Juvenile dermatomyositis: Latest advances

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ABSTRACT

Registries and biobanks for juvenile dermatomyositis (JDM) have generated statistical power to help understand pathogenesis and determine treatment and long-term outcomes in this rare and heterogeneous disease. Genotype, autoantibodies, muscle histology and early clinical features may predict prognosis and guide personalised treatment. While corticosteroids and disease-modifying anti-rheumatic drugs improve outcomes, there remain children who experience refractory disease. Ongoing research into the aberrant immune response and novel biological targets is necessary. Best practice guidelines promote prompt stepwise treatment, and there is growing appreciation of the role of exercise in improving prognosis. Validated tools standardise assessment of disease activity and damage in musculoskeletal, mucocutaneous, pulmonary, cardiac, gastrointestinal and endocrine systems. Recently, an internationally agreed dataset for JDM has been defined for clinical practice and incorporation into registries. In the future, with bigger datasets, statistical models may guide stratification for personalised medicine and discern the most relevant outcome markers for research.

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Introduction

Juvenile dermatomyositis (JDM) is a rare childhood autoimmune condition characterised by inflammation of small vessels within the skin, muscle and major organs. Prognosis is variable, ranging from monocyclic disease to chronic illness extending into adulthood with substantial complications [1]. There is increasing emphasis on early aggressive treatment to improve long-term outcomes. However, response to drug therapies is unpredictable, and many drugs have adverse effects. For a ‘treat to target’ approach, it is important to understand the underlying disease pathogenesis. Mounting evidence suggests that genotype, autoantibody status and muscle histology can provide biomarkers to help guide personalised treatments.

Pathogenesis

Genetics

Until recently, small patient numbers and low statistical power have hampered research into the genetic contribution of JDM. The international genetics consortium in myositis (MYOGEN) has expedited international multicentre DNA sample and clinical data collection. MYOGEN recently completed the first genome-wide analysis of idiopathic inflammatory myopathies including children with JDM [2]. Risk and protective alleles for JDM have been identified within the human leucocyte region, cytokine genes and lymphocyte signalling genes (Table 1). Notably, certain alleles are associated with more severe disease outcomes, such as progression to calcinosis and ulceration.

Autoantibodies

Autoantibodies are found in greater than 60% of children with JDM [5]. Autoantibodies are classified into myositis-specific autoantibodies (specific to myositis) and myositis-associated antibodies (present in various autoimmune diseases). Each child typically carries a single myositis-specific antibody [5], and children bearing the same antibody often share similar clinical features and long-term prognoses (Table 2). Certain JDM risk alleles are associated with the development of specific autoantibodies [3,4], suggesting there might be distinct genetic/serotypic JDM subsets exhibiting discrete disease trajectories.

Table 1
Risk and protective alleles for juvenile dermatomyositis [3,4].

<table>
<thead>
<tr>
<th>Risk alleles</th>
<th>Alleles associated with more severe disease</th>
<th>Protective alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B*08</td>
<td>TNFα-308A</td>
<td>HLA-DQA1*0201</td>
</tr>
<tr>
<td>HLA-DRB1*0301</td>
<td>IL-1α-889C</td>
<td>HLA-DQA1*0101</td>
</tr>
<tr>
<td>HLA-DQA1*0501</td>
<td></td>
<td>HLA-DQA1*0102</td>
</tr>
<tr>
<td>HLA-DPB1*0101</td>
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<tr>
<td>HLA-DQA1*0301</td>
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<tr>
<td>TNFα-238GG</td>
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<tr>
<td>TNFα-308AG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-1α+484TT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-1β+3953T</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM 13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM 1,3,17 5,13,21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM 3 23 5,13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KM 1,1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ptpn22 (rs2476601)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCL21 (rs951005)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLCL1 (rs6738825)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BLK (rs2736340)</td>
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</tr>
</tbody>
</table>

HLA: human leucocyte antigen; TNF: tumour necrosis factor; IL: interleukin; GM: immunoglobulin gamma heavy chain; KM: immunoglobulin kappa light chain; Ptpn: protein tyrosine phosphatase; CCL: chemokine c-c motif ligand; PLCL: phospholipase c-like; BLK: B lymphoid kinase.
<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Autoantigen target</th>
<th>Frequency in juvenile population</th>
<th>Clinical features in juvenile population</th>
</tr>
</thead>
</table>
| **MSA** Anti-TIF 1 (Anti-p155/140) | Transcriptional intermediary factor 1         | 18–35%. Highest prevalence in white race. Younger age group (median age = 7 years). | • Cutaneous ulceration  
• Greater muscle weakness (CMAS) |
| Anti-NXP2 (Anti-Mj)          | Nuclear matrix protein 2                     | 15–25%. Highest prevalence in white race. Younger age group (median age = 6 years). | • Younger age of disease onset  
• Greater muscle weakness, dysphagia and dysphonia  
• Calcinosi  
• Mild disease  
• Cutaneous ulceration  
• Arthritis  
• ILD (rapidly progressive in Japanese/Korean/Chinese cohorts)  
• Severe muscle disease  
• Decreased odds of remaining on treatment over time  
• Dysphagia  
• Oedema  
• Cutaneous feature |
| Anti-MDA5                     | Melanoma differentiation-associated gene 5    | 6–38%                            | • Myositis overlap, most commonly scleroderma overlap features  
• Risk of ILD, arthritis, Raynaud’s  
• Association described with calcinosi and lipoatrophy  
• CTD overlap  
• Increased arthralgia, Raynaud’s, ILD and musculoskeletal manifestations |
| Anti-Mi2                      | Nucleosome-remodeling deacetylase complex     | 4–10%. Larger proportion of non-white patients – mostly Hispanic. Older age of onset (median age = 11 years). | • Myositis overlap, most commonly scleroderma overlap features  
• Risk of ILD, arthritis, Raynaud’s  
• Association described with calcinosi and lipoatrophy  
• CTD overlap  
• Increased arthralgia, Raynaud’s, ILD and musculoskeletal manifestations |
| Anti-SAE                     | Small ubiquitin-like modifier activating enzyme | 6–8% in European cohorts; ~2% in Asian cohorts. | • Predominant cutaneous involvement  
• Amyopathic at onset |
| Anti-synthetase antibodies: | Aminoacyl tRNA synthetases                   | 2–5% Larger proportion of non-white patients. Older age of onset (median age = 14 years). | • Anti-synthetase syndrome: ILD, Raynauds, arthritis, fever, mechanics hands and rash  
• Lipoatrophy  
• Anti-Jo-1: Increased frequency of myositis, arthralgia and mechanic’s hands  
• Non-Jo-1 ASA-positivity: Increased frequency of DM skin lesions, fever and ILD |
| Anti-SRP                     | Signal recognition particle                  | 2% JDM. Increased prevalence in Black race. Older age of onset (median age = 15 years). | • More likely to be classified as JPM  
• Severe necrotising myopathy  
• Chronic disease course  
• Increased risk of muscle weakness and dysphagia |
| Anti-HMGCR                   | 3-hydroxy-3-methylglutaryl-coenzyme A reductase | ~1% JDM                         | • Associated with poor prognosis with decreased functional status with long-term follow-up |
| **MAA** Anti-Ro (SSA)        | 52 or 60 Kd ribonucleoproteins (hYRNA)       | 6% JDM. 14–25% myositis overlap. | • No significant associations described in IIM  
• Polymyositis/polymyositis overlap phenotype  
• Older age at disease onset. Less likely to be weak  
• Myositis overlap, most commonly scleroderma overlap features  
• Risk of ILD, arthritis, Raynaud’s  
• Association described with calcinosi and lipoatrophy  
• CTD overlap  
• Increased arthralgia, Raynaud’s, ILD and musculoskeletal manifestations |
| Anti-La (SSB)                | Ribonucleoprotein                           | 2–12% myositis overlap.          | • Associated with poor prognosis with decreased functional status with long-term follow-up |
| Anti-U1-RNP                  | U1 ribonucleoprotein (snRNP)                | 3–8% JDM. 25–40% myositis overlap. | • No significant associations described in IIM  
• Polymyositis/polymyositis overlap phenotype  
• Older age at disease onset. Less likely to be weak  
• Myositis overlap, most commonly scleroderma overlap features  
• Risk of ILD, arthritis, Raynaud’s  
• Association described with calcinosi and lipoatrophy  
• CTD overlap  
• Increased arthralgia, Raynaud’s, ILD and musculoskeletal manifestations |
| Anti PM-Scl                  | Nucleolar multi-protein complex              | 3–5%                             | • Associated with poor prognosis with decreased functional status with long-term follow-up |
| Anti-Ku                      | p70/p80 heterodimer, DNA-associated proteins | 9–19% myositis overlap.          | • Associated with poor prognosis with decreased functional status with long-term follow-up |

