Title: **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.

Key Words:

- Juvenile dermatomyositis
- Idiopathic inflammatory myopathy
- Long-term outlook
- Pathogenesis
- Health related quality of life

Text:

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 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 examined 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 disability 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 patients 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 1** 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/guidelines/). 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 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 thought 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.

Abbreviations

IIM	Idiopathic Inflammatory Myopathy

JDM	Juvenile Dermatomyositis
JPM	Juvenile Polymyositis
JCTM	Juvenile connective tissue disease-associated myositis
SSDI	Social Security Death Index
SMR	Standardised mortality ratio
MRI	Magnetic resonance imaging
PRINTO	Paediatric Rheumatology International Trials Organization
CPK	Creatinine phosphokinase
CMAS	Childhood Myositis Assessment Scale
MMT8	Manual Muscle Testing
PhyGloVAS	Physician Global Visual analogue Scale
MSA	Myositis Specific Antibodies
HRCT	High resolution computed tomography
CARRA	Childhood Arthritis and Rheumatology Research Alliance
JDCBS	Juvenile Dermatomyositis Cohort and Biomarker Study
PGA	Physician Global Assessment
DAS	Disease Activity Score
MDI	Myositis Damage Index
MYODAM	Myositis Damage Score
VAS	Visual Analogue Scale
CHAQ	Childhood Health Assessment Questionnaire
HRQOL	Health related quality of life
CRF	Cardiorespiratory Fitness
RCT	Randomised Controlled Trial
SHARE	Single Hub and Access point for Paediatric Rheumatology in Europe
CTP	Consensus Treatment Plan

Conflict of interests:

- Liza McCann– none
- Meredyth Wilkinson – was supported by fellowships from Cure JM (Early Career Investigator Award GOSH042019), NIHR Great Ormond Street Hospital (GOSH) Biomedical Research Centre (BRC) (NIHR GOSH BRC 18IR33).
- Polly Livermore – Clinical Academic Lead Role is funded by NIHR Biomedical Research Centre at Great Ormond Street Hospital London UK.
- Lucy Wedderburn - none for this work.

Funding statement:

LRW , PL and MW are supported by the NIHR Biomedical research Centre at GOSH; MW is funded by a Fellowship from CureJM and NIHR and LRWN is also supported by grants from Versus Arthritis (20164, 21593)

Acknowledgements:

The authors would like to thank the families and patients who have generously agreed to be part of the UK JDCBS (https://juveniledermatomyositis.org.uk), and all the contributors to the Juvenile Dermatomyositis Research Group.

References:

1. Pachman LM, Nolan BE, DeRanieri D, Khojah AM. Juvenile Dermatomyositis: New Clues to Diagnosis and Therapy. Curr Treat Options Rheumatol. 2021 Mar;7(1):39–62. PMID:34354904
2. Wienke J, Deakin CT, Wedderburn LR, van Wijk F, van Royen-Kerkhof A. Systemic and Tissue Inflammation in Juvenile Dermatomyositis: From Pathogenesis to the Quest for Monitoring Tools. Front Immunol. 2018 Dec 18;9:2951. PMID: 30619311
3. Wu JQ, Lu MP, Reed AM. Juvenile dermatomyositis: advances in clinical presentation, myositis-specific antibodies and treatment. World Journal of Pediatrics. 2020 Feb; 16(1):31–43. PMID:31556011
4. Papadopoulou C, McCann LJ. The vasculopathy of juvenile dermatomyositis. Front Pediatr. 2018 Oct 9;6: 284. PMID: 30356795
5. Kim H, Huber AM, Kim S. Updates on Juvenile Dermatomyositis from the Last Decade: Classification to Outcomes. Rheum Dis Clin North Am. 2021 Nov;47(4):669-690 PMID: 34635298
6. Wu Q, Wedderburn LR, McCann LJ. Juvenile dermatomyositis: Latest advances. Best Pract Res Clin Rheumatol. 2017;31(4):535-557. PMID: 29773272
7. Papadopoulou C, Wedderburn LR. Treatment of Juvenile Dermatomyositis: An Update. Pediatric Drugs. Springer International Publishing; 2017; 19:(5)423–34. PMID: 28550457
8. Pachman LM, Khojah AM. Advances in Juvenile Dermatomyositis: Myositis Specific Antibodies Aid in Understanding Disease Heterogeneity. J Pediatr. 2018 Apr;195:16–27. PMID: 29576174

9. Li D, Tansley SL. Juvenile Dermatomyositis—Clinical Phenotypes. Current Rheumatology Reports. Springer; 2019; 21(12):74. PMID: 31828535

10. Sultan SM, Isenberg DA. Re-classifying myositis. Rheumatology (Oxford, England). 2010; 49(5):831-3. PMID: 20040531

11. Brown VE, Pilkington CA, Feldman BM, Davidson JE. An international consensus survey of the diagnostic criteria for juvenile dermatomyositis (JDM). Rheumatology. 2006;45(8):990–3. PMID: 16467366

12. Lundberg IE, Miller FW, Tjärnlund A, Bottai M. Diagnosis and classification of idiopathic inflammatory myopathies. Journal of Internal Medicine. 2016; 280:39–51. PMID: 27320359

13. Lundberg IE, Tjärnlund A, Bottai M, Werth VP, Pilkington C, de Visser M, et al. 2017 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Adult and Juvenile Idiopathic Inflammatory Myopathies and Their Major Subgroups. Arthritis Rheumatol. 2017 Dec;76(12):1955-1964. PMID: 29079590

14. McCann LJ, Pilkington CA, Huber AM, Ravelli A, Appelbe D, Kirkham JJ, et al. Development of a consensus core dataset in juvenile dermatomyositis for clinical use to inform research. Ann Rheum Dis. 2018;77(2):241–50. PMID: 29084729

15. Lilleker JB, Vencovsky J, Wang G, Wedderburn LR, Diederichsen LP, Schmidt J, et al. The EuroMyositis registry: an international collaborative tool to facilitate myositis research. Ann Rheum Dis. 2018;77(1):30-39. PMID: 28855174

