juvenile onset IIM as part of the International Myositis Classification Criteria Project (IMCCP) (13). Using a data-driven approach new EULAR/ACR classification criteria have been developed and provide a score and probability of having IIM which can be used in clinical and research settings (13). These criteria were found to be superior to most previous criteria in sensitivity, specificity and diagnostic accuracy of IIM, performing well in juvenile onset and adult-onset disease. However, due to limited number of JPM cases, a data-driven distinction from JDM was not possible and further work is needed, with more juvenile onset cases other than JDM and inclusion of recently identified myositis specific antibodies in classification.

Long-term outlook of JDM
Numerous cohort studies evaluate long-term outcome of JDM but need to be interpreted with caution. They capture a large time frame of patient inclusion or recruitment, when practice at that time may not reflect current treatment regimes. Many studies come from hospital cohorts or specialist centres and thus may be biased towards more severe disease, although methodology tries to minimise this. Different

methods are used to capture long-term outcome, varying from telephone interviews with patients to face-to-face evaluation using standardised assessment tools. A number of different assessment tools are applied, with discrepancy in definitions of disease course and activity. Data collection in research registries may stop when patients enter adult care and thus true long-term data may not be captured. Despite numerous caveats, these studies remain useful when predicting disease outcome or counselling patients and their families. Recent international efforts have led to an agreed consensus dataset to be applied across cohort studies and which can be used in routine clinical care(14). Efforts are ongoing to adopt this dataset across several large registries including Euromyositis, the new Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry for JDM and the UK Juvenile Dermatomyositis Cohort and Biomarker Study (JDCBS) (15-17). Once in place, this will greatly enhance the opportunity to collate registry data and define outcomes in larger numbers of patients in the modern treatment era.

Mortality
It is well documented that mortality rate improved with the introduction of corticosteroid as a treatment of IIM; from greater than 30% to 10% in the early corticosteroid era (18, 19). Some cohort studies have documented further improvements in mortality rate for IIM to below 4% (17, 20, 21), but worldwide, mortality is still reported as high as 5–8% (22-24).
A study specifically looking at mortality evaluated 405 patients; 329 with JDM, 30 with juvenile polymyositis (JPM), and 46 with juvenile connective tissue disease-associated myositis (JCTM) in North America, establishing mortality status using the Social Security Death Index (SSDI, searched 2011). A standardised mortality ratio (SMR) for JIIM was recorded as 14.4 [95% confidence interval 12.2, 16.5]. Risk of mortality was highest for JCTM (SMR 66.9), followed by JPM (SMR 30.7), then JDM (SMR 8.3), but the low numbers of patients with JPM/

JCTM in this study meant that confidence intervals were not calculated (25). Aside from disease subtype, one of the features most strongly associated with mortality was the presence of an aminoacyl-tRNA synthetase antibody. In multivariate analysis, illness severity at onset, older age at diagnosis, weight loss and delay to diagnosis were also found to be important predictors of mortality (25).

Disease course
As mortality rates have decreased, the focus has shifted towards long-term morbidity and functional outcomes. Traditionally, disease course has been described a monocyclic (defined as no signs of disease activity 2 years post diagnosis), chronic persistent (disease activity for greater than 2 years post diagnosis), or polycyclic (recurrence of disease activity (≥1 flare) after definite remission for more than 6 months) (20, 26, 27). In 2000, Huber *et al*. questioned whether some patients with polycyclic disease were truly in remission or whether they did in fact have subclinical disease (thus representing a chronic continuous course) when sensitive tests such as MRI were used (26). This theory is backed up in a recent work by Papadopoulou *et al*. who showed that in a subgroup of patients considered clinically to have inactive disease, circulating endothelial cells were elevated, suggesting subclinical endothelial injury and disease activity not captured by laboratory parameters used in clinical practice (28).
Studies from Hungary and Western India have demonstrated a higher proportion of patients with monocyclic disease course (59-73%) compared to a persistent or polycyclic course (23, 29, 30). However, other studies from Europe and North America show increased chance (57-93%) of patients having a persistent (polycyclic or chronic) disease course (20, 27, 31-34). It is possible that the lack of standardised definitions of remission or disease inactivity contributed to variability in these studies. To this end, the Paediatric Rheumatology International Trials Organization (PRINTO) used a data-driven approach to define