Immunohistopathology

Fig. 1 summarises findings from studies to date exploring the humoural and cell-mediated immune mechanisms precipitating muscle damage in JDM. Muscle biopsy remains important in the diagnosis of JDM, and many of the changes illustrated in Fig. 1 can be detected on biopsy. A validated tool has been developed to quantify and score the histological severity of biopsies [9] with mounting interest in using this to predict disease course. Table 3 details a number of histological features and correlation with disease phenotype. Ultimately, the most powerful predictor of clinical outcome is likely to be a composite measure combining genotype, autoantibody status and muscle histology score. This is illustrated in a recent study that revealed histological severity predicted increased risk of remaining on treatment, but anti-Mi-2 autoantibody provided a protective effect. Children carrying this antibody were more likely to enter drug-free remission despite having severe disease marked on muscle biopsy [6].

Environment

It is possible that a number of environmental factors disrupt the immune system of genetically susceptible children to trigger onset or influence disease course in JDM. Many children suffer from infection before disease onset [12] and infection within 6 months of onset of illness increases the risk of a polycyclic, rather than monocyclic, disease course [13]. Gene expression profiling has revealed a prominent type I interferon signature in JDM muscle that could be related to viral exposure [14]. Greater ultraviolet light exposure in boys 1 month before diagnosis increases the risk of a chronic, compared to polycyclic, disease course [13]. Uncovering environmental triggers could improve understanding of the complex dysregulated immune response of JDM.

Treatment

To date, very few randomised controlled trials have been possible in JDM because of the disease rarity, heterogeneity and lack of standardised tools to measure clinical outcomes. Treatment decisions have been largely based on clinicians’ experiences and vary between centres. There is an ongoing duty to foster international collaborations to maximise basic science, translational and clinical research to find the best drug for each child. Parallel to developing personalised drug therapies, there is growing appreciation of the role of exercise in the management of JDM and the importance of a multidisciplinary team to help children achieve their potential in their school, home and social lives. Early intensive physiotherapy, occupational therapy, podiatry and psychology input are essential in finding ways to allow children to adapt to impairments associated with disease activity or damage and to enable regain of functional status once in remission.

Guidelines

The Single Hub and Access point for Paediatric Rheumatology in Europe (SHARE) is an initiative to optimise treatment regimens for children with rheumatic diseases. SHARE recently published best practice guidelines for the investigation and treatment of JDM, which were derived from a validated systematic literature review and consensus meetings with experienced paediatric rheumatologists. On the basis of these recommendations, a flow chart [15] was established for the treatment of JDM (Fig. 2).

The Childhood Arthritis and Rheumatology Research Alliance (CARRA), a network of paediatric rheumatologists in North America, has also described three initial Consensus Treatment Plans (CTPs) [16,17] for the treatment of moderate to severe JDM depending on expert opinion (Fig. 3). The concept of CTPs is to limit treatment practice variation to enable researchers to develop comparative effectiveness studies. This is particularly important in rare diseases where evidence is limited and randomised controlled trials are not possible because of the small patient numbers. CARRA has recently extended CTPs in JDM to include treatment of persistent skin rash and treatment of predominant skin diseases [18,19].
Fig. 1. Evidence for mechanisms contributing to juvenile dermatomyositis pathogenesis [3,4,8]. pDC: plasmacytoid dendritic cell; c: complement; Treg: regulatory T cell; IL: interleukin; MCP: monocyte chemoattractant protein; IFN: interferon; MHC: major histocompatibility complex; CXCL: Chemokine (C-X-C motif) ligand; MRP: myeloid-related protein; TLR: toll-like receptor; MAC: membrane attack complex; ICAM: intercellular adhesion molecule; VCAM: vascular cell adhesion molecule.
Recent studies

Table 4 summarises the available evidence for drugs that are commonly used in the treatment of JDM, highlighting the sparsity of evidence on which clinical practice is based.

Current practice

A survey revealed that the majority of North American paediatric rheumatologists use corticosteroids with methotrexate for ‘typical’ JDM cases, although route and pattern of corticosteroid use varies [21]. Respondents stated a tendency to add intravenous immunoglobulin (IVIG) in severe or refractory cases or those with marked cutaneous manifestations. Hydroxychloroquine is chosen for children with mild disease, or whose main symptom is rash. Cyclophosphamide is principally reserved for children with ulceration or lung disease [22]. Similarly, a survey in the United Kingdom and Ireland has shown that corticosteroids and methotrexate are often chosen as first-line therapy, while cyclophosphamide is used in severe disease, systemic involvement or cutaneous ulceration [23]. A cohort study collecting data between 1980 and 2004 revealed that while European children were more frequently managed with high-dose intravenous methylprednisolone, ciclosporin, cyclophosphamide and azathioprine, Latin American children with similar clinical features often received methotrexate and hydroxychloroquine [24]. This study documented a change in practice over time with increased use of intravenous methylprednisolone and second-line drugs. Subsequently, a randomised controlled trial has clearly demonstrated that addition of methotrexate or ciclosporin achieved better disease control than corticosteroids alone. Fewer adverse effects were seen with methotrexate compared to ciclosporin, supporting the usual practice of using prednisolone and methotrexate as first-line treatment [25] (Table 4, Figs. 2 and 3).