16. Liu K, Tomlinson G, Reed AM, Huber AM, Saarela O, Bout-Tabaku SM, et al. Pilot study of the juvenile dermatomyositis consensus treatment plans: A

CARRA registry study. J Rheumatol. 2021 Jan 1;48(1):114–22. PMID: 32238513

17. Martin N, Krol P, Smith S, Murray K, Pilkington CA, Davidson JE, et al. A national registry for juvenile dermatomyositis and other paediatric idiopathic inflammatory myopathies: 10 years' experience; the Juvenile Dermatomyositis National (UK and Ireland) Cohort Biomarker Study and Repository for Idiopathic Inflammatory Myopat. Rheumatology. 2011;50(1):137–45. PMID: 20823094
18. Bitnum S, Daeschner Jr. CW, Travis LB, Dodge WF, Hopps HC. Dermatomyositis. J Pediatr. 1964;64:101-31. PMID: 14100086
19. Huber A, Feldman BM, Address M. Long-term Outcomes in Juvenile Dermatomyositis: How Did We Get Here and Where Are We Going? Curr Rheumatol Rep. 2005;7(6):441–6. PMID: 16303103
20. Ravelli A, Trail L, Ferrari C, Ruperto N, Pistorio A, Pilkington C, et al. Long-term outcome and prognostic factors of juvenile dermatomyositis: A multinational, multicenter study of 490 patients. Arthritis Care Res (Hoboken). 2010;62(1):63–72. PMID: 20191492
21. Shah M, Mamyrova G, Targoff IN, Huber AM, Malley JD, Rice MM, et al. The clinical phenotypes of the juvenile idiopathic inflammatory myopathies. Med (United States). 2013;92(1):25–41. PMID: 23263716
22. Okong'o LO, Esser M, Wilmshurst J, Scott C. Characteristics and outcome of children with juvenile dermatomyositis in Cape Town: A cross-sectional study. Pediatr Rheumatol. 2016 Nov 11;14(1):60. PMID: 27835954
23. Sharma A, Gupta A, Rawat A, Suri D, Singh S. Long-term outcome in children with juvenile dermatomyositis: A single-center study from north

India. Int J Rheum Dis. 2020 Mar 1;23(3):392–6. PMID: 31793219

24. Sanner H, Gran JT, Sjaastad I, Flatø B. Cumulative organ damage and prognostic factors in juvenile dermatomyositis: A cross-sectional study median 16.8 years after symptom onset. Rheumatology (Oxford). 2009;48(12):1541–7. PMID: 19776224

25. Huber AM, Mamyrova G, Lachenbruch PA, Lee JA, Katz JD, Targoff IN, et al. Early illness features associated with mortality in the juvenile idiopathic inflammatory myopathies. Arthritis Care Res (Hoboken). 2014;66(5):732–40. PMID: 24151254

26. Huber AM, Lang B, LeBlanc CM, Birdi N, Bolaria RK, Malleson P, et al. Medium- and long-term functional outcomes in a multicenter cohort of children with juvenile dermatomyositis. Arthritis Rheum. 2000;43(3):541–9. PMID: 10728746

27. Mathiesen P, Hegaard H, Herlin T, Zak M, Pedersen FK, Nielsen S. Long-term outcome in patients with juvenile dermatomyositis: A cross-sectional follow-up study. Scand J Rheumatol. 2012;41(1):50–8. PMID: 22044089

28. Papadopoulou C, Hong Y, Krol P, Al Obaidi M, Pilkington C, Wedderburn LR, et al. The Vasculopathy of Juvenile Dermatomyositis: Endothelial Injury, Hypercoagulability, and Increased Arterial Stiffness. Arthritis Rheumatol. 2021; Jul;73(7):1253-1266. PMID: 33393715

29. Chickermane PR, Mankad D, Khubchandani RP, Darshan K. Disease Patterns of Juvenile Dermatomyositis From Western India. Indian Pediatrics. 2013; 50(10):961-963. PMID: 23798628

30. Constantin T, Ponyi a, Orbán I, Molnár K, Dérfalvi B, Dicso F, et al. National registry of patients with juvenile idiopathic inflammatory myopathies in

Hungary--clinical characteristics and disease course of 44 patients with juvenile dermatomyositis. Autoimmunity. 2006;39(3):223–32. PMID: 16769656

31. Stringer E, Singh-Grewal D, Feldman BM. Predicting the course of juvenile dermatomyositis: Significance of early clinical and laboratory features. Arthritis Rheum. 2008;58(11):3585–92. PMID: 18975314

32. Habers GEA, Huber AM, Mamyrova G, Targoff IN, O'Hanlon TP, Adams S, et al. Association of Myositis Autoantibodies, Clinical Features, and Environmental Exposures at Illness Onset with Disease Course in Juvenile Myositis. Arthritis Rheumatol. 2016;68(3):761–8. PMID: 26474155.

Tsaltskan V, Aldous A, Serafi S, Yakovleva A, Sami H, Mamyrova G, et al. Long-term outcomes in Juvenile Myositis patients. Semin Arthritis Rheum. 2020;50(1):149–55. PMID: 3130346

34. Rider LG, Lachenbruch PA, Monroe JB, Ravelli A, Cabalar I, Feldman BM, et al. Damage Extent and Predictors in Adult and Juvenile Dermatomyositis and Polymyositis as Determined With the Myositis Damage Index. Arthritis Rheum. 2009;60(11):3425–35. PMID: 19877055

35. Lazarevic D, Pistorio A, Palmisani E, Miettunen P, Ravelli A, Pilkington C, et al. The PRINTO criteria for clinically inactive disease in juvenile dermatomyositis. Ann Rheum Dis. 2013 May;72(5):686–93. PMID: 22736096

36. Almeida B, Campanilho-Marques R, Arnold K, Pilkington CA, Wedderburn LR, Nistala K. Analysis of Published Criteria for Clinically Inactive Disease in a Large Juvenile Dermatomyositis Cohort Shows That Skin Disease Is Underestimated. Arthritis Rheumatol. 2015;67(9):2495–502. PMID:

25988361

37. Tansley S, Wedderburn LR. Comparing and contrasting clinical and serological features of juvenile and adult-onset myositis: implications for pathogenesis and outcomes. Curr Opin Rheumatol. 2015;27(6):601–7. PMID: 26352731

38. Tansley SL. Antibodies in juvenile-onset myositis. Curr Opin Rheumatol. 2016;28(6):645–50. PMID: 27533322

39. Tansley SL, Simou S, Shaddick G, Betteridge ZE, Almeida B, Gunawardena H, et al. Autoantibodies in juvenile-onset myositis: Their diagnostic value and associated clinical phenotype in a large UK cohort. J Autoimmun. 2017; 84:55-64. PMID: 28663002

40. Betteridge Z, McHugh N. Myositis-specific autoantibodies: an important tool to support diagnosis of myositis. Journal of Internal Medicine. 2016; 280(1):8–23. PMID: 26602539

41. Satoh M, Tanaka S, Ceribelli A, Calise SJ, Chan EKL. A Comprehensive Overview on Myositis-Specific Antibodies: New and Old Biomarkers in Idiopathic Inflammatory Myopathy. Clinical Reviews in Allergy and Immunology. Humana Press Inc.; 2017; 52(1):1-19. PMID: 26424665

42. Rider LG, Shah M, Mamyrova G, Huber AM, Rice MM, Targoff IN, et al. The myositis autoantibody phenotypes of the juvenile idiopathic inflammatory myopathies. Medicine (Baltimore). 2013;92(4):223–243. PMID: 23877355

43. Tansley SL, Betteridge ZE, Gunawardena H, Jacques TS, Owens CM, Pilkington C, et al. Anti-MDA5 autoantibodies in juvenile dermatomyositis identify a distinct clinical phenotype: A prospective cohort study. Arthritis Res Ther. 2014;16(4):R138. PMID: 24989778

44. Tansley SL, Betteridge ZE, Shaddick G, Gunawardena H, Arnold K, Wedderburn LR, et al. Calcinosis in juvenile dermatomyositis is influenced by both anti-NXP2 autoantibody status and age at disease onset. Rheumatol (Oxford). 2014;53(12):2204–8. PMID: 24987158

45. Mahler M, Betteridge Z, Bentow C, Richards M, Seaman A, Chinoy H, et al. Comparison of three immunoassays for the detection of myositis specific antibodies. Front Immunol. 2019;10:848. doi: 10.3389/fimmu.2019.00848. eCollection 2019. PMID: 31114570

46. Satoh M, Tanaka S, Chan EKL. The uses and misuses of multiplex autoantibody assays in systemic autoimmune rheumatic diseases. Front Immunol. 2015;6:181. PMID: 25954274

47. Cavazzana I, Fredi M, Ceribelli A, Mordenti C, Ferrari F, Carabellese N, et al. Testing for myositis specific autoantibodies: Comparison between line blot and immunoprecipitation assays in 57 myositis sera. J Immunol Methods. 2016 Jun 1;433:1–5. PMID: 26906088

48. Espinosa-Ortega F, Holmqvist M, Alexanderson H, Storfors H, Mimori T, Lundberg IE, et al. Comparison of autoantibody specificities tested by a line blot assay and immunoprecipitation-based algorithm in patients with idiopathic inflammatory myopathies. Annals of the Rheumatic Diseases. BMJ Publishing Group; 2019 Jun;78(6):858–860. PMID: 30760469

49. Mahler M, Vulsteke JB, Bossuyt X, De Langhe E, Sotoh M. Standardisation of myositis-specific antibodies: where are we today? Ann Rheum Dis 2019; doi: 10.1136/annrheumdis-2019-216003. Epub ahead of print. PMID: 31377729

50. Varsani H, Charman SC, Li CK, Marie SKN, Amato AA, Banwell B, et al.

Validation of a score tool for measurement of histological severity in juvenile dermatomyositis and association with clinical severity of disease. Ann Rheum Dis. 2015;74(1)204-10. PMID: 24064003

51. Deakin CT, Yasin SA, Simou S, Arnold KA, Tansley SL, Betteridge ZE, et al. Muscle Biopsy Findings in Combination With Myositis-Specific Autoantibodies Aid Prediction of Outcomes in Juvenile Dermatomyositis. Arthritis Rheumatol. 2016;68(11);2806-2816. PMID: 27214289
52. Patwardhan A, Rennebohm R, Dvorchik I, Spencer CH. Is juvenile dermatomyositis a different disease in children up to three years of age at onset than in children above three years at onset? A retrospective review of 23 years of a single center's experience. Pediatr Rheumatol. 2012 Sep 20;10(1):34. PMID: 22995763
53. Martin N, Krol P, Smith S, Beard L, Pilkington CA, Davidson J, et al. Comparison of children with onset of juvenile dermatomyositis symptoms before or after their fifth birthday in a UK and Ireland juvenile dermatomyositis cohort study. Arthritis Care Res. 2012; 64(11):1665-72. PMID: 22674907
54. Sanner H, Sjaastad I, Flatø B. Disease activity and prognostic factors in juvenile dermatomyositis: A long-term follow-up study applying the Paediatric Rheumatology International Trials Organization criteria for inactive disease and the myositis disease activity assessment tool. Rheumatol (Oxford). 2014;53(9):1578–85. PMID: 24692575
55. Wedderburn LR, Mchugh NJ, Chinoy H, Cooper RG, Salway F, Ollier WEF, et al. HLA class II haplotype and autoantibody associations in children with juvenile dermatomyositis and juvenile dermatomyositis-scleroderma

overlap. Rheumatology. 2007;46(12):1786-91. PMID: 18003662

56. Barth Z, Schwartz T, Flatø B, Aaløkken TM, Koller A, Lund MB, et al. Association between nailfold capillary density and pulmonary and cardiac involvement in medium to longstanding juvenile dermatomyositis. Arthritis Care Res. 2019;71(4):492–7. PMID: 29953739