criteria for clinically inactive disease, published in 2013 (35). Whilst useful, these are highly weighted towards muscle parameters, with patients needing to achieve 3 out of 4 criteria including creatinine phosphokinase (CPK) ≤150, Childhood Myositis Assessment Scale (CMAS) ≥48/52, Manual Muscle Testing (MMT8) ≥78/80 or Physician Global Visual Analogue Scale (PhyGloVAS) ≤0.2. When tested in a large UK cohort (1114 discrete episodes in 258 patients), a group of patients with ongoing activity in extra-muscular domains (mainly skin) would have been classified incorrectly as inactive disease if these criteria were applied. To avoid this, the authors suggested that the PRINTO criteria be modified so that PhyGloVAS was an essential criterion (36).

Assessing risk of ongoing disease activity
We do not yet have robust biomarkers or prediction models to be able to determine risk of ongoing disease activity in individual patients, but a number of factors can be considered that are associated with an increase chance of ongoing disease activity.

Myositis specific antibodies
Myositis specific antibodies (MSAs) can be helpful in predicting disease phenotype or associated risks. There are comprehensive reviews describing myositis antibodies, including differences in childhood and adult onset disease, and therefore details will not be repeated here (5, 37-42). In juvenile onset disease, the presence of TIF-1, anti-HMGCR, anti-SRP or anti-synthetase antibodies may suggest risk of a more severe, chronic or treatment resistant disease course (1, 39, 42). The presence of anti-MDA5 or anti-synthetase antibody is associated with increased risk of interstitial lung disease, as is the myositis associated antibody Ro52 (1, 42, 43). Anti-NXP2 increases risk of calcinosis across all age groups but children at a young age also have a high risk of calcinosis irrespective of autoantibody phenotype (44). The presence of Mi-2 autoantibody may suggest the probability of a milder and shorter disease course with low mortality (42).

Immunoprecipitation is considered the gold standard for detection of the majority of MSAs but it is only available at a limited number of specialist laboratories and is not correct in all instances (45). ELISA, line immunoassay and dot blots are more widely available but discrepancies in test results have been reported with different methods (45-49). As well as considering MSA results in the context of clinical phenotype, it is helpful for clinicians to be familiar with the immunofluorescent ANA pattern associated with MSAs. This allows them to be suspicious of a false positive result when staining patterns are inconsistent with the MSA result. Hep-2 immunofluorescent patterns corresponding to different autoantibody specificities are well described by Satoh *et al.* in a recent review (41).

Muscle biopsy
If a muscle biopsy is taken at time of diagnosis, the histological severity as measured by an internationally agreed scoring system, together with MSA result, can be used to aid prediction of outcomes in JDM (50, 51). Patients with Mi-2 autoantibody may be more likely to enter drug free remission despite severe histology on muscle biopsy, whereas those with anti-MDA5 autoantibody are less likely to come off treatment despite less severe changes on biopsy (51).