There has been an increasing focus on early aggressive treatment, with prompt stepwise use of medications to achieve timely remission and reduce the risk of complications from disease and long-term drug toxicity [26]. A recent survey in North America revealed that clinicians are selecting various biologics for recalcitrant disease [20], including rituximab (most popular), abatacept, TNF-α blockade and tocilizumab. A randomised placebo phase design trial of rituximab in adults and children with dermatomyositis failed to reach primary or secondary endpoints, but the overall response rate, steroid-sparing effect and re-treatment response suggested that rituximab is efficacious for both muscle and skin diseases [27,28]. Further studies are essential to compare the safety and efficacy of these biological agents [29–31].

Adjunctive treatments

Children are taught to apply high-factor sunscreen daily, as ultraviolet light can trigger JDM flares [15]. Long-term corticosteroids are associated with a number of complications, and children may be co-
**Fig. 2.** Flow chart adapted from Single Hub and Access point for Paediatric Rheumatology in Europe (SHARE) recommendations for treatment of juvenile dermatomyositis. Adapted from Ref. [15]. IV: intravenous; PO: oral; MTX: methotrexate; IVIG: intravenous immunoglobulin; DMARD: disease-modifying anti-rheumatic drug; MMF: mycophenolate mofetil; MP: methylprednisolone; Rx: treatment.
Fig. 3. Flow chart adapted from Childhood Arthritis and Rheumatology Research Alliance (CARRA) Consensus Treatment Plans (CTPs) for treatment of moderate to severe juvenile dermatomyositis. Adapted from Refs. [16,17]. MP: methylprednisolone; IV: intravenous; MTX: methotrexate; SC: subcutaneous; PO: oral; IVIG: intravenous immunoglobulin; MRI: magnetic resonance imaging; EMG: electromyography; PGA: physician global assessment; CMAS: Childhood Myositis Assessment Scale; MMT: manual muscle testing; GI: gastrointestinal; ICU: intensive care unit; CNS: central nervous system; MMF: mycophenolate mofetil; AZA: azathioprine.
### Table 4

Drug studies in patients with juvenile dermatomyositis [8,20].

<table>
<thead>
<tr>
<th>Drug</th>
<th>Evidence level</th>
<th>Findings</th>
</tr>
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</table>
| CS cohort | P newly-diagnosed, retrospective, non-randomised, with propensity score matching | I IV or PO CS 5–30 mg/kg/d (n = 42 of total 76 matched)  
C CS 1–2 mg/kg/d (n = 42 of total 63 matched)  
O little difference in outcomes between the 2 groups, however, sickest patients were treated with aggressive therapy and not included in matched analysis |
| | P retrospective, non-randomised | I PO CS 2 mg/kg/d (n = 5)  
C IV CS high dose with PO CS 0.5 mg/kg/d (n = 5)  
O IV therapy achieved median remission 2 y earlier [21] |
| case series | P n = 8 | I IV CS 20 mg/kg/d for 3–6 d then twice a wk for 2–5 wk  
O good response in all patients, best in patients who had not been treated previously and when CS given earlier in disease course |
| | P n = 6 | I PO CS 50 mg/m² on d 1  
C IV CS on d 2  
O AUC of IV CS greater than PO CS but not significant difference. Inverse association between difference of AUC between IV and PO CS and nailfold ERL |
| expert opinion | IV CS for 3–5 d followed by PO CS 2 mg/kg/d (single morning dose) has lesser effects on the hypothalamic-pituitary-adrenal function and growth |
| MTX RCT | P newly-diagnosed, no previous treatment, no cutaneous/GI ulceration | I prednisolone alone (n = 47)  
C prednisone + CiA (n = 46) OR prednisone + MTX (n = 46)  
O at 6 mo, 51% of prednisone, 70% of prednisone + CiA and 72% of prednisone + MTX achieved improvement. More patients on prednisone + CiA had adverse events. More patients in prednisone + CiA and prednisone + MTX had infections |
| cohort | P consecutive patients in clinic before and after date of new policy of first-line therapy with MTX, non-randomised, retrospective | I MTX 10–20 mg/m²/wk + PO prednisolone 2 mg/kg/d, at 6 wks if muscle enzymes reduced + improved clinically, prednisone tapered by ~10% every 2 wks (n = 31)  
C PO prednisolone 2 mg/kg/d, at 6 wks tapered by ~10% every mo (n = 22)  
O study group had approximately half cumulative prednisolone dose, greater height velocity during the first year of treatment, smaller BMI increase in first 2 y, longer time to development of cataracts |
| case series | P n = 16, recalcitrant disease | I MTX + PO prednisone  
O all 12 patients who received MTX for at ≥8 mo regained normal muscle strength. In 11/12 patients, prednisone tapered to ≤5 mg/day. Active disease occurred in 5 patients when MTX stopped after remission. Complications of MTX required discontinuation in 5 patients |
| | P n = 5 | I CS + MTX (n = 3) or CS + MTX + AZA (n = 2)  
O Clinical improvement in 4 patients. 1 patient continued to experience weakness and episode of pericarditis |
| CIA RCT | see RCT in MTX above |
| case series | P n = 5 (+17 JIA patients) | I CiA mean dose 3.2 mg/kg/d over mean period 16 mo  
O prednisone stopped in 5/20 patients and reduced by >50% in 10/20 patients. No hepatic or bone marrow toxicity or lymphoproliferative disease |