57. Kishi T, Warren-Hicks W, Bayat N, Targoff IN, Huber AM, Ward MM, et al. Corticosteroid discontinuation, complete clinical response and remission in juvenile dermatomyositis. Rheumatology. 2021 May 14;60(5):2134–45. PMID: 33067611

58. Silverberg JI, Kwa L, Kwa MC, Laumann AE, Ardalan K. Cardiovascular and cerebrovascular comorbidities of juvenile dermatomyositis in US children: An analysis of the National Inpatient Sample. Rheumatol (Oxford). 2018;57(4):694–702. PMID: 29373707

59. Phillippi K, Hoeltzel M, Byun Robinson A, Kim S, Abramson LS, Anderson ES, et al. Race, Income, and Disease Outcomes in Juvenile Dermatomyositis. J Pediatr. 2017; 184:38-44.e1 PMID: 28410093

60. Deakin CT, Papadopoulou C, McCann LJ, Martin N, Al-Obaidi M, Compeyrot-Lacassagne S, et al. Identification and prediction of novel classes of long-term disease trajectories for patients with juvenile dermatomyositis using growth mixture models. Rheumatol. 2021 Apr 1;60(4):1891–1901. PMID: 33146389

61. Lim LSH, Pullenayegum E, Moineddin R, Gladman DD, Silverman ED, Feldman BM. Methods for analyzing observational longitudinal prognosis studies for rheumatic diseases: A review & worked example using a clinic-based cohort of juvenile dermatomyositis patients. Pediatr Rheumatol.

2017;15(1):18. PMID: 28356102

62. Ruperto N, Pistorio A, Oliveira S, Zulian F, Cuttica R, Ravelli A, et al. Prednisone versus prednisone plus ciclosporin versus prednisone plus methotrexate in new-onset juvenile dermatomyositis: A randomised trial. Lancet. 2016;387(10019):671–678. PMID: 26645190

63. Rider LG, Lachenbruch PA, Monroe JB, Ravelli A, Cabalar I, Feldman BM, et al. Damage extent and predictors in adult and juvenile dermatomyositis and polymyositis as determined with the myositis damage index. Arthritis Rheum. 2009 Nov;60(11):3425–35. PMID: 19877055

64. Nordal E, Pistorio A, Rygg M, Giancane G, Maghnie M, Di Iorgi N, et al. Growth and Puberty in Juvenile Dermatomyositis: A Longitudinal Cohort Study. Arthritis Care Res. 2020 Feb 1;72(2):265–73. PMID: 31507092

65. Apaz MT, Saad-Magalhães C, Pistorio A, Ravelli A, de Oliveira Sato J, Marcantoni MB, et al. Health-related quality of life of patients with juvenile dermatomyositis: results from the Pediatric Rheumatology International Trials Organisation multinational quality of life cohort study. Arthritis Rheum. 2009;61(4):509–17. PMID: 19333974

66. Tollisen A, Sanner H, Flatø B, Wahl AK. Quality of life in adults with juvenile-onset dermatomyositis: A case-control study. Arthritis Care Res. 2012;64(7):1020–7. PMID: 22328537

67. Tory HO, Carrasco R, Griffin T, Huber AM, Kahn P, Robinson AB, et al. Comparing the importance of quality measurement themes in juvenile idiopathic inflammatory myositis between patients and families and healthcare professionals. Pediatr Rheumatol. 2018 Apr 19;16(1):28. PMID: 29673367

68. Livermore P, Gray S, Mulligan K, Stinson JN, Wedderburn LR, Gibson F. Being on the juvenile dermatomyositis rollercoaster: A qualitative study. Pediatr Rheumatol. 2019;17(1):30. PMID: 31215480

69. Fawole OA, Reed M V., Harris JG, Hersh A, Rodriguez M, Onel K, et al. Engaging patients and parents to improve mental health intervention for youth with rheumatological disease. Pediatr Rheumatol. 2021 Dec 1;19(1):19. PMID: 33622346

70. Boros C, McCann L, Ambrose N, Cortina-Borja M, Simou S, Pilkington C. Juvenile dermatomyositis: What comes next? Arthritis Rheumatol. 2016;68(Supplement 10):1337.

71. Berntsen KS, Edvardsen E, Hansen BH, Flatø B, Sjaastad I, Sanner H. Cardiorespiratory fitness in long-term juvenile dermatomyositis: A controlled, cross-sectional study of active/inactive disease. Rheumatol (Oxford). 2019;58(3):492–501. PMID: 30508195

72. Blom KJ, Takken T, Huijgen BCH, Wienke J, van Royen-Kerkhof A, van Brussel M. Trajectories of cardiorespiratory fitness in patients with juvenile dermatomyositis. Rheumatol (Oxford). 2017 Dec 1;56(12):2204–2211. PMID: 29029283

73. Habers GEA, Bos GJFJ, van Royen-Kerkhof A, Lelieveld OTHM, Armbrust W, Takken T, et al. Muscles in motion: a randomized controlled trial on the feasibility, safety and efficacy of an exercise training programme in children and adolescents with juvenile dermatomyositis. Rheumatology (Oxford). 2016;55(7):1251–62. PMID: 27018060

74. Riisager M, Mathiesen PR, Vissing J, Preisler N, Ørngreen MC. Aerobic training in persons who have recovered from juvenile dermatomyositis.

Neuromuscul Disord. 2013;23(12):962–8. PMID: 24120572

75. Enders FB, Bader-Meunier B, Baildam E, Constantin T, Dolezalova P, Feldman BM, et al. Consensus-based recommendations for the management of juvenile dermatomyositis. Ann Rheum Dis. 2017; 76(2);329-340. PMID: 27515057

76. Oldroyd AGS, Newton LR, New RP, Sergeant JC, Cooper RG, Chinoy H. OP0279 The Standardised Mortality Rate in UK Adult-Onset Myositis Patients is Seven Times Higher than the UK General Population: Table 1. Ann Rheum Dis. 2015;74(Suppl 2).