*Age at disease onset and
early disease course*
The age of a patient at onset of JDM may influence disease characteristics as shown in Figure 1 (21, 44, 52-55). Stringer *et al.* found that the presence of active rash (Gottron's) at three months, or nailfold capillary abnormalities and JDM rash at six months, were predictive of a longer time to disease remission (31). Sanner *et al.* found that evidence of disease damage within the first year of diagnosis predicted ongoing active disease in long-term follow-up (54). More recently, low nailfold capillary density has been linked to risk of smaller lung volumes, reduced gas diffusion and high resolution computed tomography (HRCT)-detected airway disease (56). Recently, a North American Registry of JDM patients (n=307) has been ex-
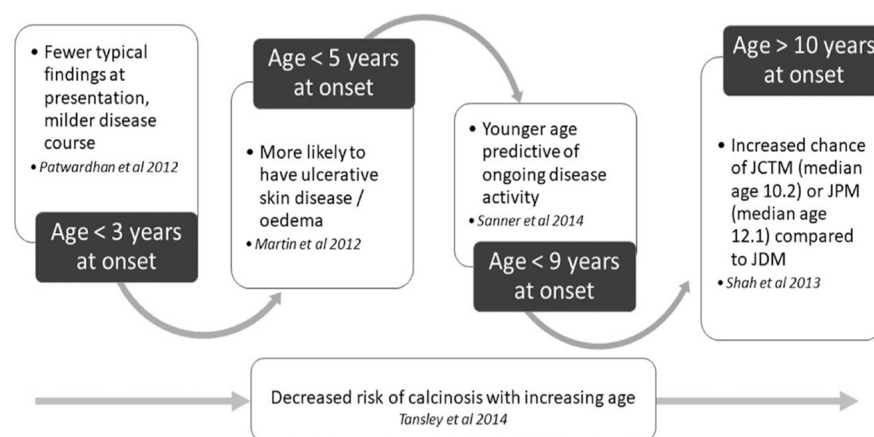

Fig. 1. Impact of age at onset on disease characteristics of JDM.
JCTM: juvenile connective tissue-disease associated myositis; JPM: juvenile polymyositis.

amined to establish factors associated with corticosteroid discontinuation, complete clinical response and remission. Overall, outcomes were favourable, with 191/307 patients achieving at least one of these outcomes. Probability of corticosteroid discontinuation was 56%, complete clinical response 38% and remission 30% by 60 months in 105 patients. The three outcomes were found to be interdependent and had a strong conditional probability. In multivariate analysis, medium time to complete clinical response was the strongest predictor of time to corticosteroid discontinuation. The presence of anti-TIF1 antibodies, and medication escalation within 12–24 months of treatment initiation was associated with longer time to remission (57).

Race and socioeconomic status
Ethnic minority races have been found to have increased risk of PM or JCTM compared to JDM (21). They are more likely to have anti-SRP auto-antibodies (associated with a JPM phenotype) and have been found to have significantly increased odds of cardiovascular and cerebrovascular comorbidities (42, 58). Analysis of subjects recruited to the CARRA Legacy Registry showed that minority subjects were more likely to have low family income and significantly worse scores on measures of disease activity, physical function and health related quality of life (59).

Predictive models
Longitudinal analytic methods have

been applied to cohorts in an attempt to identify hidden, or 'latent', subgroups of patients with similar trajectories of disease activity over time. This method was applied to 519 patients in the UK Juvenile Dermatomyositis Cohort and Biomarker Study (JDCBS). Based on Physician Global Assessment (PGA), two classes of patients were identified. Class 1 tended to improve over time whereas a smaller number of patients in class 2 tended to have more persistent disease, which was predicted by abnormal respiration, lipodystrophy and time since diagnosis. When applied to modified Disease Activity Score (DAS), three classes were identified; class 1 where DAS was high at baseline, but quickly improved, class 2 where DAS started high and remained high and class 3 where DAS was lower and improved quickly (60). Similar results were found in a Toronto cohort with smaller patient numbers (61).

**Disease damage and
long-term outcome**
Disease damage
Damage is common in JDM, but usually mild. Studies have reported percentages of patients with disease damage ranging from 60–95% when measured by the Myositis Damage Index (MDI) or Myositis Damage Score (MYODAM) Visual Analogue Scale (VAS) (20, 22-24, 27, 33, 34). Damage is most frequent in cutaneous, endocrine, muscular or skeletal domains (20, 22-24, 27, 33, 34). Disease duration is one of the most important predictors of damage (27,

33, 34, 62). Tsaltskan *et al.* identified that MDI score increased almost linearly for each year of disease, suggesting that organ damage may be ongoing throughout disease course (33). Rider *et al.* found that predictors of damage in children included functional disability, active disease duration, severity of disease at onset, global activity and certain illness features such as ulcerations (63). Sanner *et al.* found that damage was predicted by high disease activity and organ damage six months post-diagnosis (24).