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Evidence level</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MMF</strong></td>
<td><strong>case series</strong></td>
<td><strong>P</strong> n = 8&lt;br&gt;l MMF&lt;br&gt;O 6 patients showed good response. 1 complication observed: transient neutropenia</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>P</strong> n = 50&lt;br&gt;l MMF for 12 mo&lt;br&gt;O decrease in mean sDAS, mDAS, prednisone dosage. WBC count unchanged. No difference in infection rate between 12 mo pre-treatment period and first 6 mo of MMF, infection rate decreased in second 6 mo of MMF (infection rate studied in n = 26 subset who were observed for 12 mo before the start of MMF)</td>
</tr>
<tr>
<td><strong>AZA</strong></td>
<td><strong>case series</strong></td>
<td>see case series in MTX above</td>
</tr>
<tr>
<td><strong>CYC</strong></td>
<td><strong>cohort</strong></td>
<td><strong>P</strong> Juvenile Dermatomyositis Cohort and Biomarker Study and Repository (UK and Ireland)&lt;br&gt;l CYC 500 mg/m² every 2 wk for first 3 doses then 750 mg/m² every 3–4wks for total 6–10 doses (n = 83)&lt;br&gt;C remaining patients (with less severe disease) in cohort did not receive CYC (n = 442)&lt;br&gt;O at 24 mo, improvement in PGA, mDAS, CMAS and MMT8. No serious adverse effects. Ongoing analyses on disease trajectories of patients treated with CYC and patients not treated with CYC</td>
</tr>
<tr>
<td></td>
<td><strong>case series</strong></td>
<td><strong>P</strong> n = 12, severe and refractory disease&lt;br&gt;l CYC&lt;br&gt;O at 6 mo, 83% had improved muscle function and strength, LDH, skin disease, global extramuscular disease. No severe adverse effects. Reversible complications: lymphopenia, herpes zoster infection, alopecia. Two patients with severe refractory disease died after 1 dose of CYC (believed to be the result of severe disease)</td>
</tr>
<tr>
<td><strong>HCQ</strong></td>
<td><strong>case series</strong></td>
<td><strong>P</strong> n = 9, not responded to CS/exacerbation when tapering CS&lt;br&gt;l HCQ mean dose 3.6 mg/kg/d&lt;br&gt;O at 3 mo, improvement in rash, proximal and abdominal muscle strength</td>
</tr>
<tr>
<td></td>
<td><strong>expert opinion</strong></td>
<td>high dose + long duration of HCQ use are risks for ocular toxicity, maximum dose should be ≤ 5.0 mg/kg/d real weight, annual screening recommended</td>
</tr>
<tr>
<td><strong>TAC</strong></td>
<td><strong>case series</strong></td>
<td><strong>P</strong> n = 3, refractory extensive skin disease, severe muscle weakness, CS dependent&lt;br&gt;l TAC&lt;br&gt;O improvement of cutaneous lesions, no improvement of muscle strength, overall disease activity decreased, tapering of CS dosage. No adverse effects.</td>
</tr>
<tr>
<td><strong>IVIG</strong></td>
<td><strong>cohort</strong></td>
<td><strong>P</strong> retrospective, marginal structural modelling to account for confounding by indication&lt;br&gt;l IVIG (these patients had weaker muscle strength and more photosensitivity) (n = 30)&lt;br&gt;C no IVIG (n = 48)&lt;br&gt;O IVIG patients had similar/lower disease activity compared to controls, improvement most marked in CS-resistant patients</td>
</tr>
<tr>
<td></td>
<td><strong>case series</strong></td>
<td><strong>P</strong> n = 9, not responded/severe side effects to conventional treatment&lt;br&gt;l IVIG&lt;br&gt;O clinical improvement. Of 8 patients on prednisolone, dose reduced in 6 patients and kept same in 2 patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>P</strong> n = 2, refractory to CS with steroid toxicity&lt;br&gt;l IVIG&lt;br&gt;O clinical improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>P</strong> n = 18, not responded to IVIG or steroid toxicity&lt;br&gt;l IVIG&lt;br&gt;O 12 patients showed clinical improvement. CS dose was reduced by &gt;50% for &gt;3 mo</td>
</tr>
</tbody>
</table>
prescribed calcium and vitamin D to reduce risk of osteoporosis [32] and gastroprotective cover to reduce the risk of gastrointestinal bleeding and perforation [8].

Physiotherapy

It has been suggested that exercise might be able to attenuate chronic systemic inflammation underlying the pathogenesis of JDM [33]. Microvascular disturbances within the muscle might reduce perfusion during exercise [34], leading to submaximal exercise capacity, lower muscle strength, poorer lung function and reduced quality of life [35]. Reduced physical activity can result in deconditioning, obesity, cardiovascular disease and metabolic syndrome [8]. This is of particular concern in children taking long-term corticosteroids and in subsets of JDM with lipodystrophy (associated with insulin resistance, diabetes mellitus and hyperlipidaemia).

### Table 4 (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Evidence level</th>
<th>Findings</th>
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<tbody>
<tr>
<td></td>
<td>P n = 5, not responded to CS/other immunosuppressive therapy toxicity</td>
<td>IVIG</td>
</tr>
<tr>
<td>expert opinion</td>
<td>IVIG once every 2 wks for 3 cycles then monthly is the preferred regimen</td>
<td></td>
</tr>
<tr>
<td>RTX</td>
<td>RCT P adults with refractory PM + adults and children with refractory DM</td>
<td>RTX at wk 0 (n = 93)</td>
</tr>
<tr>
<td>cohort</td>
<td>P retrospective analysis of RTX above</td>
<td>anti-Jo-1 and anti-Mi-2 autoantibody predicted shorter time for improvement. JDM demonstrated trend towards better clinical improvement compared to adult subgroups (p = .06) prior to wk 20</td>
</tr>
<tr>
<td>case series</td>
<td>P n = 9, severe +/or refractory muscle involvement, severe calcinosis, abdominal lipomatosis</td>
<td>RTX</td>
</tr>
<tr>
<td>IFX</td>
<td>cohort P Juvenile Dermatomyositis Cohort and Biomarker Study and Repository (UK and Ireland)</td>
<td>anti-TNF agents (n = 66)</td>
</tr>
<tr>
<td>case series</td>
<td>P n = 5, refractory disease</td>
<td>IFX IV 3 mg/kg at 0, 2, 6, 8 wks</td>
</tr>
<tr>
<td>ADA</td>
<td>cohort see cohort study in IFX above</td>
<td></td>
</tr>
<tr>
<td>ETN</td>
<td>cohort P n = 9</td>
<td>ETN 0.4 mg/kg SC twice weekly for 12 wks and followed up for 12 wks after last dose ETN</td>
</tr>
<tr>
<td></td>
<td>O At 24 wks, 1 patient stable, 2 patients had worsening DAS. 3 patients had improved DAS. Trend of worsening NFC at wk 12 and improvement at wk 24. No change in muscle enzymes or CMAS. 1 patient stopped after fifth ETN dose (marked worsening of rash).</td>
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P: population; I: intervention; C: comparison; O: outcome; RCT: randomised controlled trial; CS: corticosteroid; IV: intravenous; PO: oral; d: day; y: year; wk: week; AUC: area under curve; ERL: end row loops; MTX: methotrexate; GI: ciclosporin; mo: month; BMI: body mass index; AZA: azathioprine; JIA: juvenile idiopathic arthritis; MMF: mycophenolate mofetil; sDAS: skin disease activity score; mDAS: muscle disease activity score; WBC: white blood cell; PGA: physician global assessment; CMAS: childhood myositis assessment score; MMT8: manual muscle testing 8; CYC: cyclophosphamide; LDH: lactate dehydrogenase; HCQ: hydroxychloroquine; TAC: tacrolimus; IVIG: intravenous immunoglobulin; RTX: rituximab; IMACS: International Myositis Assessment and Clinical Studies Group; DOI: definition of improvement; JDM: juvenile dermatomyositis; IFX: infliximab; pVAS: physician visual analogue scale; CHAQ: childhood health assessment questionnaire; ADA: adalimumab; ETN: etanercept; SC: subcutaneous; NFC: nailfold capillary.
Using myometry, magnetic resonance imaging (MRI) and measurement of serum creatine kinase (CK)/lactate dehydrogenase (LDH) levels, a study demonstrated that exercise did not increase muscle inflammation in children with JDM [36]. Subsequently, a longitudinal study showed that 12 weeks of twice-a-week aerobic and resistance training exercise for children with mild chronic JDM improved muscle strength and function, bone density, aerobic conditioning and quality of life [33]. A more recent randomised controlled trial demonstrated that a 12-week home exercise programme was safe and led to significant improvement in long jump distance, number of push ups and parental child health assessment questionnaire score, but statistical significance was not achieved between the two groups for maximal oxygen uptake, isometric muscle strength and fatigue, possibly because patients were on average leading active lifestyles with high baseline levels [37]. Beyond childhood, 12 weeks of moderate intensity aerobic training for adolescents and adults in remission has been found to increase cardiovascular fitness and oxidative capacity [37].