77. Cantez S, Gross GJ, MacLusky I, Feldman BM. Cardiac findings in children with juvenile Dermatomyositis at disease presentation. Pediatr Rheumatol. 2017 Jul 11;15(1):54. PMID: 28693511

78. Schwartz T, Sanner H, Husebye T, Flato B, Sjaastad I. Cardiac dysfunction in juvenile dermatomyositis: a case-control study. Ann Rheum Dis. 2011;70(5):766–71. PMID: 21216816

79. Coyle K, Rother KI, Weise M, Ahmed A, Miller FW, Rider LG. Metabolic abnormalities and cardiovascular risk factors in children with myositis. J Pediatr. 2009;155(6):882–7. PMID: 19643439

80. Schwartz T, Sjaastad I, Flatø B, Vistnes M, Christensen G, Sanner H. In active juvenile dermatomyositis, elevated eotaxin and MCP-1 and cholesterol levels in the upper normal range are associated with cardiac dysfunction. Rheumatol (Oxford). 2014 Dec;53(12):2214-22. PMID: 24996906

81. Wienke J, Enders FB, Lim J, Mertens JS, Van Den Hoogen LL, Wijngaarde CA, et al. Galectin-9 and CXCL10 as Biomarkers for Disease Activity in

Juvenile Dermatomyositis: A Longitudinal Cohort Study and Multicohort Validation. Arthritis Rheumatol. 2019;71(8):1377–90. PMID: 30861625

82. Lerkvaleekul B, Veldkamp SR, van der Wal MM, Schatorjé EJH, Kamphuis SSM, van den Berg JM, et al. Siglec-1 expression on monocytes is associated with the interferon signature in juvenile dermatomyositis and can predict treatment response. Rheumatology. 2021; Aug 13;keab601 doi: 10.1093/rheumatology/keab601 Online ahead of print. PMID: 34387304

83. Dvergsten JA, Reed AM, Landerman L, Pisetsky DS, Ilkayeva O, Huffman KM. Metabolomics analysis identifies a lipidomic profile in treatment-naïve juvenile dermatomyositis patients vs healthy control subjects. Rheumatology. 2021;keab520. doi: 10.1093/rheumatology/keab520. Online ahead of print. PMID: 34185053

84. Tawalbeh SM, Marin W, Morgan GA, Dang UJ, Hathout Y, Pachman LM. Serum protein biomarkers for juvenile dermatomyositis: a pilot study. BMC Rheumatol. 2020 Oct 1;4:52. doi: 10.1186/s41927-020-00150-7. eCollection 2020. PMID: 33015544

85. Sabbagh SE, Pinal-Fernandez I, Casal-Dominguez M, Albayda J, Paik JJ, Miller FW, et al. Anti-mitochondrial autoantibodies are associated with cardiomyopathy, dysphagia, and features of more severe disease in adult-onset myositis. Clin Rheumatol. 2021 Oct;40(10):4095-4100. PMID: 33851273

86. Rietveld A, Wienke J, Visser E, Vree W, Schlumberger W, Van Engelen B, et al. Anti-Cytosolic-5′-Nucleotidase 1A Autoantibodies Are Absent in Juvenile Dermatomyositis. Arthritis Rheumatol. 2021;73(7):1329–33. PMID: 33497020

87. Al-Mayouf S, Al-Mazyed A, Bahabri S. Efficacy of Early Treatment of Severe Juvenile Dermatomyositis with Intravenous Methylprednisolone and Methotrexate. Clin Rheumatol. 2000;19(2):138-41. PMID: 10791626

88. Ramanan A V., Campbell-Webster N, Ota S, Parker S, Tran D, Tyrrell PN, et al. The effectiveness of treating juvenile dermatomyositis with methotrexate and aggressively tapered corticosteroids. Arthritis Rheum. 2005;52(11):3570–8. PMID: 16255046

89. Fisler RE, Liang MG, Fuhlbrigge RC, Yalcindag A, Sundel RP. Aggressive management of juvenile dermatomyositis results in improved outcome and decreased incidence of calcinosis. J Am Acad Dermatol. 2002;47(4):505–11. PMID: 12271292

90. Fischer TJ, Rachelefsky GS, Klein RB, Paulus HE, Stiehm ER. Childhood Dermatomyositis and Polymyositis: Treatment With Methotrexate and Prednisone. Am J Dis Child. 1979;133(4):386-9. PMID: 433855

91. Miller LC, Sisson BA, Tucker LB, Denardo BA, Schaller JG. Methotrexate treatment of recalcitrant childhood dermatomyositis. Arthritis Rheum. 1992;35(10):1143-9. PMID: 1418005

92. Heckmatt J, Saunders C, Peters AM, Rose M, Hasson N, Thompson N, et al. Cyclosporin in Juvenile Dermatomyositis. Lancet. 1989;1(8646):1063–6. PMID: 2566009

93. Hamill G, Saunders C, Heckmatt J, Dubowitz V, Stanhope R. “Catch-up” growth in steroid dependent dermatomyositis treated with cyclosporin-A. Eur J Med. 1992;1(1): 16-18. PMID: 1341971

94. Reiff A, Rawlings DJ, Shaham B, Franke E, Richardson L, Szer IS, et al. Preliminary evidence for cyclosporin A as an alternative in the treatment

of recalcitrant juvenile rheumatoid arthritis and juvenile dermatomyositis. J Rheumatol. 1997;24(12):2436-43. PMID: 9415655

95. Kishi T, Tani Y, Okiyama N, Mizuochi K, Ichimura Y, Harigai M, et al. Anti-SAE autoantibody-positive Japanese patient with juvenile dermatomyositis complicated with interstitial lung disease - a case report. Pediatr Rheumatol. 2021;19(1): 34. PMID: 33740993

96. Pistoia V, Buoncompagni A, Scribanis R, Fasce L, Alpigiani G, Cordone G, et al. Cyclosporin A in the treatment of juvenile chronic arthritis and childhood polymyositis-dermatomyositis. Results of a preliminary study. Clin Exp Rheumatol. 1993;11(2):203-8. PMID: 8508564