Growth and puberty
A 2-year follow-up cohort study analysing anthropometric data from a prospective multinational PRINTO study on JDM (n=196) demonstrated that parent-adjusted height was significantly affected over time but catch-up growth was seen. At the final study visit, growth failure was seen in 20/97 (21%) female patients and 11/73 (15%) male patients. Delayed puberty was seen in 20/55 (36.4%) female patients and 11/31 (35.5%) of male patients. Children with recent onset of puberty during the active phase of treatment or previous growth failure had the highest risk of delayed pubertal development and further growth retardation (64).

Functional impairment and pain
Severe functional impairment, defined as a Childhood Health Assessment Score (CHAQ) of >1.0 or >1.5 (score range 0-3) in different studies, is unusual in JDM and reported at a frequency of 6.5-9.4% of patients (20, 26, 27). However, it is common to have a degree of functional impairment (reported in up to 41% of cases), particularly in females (20, 23, 24, 26, 27, 33). Pain is reported in 22-35% of patients with JDM, with increased reports of pain associated with higher CHAQ scores (20, 26).

Health-Related Quality of Life (HRQOL)
The impact of JDM on HRQOL is an important consideration which is often overlooked. Apaz *et al.* found that patients with JDM had poorer physical and psychosocial well-being compared to healthy controls, with physical dis-

ability being the most important determinant of HRQOL (65). These findings are supported by Tollisen *et al.* who equally identified a correlation between physical disability and worsening HRQOL, whilst also including disease activity and disease damage as having a strong correlation with reduced HRQOL (66). Ravelli *et al.* however found less marked HRQOL impairment with both the physical and psychosocial domains equally affected, with only a small fraction having significant decreased HRQOL (20). Families of patients with juvenile idiopathic inflammatory myositis rated quality of life over 18 other items, as the most important variable of high quality care (67). In a study by Livermore *et al.* uncertainty was a prominent feature for children and young people living with JDM and in a recent study by Fawole *et al.* youth with rheumatic disease including JDM had high rates of both clinical and self-diagnosed mental health problems, specifically anxiety and depression (68, 69). These studies provide a starting point for clinicians to consider HRQOL and impact of JDM, but clearly further studies are needed.

Impact of disease on lifestyle
A study by Boros *et al.* evaluated long-term outlook via a questionnaire survey sent to patients over 16 years of age whose details were held in the UK JDCBS. 84/190 (44%) questionnaires were returned. At an average time of 12.4 years since diagnosis, 58% of patients self-reported persistently active disease, which was also reflected in their documented use of medication. The study demonstrated a significant impact of disease on lifestyle, with 44% stating that disease affected their academic results. Patients aged >18 years of age were twice as likely to be unemployed compared to UK Office of National Statistics data and three times more likely to be living at home (70).

Cardiorespiratory fitness
A case controlled study from Norway of 45 patients with JDM aged 10.2–50.9 years of age with a mean disease duration of 20.8 years, demonstrated lower cardiorespiratory fitness (CRF) in pa-

tients compared to controls in both active and inactive disease states (71). A study of 36 patients in the Netherlands with a median age at diagnosis of 8.3 years of age, evaluated CRF on multiple occasions (average, five times) up to 10 years post diagnosis. Decreased CRF trajectories were seen in both monocyclic and polycyclic disease course and were predicted by younger age at disease onset, longer disease duration and higher prednisolone dose (72). A decline in CRF in the active phase of disease was followed by an initial improvement but then a plateau phase where there was no further increased in CRF (72). This is important in clinical practice as interventions have been shown to improve CRF (73, 74). These studies support the need for a safe and appropriate exercise programme led and monitored by a specialist physiotherapist / occupational therapist to improve QoL and function in JDM (75).