**Psychological interventions**

Children with JDM, their siblings and parents are vulnerable to psychological distress and could benefit from psychosocial assessments and interventions at disease onset and throughout the illness course [38]. In a recent study, parents of children with JDM reported difficulties in family communication and functioning and increased conflicts and worry [38]. It has been shown that children from families with poor family functioning have reduced ability to adjust [39]. This highlights the value of focusing psychological assessment and therapy on not only the child but also the entire family unit. Corticosteroid use has also been associated with anxiety, low mood, hypomania and psychotic symptoms in susceptible individuals [40]. Many paediatric rheumatology services now have dedicated psychologists and social workers.

Disease activity may affect school attendance, exam performance and disrupt friendships. Without adequate support, this might limit educational and career prospects, impair the ability to form social relationships and damage self-esteem. In a study examining functional outcomes, three of the 65 patients studied reported failing a grade related to missing school because of JDM [41]. Subsequently, all 65 children within the cohort achieved good education and reported that JDM did not interfere with employment.

**Long-term prognosis and management of complications**

The variability of outcome in JDM makes discussions on prognosis challenging [1,41,42]. Furthermore, outcomes have evolved significantly because of early aggressive treatment with corticosteroids, DMARDS and biologics. As a result, published long-term outcome data might not accurately reflect the present JDM disease course. Currently identified risk factors for chronic illness include longer duration of untreated disease and higher skin disease activity at diagnosis, persistent Gottron’s papules at 3 and 6 months and periungual nailfold capillary changes at 6 months after diagnosis, documented infection within 6 months of diagnosis, abnormal subcutaneous fat signal on MRI at diagnosis, initial muscle biopsy showing extensive active myopathic changes, severe arteriopathic changes, severe capillary loss and muscle infarcts and the presence of anti-p155/140 (anti-TIF-1) and anti-Ro antibodies [4]. In addition, a recent study suggests that patients with either anti-TIF-1 or anti-MDA-5 antibodies have a higher chance of still being on disease-modifying medication for 5 years (as a surrogate measure of chronicity or disease severity) after diagnosis than those with anti-Mi-2 antibodies [6].

**Musculoskeletal and mucocutaneous**

Long-term active muscle disease results in chronic muscle weakness or dysfunction and has been found in 34% of patients in a multicentre study across Europe and Latin America [43]. Chronic skin disease can lead to long-term damage such as cutaneous scarring or atrophy, which was seen in 53% of patients [43].

Reported prevalence of calcinosis in JDM cohorts is between 10% and 70% [44], influenced by methods of data collection, length of follow-up and changing treatment practices over time. It occurs more often within 5 years post JDM onset but can range from time of onset to many years after...
Myositis Assessment Scale (CMAS) (routinely assessed in clinic in some cohorts of patients) [45], and by damage outcome [51]. Respiratory muscle weakness does not appear to correlate with the Childhood interpretation in young children [15] because of the difficulty in engaging them in the test and limited reference data for this age group. The radiation risk of repeated CT scanning needs to be considered [15]. A number of treatment options for calcinosis have been explored, including immunosuppressants and drugs targeting calcium metabolism and surgery; however, no intervention is reproducibly effective, and evidence is limited to small case reports [44]. Furthermore, there is no scoring system to grade the extent and severity of calcinosis. Development of a tool may be helpful in determining the efficacy of drugs and identifying children at the highest risk of complications. Complications of calcinosis include pain, joint contractures and risk of infection from staphylococcal, streptococcal or mycobacterial organisms if deposits break the skin surface [44]. Over time, calcinosis can spontaneously regress (most likely with inactive disease or superficial lesions) or enlarge [44]. Consensus guidance recommends a prompt stepwise increase in immunosuppressive medication in the presence of calcinosis because reports suggest that aggressive therapy may decrease the incidence of calcinosis and aid regression of established lesions [18,44].

Lipodystrophy occurs in 10–30% of patients [47,48], most commonly 5 years after the diagnosis of JDM [49]. Associated conditions include joint contractures, calcinosis, muscle atrophy, chronic continuous illness course and facial erythema [49]. Erythroderma and the presence of p155 autoantibody are associated specifically with generalised lipodystrophy. Erythroderma is also associated with partial lipodystrophy, while panniculitis and dysphonia are associated with focal lipodystrophy [49]. It has been suggested that MRI could be useful in confirming diagnosis of lipodystrophy or monitoring response to treatment [49]. Patients with all types of lipodystrophy are at increased risk of hypertriglyceridaemia and those with generalised and partial disease have increased risk of insulin resistance and diabetes [49]. Complications include steatosis and ovarian enlargement [49]. Acanthosis nigricans, hypertrichosis and low leptin levels can be found in patients with generalised disease, while fat redistribution is seen in those with partial disease [49]. The most appropriate treatment of JDM-associated lipodystrophy is not well established. Metabolic abnormalities in patients with various forms of lipodystrophy respond to metabolic therapies such as troglitazone [50], but further research is needed to study the safety and efficacy of metabolic therapies in JDM.

Pulmonary

Children with JDM may suffer from interstitial lung disease (ILD) and respiratory muscle weakness. Pulmonary involvement is reported early in the disease course and deteriorates at times of high disease activity [51]. ILD has been associated with the presence of anti-MDA-5 autoantibodies [52] and elevated Krebs von den Lungen-6 levels (produced by type II pneumocytes and respiratory bronchiolar epithelial cells) [53]. Typical appearances on high-resolution computed tomography (CT) include linear atelectasis, micronodules, ground-glass attenuation, expiratory trapping, thickening of bronchial walls, bronchiectasis, fibrosis and consolidation [54]. Pulmonary function tests can reveal either restrictive and obstructive defects [54]. Restrictive lung disease has been associated with a greater long-term damage outcome [51]. Respiratory muscle weakness does not appear to correlate with the Childhood Myositis Assessment Scale (CMAS) (routinely assessed in clinic in some cohorts of patients) [54], and by the time children exhibit respiratory symptoms, damage to lung parenchyma could be irreversible. These issues underline the value of early identification of children with pulmonary involvement.