97. Rouster-Stevens K a, Morgan G a, Wang D, Pachman LM. Mycophenolate mofetil: a possible therapeutic agent for children with juvenile dermatomyositis. Arthritis Care Res (Hoboken). 2010;62(10):1446–51. PMID: 20521307

98. Dagher R, Desjonquères M, Duquesne A, Quartier P, Bader-Meunier B, Fischbach M, et al. Mycophenolate mofetil in juvenile dermatomyositis: A case series. Rheumatol Int. 2012;32(3):711–6. PMID: 21152922

99. Çakan M, Karadağ ŞG, Ayaz NA. Complete and sustained resolution of calcinosis universalis in a juvenile dermatomyositis case with mycophenolate mofetil. Turk J Pediatr. 2019;61(5):771-775. PMID: 32105011

100. Sterba Y, Wahezi D. Cross-sectional evaluation of hydroxychloroquine (HCQ) therapy in children with juvenile dermatomyositis (JDM) enrolled in the childhood arthritis and rheumatology research alliance (CARRA) registry. Arthritis and Rheumatology. 2014;66[abstract].

101. Ang GC, Werth VP. Combination antimalarials in the treatment of cutaneous dermatomyositis: A retrospective study. Arch Dermatol. 2005;141(7): 855-9. PMMID: 16027300

102. Olson NY, Lindsley CB. Adjunctive use of hydroxychloroquine in childhood dermatomyositis. J Rheumatol. 1989;16(12):1545–7. PMID 2483176

103. Kishi T, Bayat N, Ward MM, Huber AM, Wu L, Mamyrova G, et al. Medications received by patients with juvenile dermatomyositis. Semin Arthritis Rheum. 2018;48(3):513-522. PMID: 29773230

104. Kim S, Kahn P, Robinson AB, Lang B, Shulman A, Oberle EJ, et al. Childhood Arthritis and Rheumatology Research Alliance consensus clinical treatment plans for juvenile dermatomyositis with skin predominant disease. Pediatr Rheumatol. 2017 Dec 11;15(1):1. PMID: 28077146

105. Jacobs JC. Methotrexate and azathioprine treatment of childhood dermatomyositis. Pediatrics. 1977;59(2):212–8. PMID: 299938

106. Ng YT, Ouvrier RA, Wu T. Drug therapy in juvenile dermatomyositis: Follow-up study. J Child Neurol. 1998;13(3). PMID: 9535235

107. Rao AP, Kolli V, Rajarathinam I, Raghuram J. Tacrolimus in refractory juvenile dermatomyositis: Case report and review of literature. Indian Journal of Rheumatology. 2020; 15(6):205

108. Hassan J, van der Net JJ, van Royen-Kerkhof A. Treatment of refractory juvenile dermatomyositis with tacrolimus. Clin Rheumatol. 2008;27(11):1469–71. PMID: 18716733

109. Yamada A, Ohshima Y, Omata N, Yasutomi M, Mayumi M. Steroid-sparing effect of tacrolimus in a patient with juvenile dermatomyositis presenting poor bioavailability of cyclosporine A. Eur J Pediatr. 2004;163(9):561-2.

PMID: 15243811

110. Oddis C V., Reed AM, Aggarwal R, Rider LG, Ascherman DP, Levesque MC, et al. Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: A randomized, placebo-phase trial. Arthritis Rheum. 2013;65(2):314–24. PMID: 23124935

111. Aggarwal R, Bandos A, Reed AM, Ascherman DP, Barohn RJ, Feldman BM, et al. Predictors of clinical improvement in rituximab-treated refractory adult and juvenile Dermatomyositis and adult polymyositis. Arthritis Rheumatol. 2014;66(3):740–9. PMID: 24574235

112. Vargas Lebrón C, Ruiz Montesino MD, Moreira Navarrete V, Toyos Sainz de Miera FJ. Treatment With Rituximab in Juvenile Dermatomyositis: Effect on Calcinosis. Reumatol Clin (Engl Ed). 2020 Sep-Oct;16(5 Pt 1):368-370. English, Spanish. doi: 10.1016/j.reuma.2018.06.010. Epub 2018 Jul 24. PMID: 30054253

113. Aggarwal R, Longanathan P, Koontz, Qi Z, Reed AM, Oddis CV. Cutaneous improvement in refractory adult and juvenile dermatomyositis after treatment with rituximab. Rheumatology (Oxford) 2017; 56:247-254. PMID: 27837048

114. Bader-Meunier B, Decaluwe H, Barnerias C, Gherardi R, Quartier P, Faye A, et al. Safety and efficacy of rituximab in severe juvenile dermatomyositis: Results from 9 patients from the French autoimmunity and rituximab registry. J Rheumatol. 2011;38(7):1436-40. PMID: 21677003

115. Cooper MA, Willingham DL, Brown DE, French AR, Shih FF, White AJ. Rituximab for the treatment of juvenile dermatomyositis: A report of four pediatric patients. Arthritis Rheum. 2007;56(9):3107–11. PMID:

17763414.

116. Deakin CT, Campanilho-Marques R, Simou S, Moraitis E, Wedderburn LR, Pullenayegum E, et al. Efficacy and Safety of Cyclophosphamide Treatment in Severe Juvenile Dermatomyositis Shown by Marginal Structural Modeling. Arthritis Rheumatol. 2018;70(5):785-793. PMID: 29342499

117. Riley P, Maillard SM, Wedderburn LR, Woo P, Murray KJ, Pilkington CA. Intravenous cyclophosphamide pulse therapy in juvenile dermatomyositis. A review of efficacy and safety. Rheumatology (Oxford) 2004;43(4):491–6. PMID: 14722349

118. Doudouliaki T, Papadopoulou C, Deakin CT. Use of Rescue Therapy with IVIG or Cyclophosphamide in Juvenile Myositis. Current Rheumatology Reports. 2021;23(4):24. PMID: 33686540

119. Lam CG, Manlhiot C, Pullenayegum EM, Feldman BM. Efficacy of intravenous Ig therapy in juvenile dermatomyositis. Ann Rheum Dis. 2011;70(12):2089–94. PMID: 21978999