Cardiovascular risk
Cardiovascular disease is an important cause of mortality and morbidity in adult onset IIM (76). In contrast, in children, although cardiac abnormalities are frequent at disease onset, they are rarely serious and long-term damage in the cardiovascular domain is unusual relative to other domains (20, 24, 27, 33, 63, 77). However, a case-controlled study of 59 patients in Norway examined a median of 16.8 years post diagnosis showed evidence of subclinical cardiac dysfunction, not seen in controls (78). JDM patients have also been found to have increased metabolic abnormalities and atherosclerotic risk factors compared to age and sex-matched controls (58, 79, 80). Papadopoulou *et al.* have recently described increased arterial stiffness on pulse wave velocity in patients with JDM (28). All of these factors may lead to a greater long-term risk of cardiovascular or cerebrovascular disease.

Pathogenic mechanism and biomarkers
Although much of the literature addresses the role and underlying biology of type I interferon in JDM there are other pathogenic mechanisms and

biomarkers being explored. Biomarkers related to the type I interferon signature have been shown to track disease activity. These include serum galectin-9, CXCL10 and more recently , expression Siglec-1 on monocytes (81, 82). Work is ongoing to define which of these can accurately predict change in disease activity ahead of clinical symptoms of flare.

A recent cross-sectional study investigated markers of vasculopathy in JDM. The study included 90 JDM patients and 79 healthy controls. Analysis of circulating endothelial cells (CEC) showed an increase in all patients compared to controls (median 96 cells/ml [IQR; 40– 192] and 12 cells/ml [IQR; 8– 24], respectively; $p<0.0001$). Circulating microparticles (MPs), predominantly of platelet and endothelial origin, were significantly higher in JDM patients with active disease compared to controls (median 204.7×103/ml [IQR 87.9–412.6] and 44.3×103 /ml [IQR 15.0–249.1], respectively; $p<0.0001$). Additional data showed that there was increased plasma thrombin generation and increased arterial stiffness in JDM compared to controls. This study showed evidence of increased endothelial injury in JDM patients with active disease and demonstrated multiple measurable markers associated with this pathogenesis (28). Two recent pilot studies have used metabolomic and proteomic analysis to identify biomarkers of disease (83, 84). An exploratory study of ten JDM patients and nine healthy controls analysed the JDM serum metabolic profile. The results showed 1 of the 45 targeted acylcarnitines and 1 of the 15 targeted ceramides were significantly associated with JDM. This initial study could lead to exploring this profile in a larger cohort (83). A pilot study investigated serum proteome screening of 8 un-treated JDM patients compared to 12 healthy controls. The data showed of 1305 proteins, 202 were elevated and 49 decreased ($p<0.001$). New biomarkers identified included Il-22, angiopoetin-2 and IL-17B. These findings could prompt larger studies and further investigation into the roles of these proteins in JDM (84).

Auto-antibodies provide an important tool to assess the clinical manifestations of the disease. Novel auto-antibodies have been recently investigated in JDM. A recent longitudinal study in adult and juvenile dermatomyositis measured anti-mitochondrial autoantibody (AMA) presence in serum. The authors found that 1% (4 of 371) of children with JDM and healthy controls (1 of 92) had AMA detected by ELISA. All 4 JDM patients with AMA had severe disease at onset with falling episodes and 3 out of the 4 had dysphagia (85). Though the detection of AMA was shown to be very rare in JDM patient sera this study suggested that it may predict worse disease for these patients. Further investigation could explore other anti-mitochondrial bands detected in serum. Another recent study of the prevalence of anti-cN-1A antibodies in JDM found this antibody to be very rare in JDM, and not increased compared to controls (86). Further work is needed to define the targets of patients with a positive ANA in whom no defined MSA can be detected.

Treatments
Current treatments widely used in JDM are summarised in Table I and described by others in recent reviews (1, 3, 5-8). With the exception of two randomised controlled trials (RCTs) in JDM, all other evidence comes from cohort studies, case series or case reports. There is an unmet need for head-to-head comparisons of current treatments in addition to defining novel biologic targets for children with recalcitrant disease and complications such as calcinosis or interstitial lung disease.