SHARE recommends all children with JDM should have pulmonary function tests including carbon monoxide diffusion capacity at the time of diagnosis with further testing (such as high-resolution CT chest) in those with restrictive disease [15]. Results of pulmonary function tests can be difficult to interpret in young children [15] because of the difficulty in engaging them in the test and limited reference data for this age group. The radiation risk of repeated CT scanning needs to be considered [15]. SHARE advises that there is insufficient evidence to guide on frequency of tests, although clinicians should be aware of the risk of lung involvement, particularly in children with high myositis damage index (MDI) scores and those with anti-RNA synthetase antibodies [15].

Children identified with ILD should be treated aggressively with a combination of corticosteroids and immunosuppressant drugs [55]. In acute disease with respiratory insufficiency, treatment with
cyclophosphamide or IVIG can be effective [23]. It is necessary to balance drug complications against deterioration of pulmonary function on an individual basis, and there is ongoing need to investigate if these therapies improve long-term pulmonary and overall outcomes.

**Cardiac**

Systolic and diastolic dysfunction has been observed in JDM and correlates with skin (not muscle) disease activity at 1 year post JDM onset and persists even when the disease is inactive [56]. Long-term studies are needed to investigate clinical implications of pump dysfunction and whether dysfunction is an early marker of systolic and diastolic failure. Children with JDM have increased rates of hypertension and dyslipidaemia [57]. There are no studies to date on coronary artery disease in JDM; however, it is possible that these metabolic disturbances could accelerate coronary artery atherosclerosis, making young adults with JDM more susceptible to ischaemic heart disease. Children with JDM have increased prevalence of ECG abnormalities and reduced heart rate variability (believed to be an indicator of autonomic dysfunction associated with an increased rate of cardiac events [58]) [57]. Pericarditis and myocarditis have also been reported in a small number of studies [57].

SHARE guidelines recommend ECG and echocardiography for all children with JDM [15]. Assessment of long-axis strain and E/e (E, early diastolic transmitral flow; e, early diastolic tissue velocity) as markers for systolic and diastolic involvement on echo have been recommended [57]. SHARE advises repeated investigations for those with hypertension, high disease activity 1 year post diagnosis, long-term high corticosteroid burden or chronic ongoing active disease, in addition to long-term follow-up for high-risk children. There is currently insufficient evidence to recommend on frequency of investigations or length of follow-up. In addition to aggressive immunosuppression, there is limited experience on the use of cardiac drugs in JDM. Longitudinal follow-up is necessary to understand long-term implications of cardiac involvement and the safety and efficacy of treatments.

**Gastrointestinal**

Risk of aspiration is greatest around the time of diagnosis or soon after when disease is at its most severe, and this does not always correlate with validated muscle weakness scores such as the CMAS or manual muscle testing (MMT) scores [15]. It is crucial that all children presenting with cough during swallowing or nasal speech have formal assessments (such as speech and language therapy assessment, video fluoroscopy or barium studies) [15], particularly because pharyngeal involvement has been associated with poor prognosis [59]. Nasogastric feeding may be necessary for short periods to time to reduce the risk of aspiration. Vasculitis and thromboses of vessels supplying the gastrointestinal tract can lead to malabsorption and intestinal ulceration with perforation in severe cases [60,61]. Ulceration and perforation can occur early or late in disease, even when muscle and skin disease activity is mild [60,62]. Symptoms may include persistent or severe abdominal pain with vomiting, haematemesis, constipation or bloody stools. In some cases, abdominal pain can be the only symptom, and long-term corticosteroids can mask abdominal signs, so careful assessment is needed [62]. It has been suggested that aggressive biological treatments and timely surgical interventions are important in reducing mortality rate in ulceration and perforation [62].

**Endocrine**

Growth failure is a feature of cumulative damage in JDM and occurs in around 10% of patients [46]. Reduced bone mineral density (BMD) has been identified at diagnosis and during disease course. Predictors include longer duration of untreated disease [63] and lower weight [64]. High disease activity, high-dose corticosteroids, reduced mobility during muscle weakness, active avoidance of sunlight, anorexia, gastrointestinal vasculitis impairing absorption of vitamin D and calcium and ovarian failure associated with disease or cytotoxic therapy are speculated to be associated with low BMD [64], but more studies are necessary to investigate these associations. Peak BMD achieved in early adulthood is a significant determinant of later life osteoporosis, so it is important to consider prophylaxis with vitamin D and calcium [63]. Age at menarche was found to be older in JDM patients compared to that in the general population, with higher follicle-stimulating hormone (lower ovarian reserve), lower prolactin and higher progesterone (possible luteal dysfunction) [65]. Dysregulation of hormone levels could be associated with disease pathogenesis or
treatment with corticosteroids, which can interfere with the hypothalamic-pituitary-ovarian axis. No difference in the frequency of menstrual disturbances or the development of secondary sexual characteristics has been observed [65].

Mortality
While overall mortality rate has significantly improved (falling from 30% [66] to less than 2% [41]) since the introduction of corticosteroids, DMARDS and novel biologics, the systemic inflammatory response remains profound in some children with JDM, and for a small subset, the resulting pulmonary, gastrointestinal or multisystem failure is fatal [67]. Risk factors include delay to treatment, older age, severe disease activity at onset and weight loss [67]. This reiterates the importance of close clinical monitoring and escalating immunosuppressive treatments for children at risk.

Future treatments
With significant investment into basic science, the enthusiasm and contributions of many children (and parents) with JDM, and collaboration with the pharmaceutical industry, novel targets and new therapies have been identified. Recent evidence suggested the dysregulation of interferon (IFN) in JDM [68]. Janus kinase (JAK) acts downstream of IFN, and JAK inhibitors have been used for good effect in children with interferonopathies (some of these children bear clinical features similar to those of JDM) [8]. Use of JAK inhibitors in JDM is being trialled in North America and Europe, and it is believed that children with evidence of chronic endothelial injury may be most suitable for this therapy.

Cytotoxic T-cell lymphocyte antigen-4 (CTLA-4), CD28 and CD86 are expressed on muscle cells or inflammatory cells within muscles in inflammatory myopathies [8]. Abatacept is a CTLA-4 fusion protein that binds to CD80/CD86 present on antigen presenting cells, thereby preventing the binding of CD80/CD86 to CD28 on T-cells and inhibiting T-cell activation. Abatacept in combination with sodium thiosulfate was reported to control muscle and skin disease, stop progression of calcinosis and reduce corticosteroid burden in a child with severe resistant JDM [69]. Currently, a trial of abatacept in refractory moderately active JDM is in progress in the United States.

Serum IL-6 has been correlated with disease activity in JDM [68]. Case reports of adults with polymyositis and an adult with overlap syndrome identify improvement in skin and muscle disease with tocilizumab (IL-6 receptor antibody) [8]. To date, experience of tocilizumab in JDM is very limited.

Clinical monitoring
Regular monitoring in JDM is essential; management plans should be tailored to fluctuating disease activity levels, evidence of disease damage and the evolving psychosocial needs of the developing child. A thorough history and examination, including muscle strength testing and skin examination is necessary at diagnosis and at every encounter. There has been increasing emphasis on frequent observation, early detection and prompt treatment of skin disease even in the absence of muscle pathology [70]. In view of its prognostic implications [42], it is useful to review periungual capillary changes at each opportunity. While some studies suggest that nailfold capillary density is a marker of both skin and muscle disease activity [71,72], other researchers show end row capillary loss to correlate solely with skin disease [70].