120. Al-Mayouf SM, Laxer RM, Schneider R, Silverman ED, Feldman BM. Intravenous immunoglobulin therapy for juvenile dermatomyositis: Efficacy and safety. J Rheumatol. 2000;27(10):2498-503. PMID: 11036850

121. Sansome A, Dubowitz V. Intravenous immunoglobulin in juvenile dermatomyositis - Four year review of nine cases. Arch Dis Child. 1995;72(1):25-28. PMID: 7717731

122. Campanilho-Marques R, Deakin CT, Simou S, Papadopoulou C, Wedderburn LR, Pilkington CA, et al. Retrospective analysis of infliximab and adalimumab treatment in a large cohort of juvenile dermatomyositis patients. Arthritis Res Ther. 2020;22(1):79. PMID: 32293539

123. Riley P, Mccann LJ, Maillard SM, Woo P, Murray KJ, Pilkington CA. Effectiveness of infliximab in the treatment of refractory juvenile dermatomyositis with calcinosis. Rheumatology. 2008;47(6):877-80. PMID: 1843404

124. Boulter EL, Beard L, Ryder C, Pilkington C. Effectiveness of anti-tumor necrosis factor-agents in the treatment of refractory juvenile dermatomyositis. Pediatr Rheumatol 9**,** O29 (2011). https://doi.org/10.1186/1546-0096-9-S1-O29

125. Spencer C, Rouster-Stevens K, Gewanter H, Syverson G, Modica R, Schmidt K, et al. Biologic therapies for refractory juvenile dermatomyositis: five years of experience of the Childhood Arthritis and Rheumatology Research Alliance in North America. Pediatr Rheumatol Online J. 2017, Jun 13;15(1):50. PMID: 28610606

126. Rouster-Stevens KA, Ferguson L, Morgan G, Huang CC, Pachman LM. Pilot study of etanercept in patients with refractory juvenile dermatomyositis. Arthritis Care Res. 2014;66(5):783–7. PMID: 24127327

127. Green KL, Twilt M, Southwood T. The role of etanercept in juvenile dermatomyositis (JDMS) in children. Pediatr Rheumatol. 2014;12(S1). PMCID: PMC4191547

128. DeGuzman M, Singla S, Mizesko M, Sagcal-Gironella AC. Abatacept as adjunct therapy for the calcinosis of juvenile dermatomyositis: A single-center experience. Arthritis Rheum. 2017;69(suppl 4)

129. Sukumaran S, Vijayan V. Risk of serious infections in juvenile dermatomyositis patients treated with biological response modifiers including rituximab and abatacept. Arthritis Rheumatol. 2017;69(suppl 4).

130. Sukumaran S, Vijayan V. Case Report Abatacept in the Treatment of Juvenile Dermatomyositis-Associated Calcifications in a 16-Year-Old Girl. Case Rep Rheumatology 2020; May 28;2020:4073879. doi: 10.1155/2020/4073879. PMID: 32550037

131. Arabshahi B, Silverman RA, Jones OY, Rider LG. Abatacept and sodium thiosulfate for treatment of recalcitrant juvenile dermatomyositis complicated by ulceration and calcinosis. J Pediatr. 2012;160(3). PMCID: PMC3306811

132. Cabrera N, Duquesne A, Desjonquères M, Larbre JP, Lega JC, Fabien N, Belot A. Tocilizumab in the treatment of mixed connective tissue disease and overlap syndrome in children. RMD Open. 2016 Sep 15;2(2):e000271. doi: 10.1136/rmdopen-2016-000271. PMID: 27738519; PMCID: PMC5030575.

133. Kim H, Dill S, O'Brien M, Vian L, Li X, Manukyan M, et al. Janus kinase (JAK) inhibition with baricitinib in refractory juvenile dermatomyositis. Ann Rheum Dis. 2020 Aug 25:annrheumdis-2020-218690. doi: 10.1136/annrheumdis-2020-218690. Epub ahead of print. PMID: 32843325; PMCID: PMC7904969.

134. Yu Z, Wang L, Quan M, Zhang T, Song H. Successful management with Janus kinase inhibitor tofacitinib in refractory juvenile dermatomyositis: A pilot study and literature review. Rheumatology (Oxford). 2021;60(4):1700-1707 PMID: 33024992.

135. Sabbagh S, De Jesus AA, Hwang SJ, Kuehn HS, Kim H, Jung L, et al. Treatment of anti-MDA5 autoantibody-positive juvenile dermatomyositis using tofacitinib. Brain. 2019; 142(11):e59. PMID:31603187

136. Aeschlimann FA, Frémond ML, Duffy D, Rice GI, Charuel JL, Bondet V, et al. A child with severe juvenile dermatomyositis treated with ruxolitinib. Brain. 2018; 141(11):e80. PMID: 30335130

137. Papadopoulou C, Hong Y, Omoyinmi E, Brogan PA, Eleftheriou D. Janus kinase 1/2 inhibition with baricitinib in the treatment of juvenile dermatomyositis. Brain. 2019; 142(3):e8. PMID: 30715143

138. Wilkinson MGL, Deakin CT, Papadopoulou C, Eleftheriou D, Wedderburn LR. JAK inhibitors: a potential treatment for JDM in the context of the role of interferon-driven pathology. Pediatr Rheumatol Online J. 2021 Sep 25;19(1):146. PMID 34563217

139. Le Voyer T, Gitiaux C, Authier F-J, Bodemer C, Melki I, Quartier P, et al. JAK inhibitors are effective in a subset of patients with juvenile dermatomyositis: a monocentric retrospective study. Rheumatology (Oxford) 2021;60(12):5801–5808. PMID: 33576769

140. Wulffraat VP, Rheumatology. Time to share. Pediatr Rheumatol Online J. 2013;11(1):5. PMID: 23414510

141. Huber AM, Giannini EH, Bowyer SL, Kim S, Lang B, Lindsley CB, et al. Protocols for the initial treatment of moderately severe juvenile dermatomyositis: Results of a children's arthritis and rheumatology research alliance consensus conference. Arthritis Care and Research (Hoboken). 2010 Feb; 62(2):219–25. PMID: 2019521

142. Huber AM, Robinson AB, Reed AM, Abramson L, Bout-Tabaku S, Carrasco R, et al. Consensus treatments for moderate juvenile dermatomyositis: Beyond the first two months. Results of the second Childhood Arthritis and Rheumatology Research Alliance consensus conference. Arthritis Care Res.