Consensus recommendations for treatment have been published as part of an initiative to define optimal care for children with rheumatic diseases across Europe – the Single Hub and Access point for Paediatric Rheumatology in Europe (SHARE) (75, 140). These recommendations were derived by consensus informed by a systematic literature review (75). Evidence based guidelines have also been written for the British Society of Rheumatology on management of paediatric, adolescent and adult-onset IIM (https://www.rheumatology.org.uk/practice-quality/guide-lines/). CARRA have published a series of Consensus Treatment Plans (CTPs) with the aim of limiting treatment variation and allowing researchers to develop comparative effectiveness studies (104, 141-143). A pilot study has demonstrated that comparing CTPs is feasible but larger patient numbers are needed (16). Uniform data collection across registries will allow analysis of larger patient numbers including those with rare complications or disease phenotypes (14).

Novel therapies
JDM is a disease which has a defined type I interferon signature in both protein and gene expression, demonstrated in blood, muscle and skin (2, 144). JAK kinase inhibitors, which block production of type-1 interferons show great promise in JDM but evidence is currently limited to case series or case reports (133-137, 139, 145-147). Based on this evidence in a total of 49 patients (48 with refractory disease, 1 new onset), JAK kinase inhibitors appear to demonstrate efficacy for skin and muscle disease (144). The role of interferon in JDM including therapeutic interventions and comparison to interferonopathies has recently been reviewed (138, 144). Monoclonal antibodies targeting IFN-α such as sifalimumab or anifrolumab may be beneficial in IIM and have been evaluated in early phase studies in adult onset disease, but not yet tested in children or young people (148, 149).

Abatacept has been shown to be effective in adult-onset myositis in a prospective delayed start study (150) but evidence in juvenile-onset disease is limited to case reports where it has shown benefit in recalcitrant calcinosis (128, 130, 131). A trial of abatacept in refractory JDM (clinicaltrials.gov/ct2/show/NCT02594735) is yet to be reported.

Other biologics such as basiliximab (monoclonal antibody targeting alpha sub-unit of IL-2 receptor), apremilast (phosphodiesterase 4 inhibitor), gevokizumab (humanised IgG2 monoclonal antibody against IL-1β), anakinra (IL-1 blocker), alemtuzumab (targeting CD52), and eculizumab (anti-terminal complement components) may show promise but have not been used in

Table I. Drug treatments used in JDM.