At diagnosis, full blood count, erythrocyte sedimentation rate, urea and electrolytes, liver function tests, muscle enzymes and autoantibodies are recommended [15]. Serum muscle enzymes can be indicators of disease activity, but often are normal, particularly later in the disease course [47]. It is valuable to measure CK, LDH, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and, where available, aldolase levels to maximise the chance of finding at least one elevated enzyme. A number of sensitive disease activity biomarkers in the peripheral blood are currently under investigation, including type I IFN gene and chemokine levels, galectin, IL-6, IL-8 and TNF levels [73].

Radiological investigations are helpful in determining the extent of muscle disease and major organ involvement. MRI (T2-weighted protocols), when reported by experienced radiologists, may be useful to monitor disease activity [74]. A recently developed MRI scoring tool designed for defining muscle inflammation was shown to be accurate for a single reader, but variable between individuals; hence, it requires further validation before this can be incorporated into clinical practice [74].
Clinical and research tools are available to help quantify muscle and skin disease, major organ involvement, functional ability and quality of life. These standardised assessments of disease activity (reversible aspects related to active inflammation) and damage (irreversible scarring from repeated inflammation or secondary to treatment) are useful for monitoring disease over time. They can help guide decisions on treatment escalation or reduction and streamline data collection to facilitate collaboration and meta-analyses [75]. Many of these tools were initially designed for research purposes within Paediatric Rheumatology International Trials Organisation (PRINTO) [76] and International Myositis Assessment and Clinical Studies Group (IMACS) [76] core sets (Table 5), but now they are increasingly being incorporated into clinical practice. Recently, IMACS and PRINTO have engaged in a joint effort to develop validated response criteria for JDM, including criteria for minimal, moderate and major clinical response, allowing either IMACS or PRINTO core set measures to be used, thus resolving the differences between IMACS and PRINTO core sets [76].

**Disease activity tools**

**Clinician-completed**

**Muscle.** CMAS and MMT are validated examination tools for assessing muscle disease. CMAS uses 14 manoeuvres to measure strength, function and endurance [77]. As for many assessments in children, thresholds for active disease may need to be adjusted according to the child’s age because it has been shown that healthy children up to 9 years may not always achieve the maximum CMAS score [78,79]. Total MMT is an extensive assessment of 26 bilateral muscle groups. Recently, this has been condensed to MMT8 (measurement of 8 axial, proximal and distal muscles unilaterally, which correlates well with total MMT) for practical use within the busy clinical environment [80]. CMAS and MMT share many similarities, and there is potential to investigate for redundancy between these tools and to validate a combined shortened tool for clinical practice.

**Skin.** Many tools have been used to assess the extent of skin involvement, although it is yet to be determined which tool is most accurate and reliable in JDM. The Cutaneous Assessment Tool (CAT) measures the full range of skin activity and damage and has been partially validated in a large JDM cohort, demonstrating good reliability [81]. An abbreviated CAT performs similarly to the full CAT and is favoured in clinical practice [81]. A recent study comparing the CAT, skin DAS and Myositis Intention to Treat Activities Index (MITAX) tools for assessing skin in JDM suggested that a new tool may be required which can incorporate all aspects of skin disease [82]. The modified Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI - version 2) evaluates three disease activity measures (erythema, scale and erosion/ulceration) and two damage features (poikiloderma and calcinosis) and activity and/or damage due to Gottron’s patches, periungual changes and alopecia. A recent study

| **Table 5** |
| Comparison of Paediatric Rheumatology International Trials Organisation and International Myositis Assessment and Clinical Studies group core response variables [76]. |

<table>
<thead>
<tr>
<th>PRINTO</th>
<th>IMACS</th>
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<tbody>
<tr>
<td><strong>Muscle</strong></td>
<td><strong>disease activity measures completed by clinician</strong></td>
</tr>
<tr>
<td>CMAS (or MMT)</td>
<td>MMT</td>
</tr>
<tr>
<td>–</td>
<td>≥2 of CK, aldolase, LDH, AST, ALT</td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td><strong>disease activity measures completed by patient</strong></td>
</tr>
<tr>
<td>DAS (or MDAAT)</td>
<td>CHAQ</td>
</tr>
<tr>
<td>physician global activity</td>
<td>parent/patient global activity</td>
</tr>
<tr>
<td><strong>Global</strong></td>
<td><strong>physician global activity</strong></td>
</tr>
<tr>
<td>MDAAT</td>
<td>parent/patient global activity</td>
</tr>
<tr>
<td><strong>Quality of life</strong></td>
<td>–</td>
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<tr>
<td>CHQ</td>
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</table>

PRINTO: Paediatric Rheumatology International Trials Organisation; IMACS: International Myositis Assessment and Clinical Studies Group; CMAS: Childhood Myositis Assessment Scale; MMT: Manual Muscle Test; CK: creatine kinase; LDH: lactate dehydrogenase; AST: Aspartate transaminase; ALT: Alanine transaminase; MDAAT: Myositis Disease Activity Assessment Tool; DAS: Disease Activity Score; CHAQ: Childhood Assessment Questionnaire; CHQ: Child Health Questionnaire.
compared the CDASI and CAT in JDM (n = 14) and found both tools to be reliable when used by paediatric dermatologists or rheumatologists [83].

Global. The Myositis Disease Activity Assessment Tool integrates the Myositis Disease Activity Assessment Visual Analogue Scale (MYOACT) and (MITAX). It appraises in detail disease activity in muscle, skin and several extra-muscular/extra-cutaneous systems (skeletal, gastrointestinal, pulmonary, cardiac and constitutional) and has been shown to have good validity and reliability [77]. The Disease Activity Score (DAS) assesses overall muscle and skin disease activity and is reported as separate or combined muscle and skin scores (where there is approximately equal weighting between the two systems). DAS is believed to sensitively detect clinically important changes in disease activity over time, although the sensitivity and specificity may diminish in children with the most severe damage [77]. Physician Visual Analogue Scale (VAS) is a global judgement based on all the information available at the time of evaluation, including history, examination, blood results and prescribed medications. It has good validity, reliability and responsiveness in longitudinal monitoring [77].

Patient-completed

Global. Patient/parent VAS is a global judgement made by the older child or parent depending on disease activity in muscle, skin and major organs. Notably, physician VAS and patient VAS are not collinear [84], reflecting the contrasting emphasis placed by clinician and patient on different facets of a very multidimensional disease. The Childhood Assessment Questionnaire is a quick and simple instrument that measures the overall well-being, physical function, pain intensity and disability. It has good reliability, validity and responsiveness, therefore suitable for longitudinal monitoring [77]. However, this tool has floor (scores cluster near zero in mild disease) and ceiling effects (does not distinguish between activity and damage, thus resulting in poor sensitivity and specificity for children with most severe damage) [77,85].