2012;64(4):546–53. PMID: 22076847

143. Huber AM, Kim S, Reed AM, Carrasco R, Feldman BM, Hong SD, et al. Childhood arthritis and rheumatology research alliance consensus clinical treatment plans for juvenile dermatomyositis with persistent skin rash. J Rheumatol. 2017; Jan; 44(1):110-116. PMID: 27803135

144. Kim H. Updates on interferon in juvenile dermatomyositis: pathogenesis and therapy. Curr Opin Rheumatol. 2021 Sep;33(5):371–377. PMID: 34230439

145. Ding Y, Huang B, Wang Y, Hou J, Chi Y, Zhou Z, et al. Janus kinase inhibitor significantly improved rash and muscle strength in juvenile dermatomyositis. Annals of the Rheumatic Diseases. 2020;80(4):543–5. PMID: 33115762

146. Heinen A, Schnabel A, Brück N, Smitka M, Wolf C, Lucas N, et al. Interferon signature guiding therapeutic decision making: Ruxolitinib as first-line therapy for severe juvenile dermatomyositis? Rheumatology (Oxford). 2021; Apr 6; 60(4):e136-e138. PMID: 33200187

147. Sözeri B, Demir F. A striking treatment option for recalcitrant calcinosis in juvenile dermatomyositis: tofacitinib citrate. Rheumatology (Oxford) 2020 Dec 1;59(12)e140-e141. PMID: 32754736

148. van den Hoogen LL, van Laar JM. Targeted therapies in systemic sclerosis, myositis, antiphospholipid syndrome, and Sjögren's syndrome. Best Practice and Research: Clinical Rheumatology. 2020; 34(1):101485. PMID: 32067925

149. Khoo T, Limaye V. Biologic therapy in the idiopathic inflammatory myopathies. Rheumatology Int. 2020;40(2):191–205. PMID: 31680207

150. Tjärnlund A, Tang Q, Wick C, Dastmalchi M, Mann H, Studýnková JT, et al. Abatacept in the treatment of adult dermatomyositis and polymyositis: A randomised, phase IIb treatment delayed-start trial. Ann Rheum Dis. 2018;77(1):55-62. doi: 10.1177/1759720X19886494 PMID: 28993346 PMCID: PMC6950531

151. Glaubitz S, Zeng R, Schmidt J. New insights into the treatment of myositis. Vol. 12, Therapeutic Advances in Musculoskeletal Disease. 2020 Jan 8;12: 1759720X19886494 doi: 10.1177/1759720X19886494. eCollection 2020. PMID: 31949477

152. Patwardhan A, Spencer CH. Biologics in refractory myositis: experience in juvenile vs. adult myositis; part II: emerging biologic and other therapies on the horizon. Pediatr Rheumatol Online J. 2019 Aug 20;17(1):56. PMID: 31429786

153. Werth VP, Pearson D, Okawa J, Feng R, Concha J, Patel B, et al. 610 Safety and efficacy of lenabasum in refractory skin-predominant dermatomyositis subjects treated on an open-label extension of trial JBT101-DM-001. Journal of Investigative Dermatology. 139. S105. 10.1016/j.jid.2019.03.686.

Table / Figure legends:

Table 1: Drug treatments used in JDM

Figure 1: Impact of age at onset on disease characteristics of JDM

Table 1: Drug treatments used in JDM

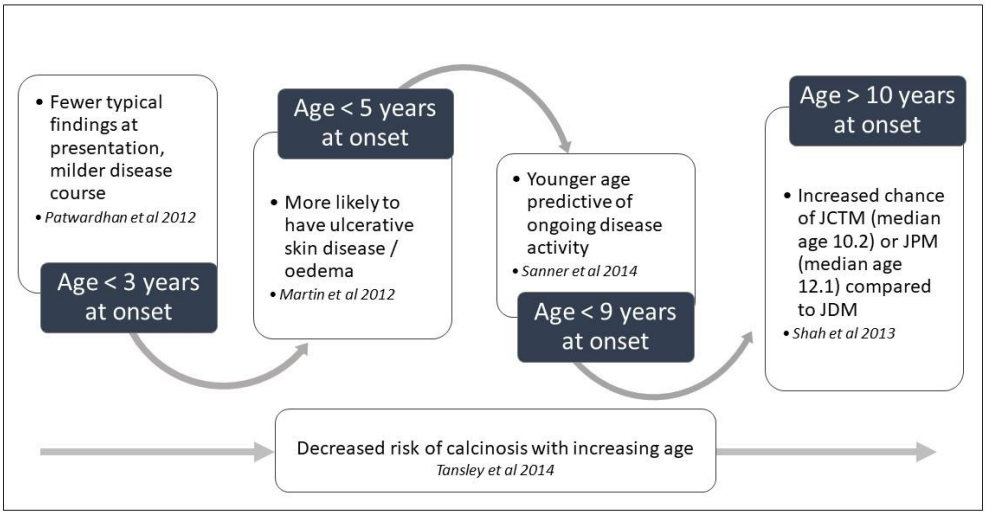
Drug	Mechanism of action	Level of evidence	Comments
Methotrexate	Folate antagonist, inhibits key enzymes involved in the biosynthesis of purines and pyrimidines, with effects on T cell proliferation, and inflammatory function.	Randomised Controlled Trial (RCT), cohort studies & case series(62,87–91).	First line treatment in most cases of JDM in combination with corticosteroid.
Ciclosporin	Calcineurin inhibitor, exerts an immunomodulatory 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 Immunoglobulin (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 immunoglobulin 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 immunoglobulin, 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.

Figure 1



JCTM = Juvenile connective tissue-disease associated myositis. JPM = Juvenile polymyositis.