Drug	Mechanism of action	Level of evidence	Comments
Methotrexate	Folate antagonist, inhibits key enzymes involved in the biosynthesis of purines and pyrimidines, with effects on T cell proliferation, and inflammatory function.	Randomised controlled trial (RCT), cohort studies & case series (62, 87-91).	First line treatment in most cases of JDM in combination with corticosteroid.
Ciclosporin	Calcineurin inhibitor, exerts an immuno-modulatory action, by binding to cyclophilin interfering with T cell activation and inhibiting production of IL-2.	RCT, case series (62,92-96).	Efficacy in RCT in combination with corticosteroid, but methotrexate favoured due to safety profile.
Mycophenolate mofetil (MMF)	Converted to mycophenolic acid (MPA) which selectively inhibits *de novo* purine metabolism.	Case series - moderate patient numbers, case report (97-99).	Treatment option to improve muscle or skin disease and may be used when inefficacy / intolerance to methotrexate.
Hydroxychloroquine	Mechanism of action in IIM not fully defined but thought to interfere with lysosomal activity and autophagy, resulting in inhibition of cytokine production.	Cohort study - large patient numbers, case series - small patient numbers (100-103)	Adjunctive treatment for skin disease & arthritis, included in CARRA CTPs for skin predominant disease(104).
Azathioprine	Inhibits purine synthesis, causing immunosuppression.	Case series, cohort studies - small patient numbers (105, 106).	Limited evidence; less frequently used in JDM than other DMARDS.
Tacrolimus	Calcineurin inhibitor, suppresses IL-2 dependent T cell activation.	Case series, case reports - small patient numbers (107-109).	Evidence limited in JDM. More evidence in adult onset IIM, including IIM associated ILD.
Rituximab	Chimeric monoclonal antibody directed against the human CD20 receptor which acts by depleting circulating B cells.	RCT, cohort studies, case series (110-115).	Treatment option for refractory myositis or skin disease. Failed to meet primary / secondary endpoints in RCT but 83% of patients met definition of improvement; patients with juvenile onset disease more likely to respond.
Cyclophosphamide	Alkylating agent that interferes with DNA replication.	Case series case reports, cohort studies - moderate patient numbers (116-118).	Treatment option for severe disease (such as major organ involvement / extensive ulcerative skin disease).
Intravenous Immuno-globulin (IVIG)	Exact mechanism of action unclear – acts as an immunomodulatory drug, reduces autoantibody production and causes cytokine suppression or blockage.	Cohort studies, case series - moderate patient numbers (118–121).	Treatment option for severe or refractory muscle inflammation, dysphagia or skin disease.
Infliximab	Chimeric human-murine Immunoglobulin G1 monoclonal antibody against tumour necrosis factor (TNF).	Cohort studies, case series, case reports - moderate patient numbers (122-124).	Used off label for refractory JDM, showing efficacy in muscle & skin disease; use may be limited by country specific regulations (75,125).
Adalimumab	Fully human recombinant immuno-globulin G1 monoclonal antibody that binds and neutralises soluble and membrane-bound TNF.	Cohort studies, case series - moderate patient numbers (122,124).	Used off label in refractory JDM, showing efficacy in muscle & skin disease; use may be limited by country specific regulations.
Etanercept	Recombinant human soluble TNF receptor linked to an Fc portion of immunoglobulin, binding TNF-alpha and TNF-beta.	Cohort study - small patient numbers (126,127).	Mixed reports of efficacy - infliximab/ adalimumab preferable TNF blockers for IIM.
Abatacept	Fully human soluble fusion protein of cytotoxic T lymphocyte-associated antigen 4 and Fc portion of immuno-globulin, blocks binding of CD28 on T cells with anti-inflammatory effect.	Case series, case reports - small patient numbers (128-131).	Can be considered in resistant disease, including calcinosis.
Tocilizumab	Fully human monoclonal antibody that competitively inhibits the binding of IL-6 to its receptor (IL-6R)	Case report (132) of myositis overlap syndrome (limited efficacy).	Limited evidence in adult/juvenile onset disease.
JAK kinase inhibitors	Inhibit JAK-STAT pathway, thereby inhibiting interferon signalling.	Case series, case reports - with increasing patient numbers (133-139).	Initial case reports/case series show promise for refractory disease including skin disease.

RCT: randomised controlled trial; DNA: deoxyribonucleic acid; CARRA: Childhood Arthritis and Rheumatology Research Alliance; CTP: consensus treatment plans; TNF: tumour necrosis factor; IIM: idiopathic inflammatory myopathy; IL: interleukin; ILD: interstitial lung disease.

JDM. Evidence in adult onset disease is limited but well described in recent reviews (148, 149, 151, 152).

Lenabasum is a synthetic non-immunosuppressive, selective cannabinoid receptor type-2 agonist that has shown safety and efficacy in adult-onset refractory skin-predominant dermatomyositis (153). It is being studied in a phase 3 randomised placebo-controlled study in adult-onset myositis (clinicaltrials.gov/ct2/show/NCT03813160) but has not yet been used in juvenile onset disease.

Conclusions

A key unmet need in JDM is to be able to predict disease course in individual patients, to be able to target those with more severe disease that need more intensive treatment but minimising treatment in those with milder disease to avoid damage through adverse effects of medication. Holistic care is essential in this complex condition, including therapy led exercise programmes as well as practical and psychological support from clinical nurse specialists and psychologists. Targeted treatment approaches are needed along with head-to-head comparisons to better determine management of resistant disease, as well as complications such as calcinosis and interstitial lung disease. Advances in disease pathogenesis may help with this quest to determine therapeutic targets.

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