Quality of life. A large number of quality of life tools are available, and in recent years, instruments specifically tailored to the needs of children with JDM are emerging. The Child Health Questionnaire is a widely used set of questions, validated for use in JDM, assessing the physical and psychological well-being, ability to participate in activities of daily living and psychosocial effects on the family [77]. The Juvenile Dermatomyositis Multidimensional Assessment Report is a JDM-specific tool currently undergoing further validation. It aims to assess function, quality of life, fatigue and treatment adverse effects [86].

Disease damage tools

The MDI is a clinician-based assessment that has been partially validated in JDM [77]. It is a useful measure of global damage secondary to chronic inflammation and drug toxicity. It scores the severity of long-term damage in different organ systems including muscle, skin, gastrointestinal, pulmonary, cardiac, peripheral vascular and endocrine systems and eyes and also the occurrence of infection and malignancy. This tool has been useful in facilitating understanding of long-term outcomes of JDM and has highlighted that a considerable number of adolescents and adults with JDM suffer from moderate to severe damage as a result of chronic inflammation [1,43,46].

Remission criteria

PRINTO has established data-driven criteria for clinically inactive disease (CID) to guide clinical practice and research [87]. Patients are classified as having CID if they obtain at least three of four variables of CPK ≤150, CMAS ≥48, MMT ≥78 and physician global assessment (PGA) ≤0.2. However, because three of these variables are muscle specific, this score may underestimate skin involvement. It has been suggested that PGA should be an essential criterion when defining CID to avoid this limitation [88].
Registries and common datasets

Through a robust consensus process, an internationally agreed dataset for JDM has been defined, along with an accompanying glossary of definitions, for use in clinical practice [89]. The aim is to incorporate this into existing national and international research registries to allow comparison of data between groups. The development of registries is a smart strategy to build statistical power, maximise yield from precious patient data and samples and save on overall research costs, thereby increasing efficiency and accelerating acquisition of knowledge in a rare and heterogeneous disease [90,91]. Registries aid in identification of patients for interventional trials, are an important resource in epidemiological research, help estimation of disease burden, determination of long-term comorbidities including rare events and provide quality assurance in safety of medications. When linked to biobanks, they facilitate identification of prognostic markers of disease and understanding of sub-phenotypes [90,91]. Registries could also be beneficial in clinical practice; those that are easily accessible and have user-friendly interfaces are valuable aid memoirs for assessing patients in clinic, particularly for trainees less familiar with JDM.

The Juvenile Dermatomyositis Cohort and Biomarker Study and Repository (UK and Ireland) has facilitated research by collecting prospective clinical data linked to serial biological sampling [92]. Projects led by group members and outside investigators have included work on genetics, autoantibodies, muscle biopsy pathology, imaging studies, exercise and therapeutic targets in JDM. CARRA has developed a multicentre registry in the United States and Canada for paediatric rheumatic diseases and is in the final stage of including JDM (https://carragroup.org/). Euromyositis is web-based registry and biobank for adults and children with inflammatory myopathies in Europe that also welcomes applications internationally [93].

Statistical models

As registry databases are collating growing numbers of observations and variables, paediatric rheumatologists are not only encountering new challenges in data cleaning, preparation and analysis but also finding opportunities to explore novel research methods. A recent study explored the possibility of modelling longitudinal outcomes in JDM [94]. Using data from almost 3000 clinic visits, clinical markers and symptoms were used as covariates in a regression model to predict disease activity outcomes. In the future, with bigger datasets and increasingly reliable models, statistical models may play a revolutionary role in stratifying children for personalised medicine and maximising research efficiency through discerning the most relevant outcome markers for research studies [94].

Summary

Advances in genetics, immunology and histology are accelerating understanding of JDM pathogenesis, influencing management and improving prognosis. MSAs and muscle biopsies are now routinely taken in specialist centres and used alongside standard assessments to guide treatment. Further research is needed to develop tools (combining genotype, autoantibody status and muscle histology) to predict drug response and long-term complications. Understanding aberrant immune pathways has facilitated the introduction of several biologics off-label, which have significantly improved outcomes for some children. Where expectations are evolving towards sustained clinical disease inactivity for every child, ongoing studies are necessary to identify novel targets for children with calcineurin disease and to compare the safety and efficacy of drugs. In this rare and heterogeneous disease, national and international collaborations and registries (with linked biobanks) have been pivotal in driving research progress that was previously hampered by low statistical power. Over recent years, multicentre collaborations have defined genetic/serotypic disease subtypes, exposed new therapeutic targets, explored novel imaging techniques and determined the role of exercise in the management of JDM. A new challenge that researchers face is how to exploit the full potential of increasingly large volumes of data that accumulate in registries. There is mounting interest in integrating clinical practice and research to maximise efficiency. Recently, an internationally agreed dataset for JDM for use in clinical practice was defined, with the aim to facilitate data comparison if
incorporated into registries. While impressive advances have been achieved, subsets of children continue to experience active disease into adulthood. There is an ongoing duty to foster international collaborations to maximise basic science, translational and clinical research to ensure the best outcome for every child in the future.

**Practice points**

- Early aggressive treatment with stepwise use of a combination of corticosteroids, disease-modifying anti-rheumatic drugs and biologics could achieve early remission and reduce the risk of complications from disease and long-term drug toxicity.
- Frequent observation, early detection and prompt treatment of skin disease even in the absence of muscle pathology have prognostic importance.
- Using consensus treatment plans during daily clinical practice could limit treatment practice variation to facilitate development of comparative effectiveness studies.
- Exercise programmes are safe and could improve muscle strength and function, aerobic conditioning and quality of life in children with JDM.
- Children with JDM, their siblings and parents could benefit from psychosocial assessments and interventions at disease onset and throughout illness course.
- Disease activity and damage tools standardise assessment of muscle and skin disease, major organ involvement, functional ability and quality of life and are helpful in guiding decisions on treatment.

**Research agenda**

- Genotype, autoantibody status, muscle histology score and early clinical features should be important biomarkers to predict disease prognosis and guide personalised treatment.
- Reliable, sensitive and easy to measure biomarkers are needed to monitor disease activity. Peripheral blood levels of type I IFN gene and chemokine levels, galectin, IL-6, IL-8 and TNF are potential candidates.
- Further research is necessary to find novel biological targets for children with recalcitrant disease and to compare the safety and efficacy of biological agents. JAK inhibitors and abatacept are being trialled in JDM and could be beneficial for certain genetic/serotypic subsets of patients.
- Registries should not only be useful in building statistical power for research but also facilitate daily clinical practice such as acting as aid memoirs for assessing patients.
- Incorporation of the newly defined internationally agreed dataset for JDM into clinical practice and existing registries will facilitate comparison and merging of data between groups.
- With larger datasets, modelling of longitudinal outcomes, stratification of children for personalised medicine and defining most relevant outcome markers for research may be possible.

**Conflict of interest statement**

There are no conflicts of interest to declare for any authors.

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