JAK inhibitors: a potential treatment for JDM in the context of the role of interferon-driven pathology

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Abstract

Juvenile Idiopathic Inflammatory Myopathies (IIM) are a group of rare diseases that are heterogeneous in terms of pathology that can include proximal muscle weakness, associated skin changes and systemic involvement. Despite options for treatment, many patients continue to suffer resistant disease and lasting side-effects. Advances in the understanding of the immunopathology and genetics underlying IIM may specify new therapeutic targets, particularly where conventional treatment has not achieved a clinical response. An upregulated type I interferon signature is strongly associated with disease and could be a prime target for developing more specific therapeutics. There are multiple components of the IFN pathway that could be targeted for blockade therapy.

Downstream of the cytokine receptor complexes are the Janus kinase-signal transducers and activators of transcription (JAK-STAT) pathway, which consists of JAK1–3, TYK2, and STAT1–6. Therapeutic inhibitors have been developed to target components of this pathway. Promising results have been observed in case studies reporting the use of the JAK inhibitors, Baricitinib, Tofacitinib and Ruxolitinib in the treatment of refractory Juvenile Dermatomyositis (JDM). There is still the question of safety and efficacy for the use of JAK inhibitors in JDM that need to be addressed by clinical trials. Here we review the future for the use of JAK inhibitors as a treatment for JDM.

Keywords: Juvenile dermatomyositis, JDM, IIM, JAK inhibitors, IFN, JAK/STAT pathway, Treatment

Introduction

Idiopathic Inflammatory Myopathies (IIM) are a group of rare immune-mediated diseases that are heterogeneous in terms of pathology, clinical phenotypes and age of onset (Table 1). JDM is very rare with an annual incidence of three cases per million children [2, 23, 24] and median age of onset 6.3 years old (IQR: 3.8–9.6) [1]. Children typically present with symmetrical proximal and axial muscle weakness and characteristic skin changes including Gottron’s papules and heliotrope rash. Long-term complications include lung fibrosis, lipodystrophy and calcinosis [25–29]. In most JDM cohorts, 60–70% of children with JDM are positive for an autoantibody [30–33]. A number of myositis specific antibodies (MSA) have been described associated with a variety of phenotypes in JDM [10].

The need for new treatments

The mainstay treatments for IIM are prednisolone and methotrexate, and even those patients who respond well to these drugs can have prolonged disease [34, 35]. Other immunotherapy treatments used include...
mycophenolate mofetil, cyclophosphamide, intravenous immunoglobulin (IvIG), azathioprine, cyclosporine and tacrolimus [36–38]. Biological targets include blockade of tumour necrosis factor alpha (TNFα) and B cells (anti-CD20). As potential treatments for JDM, efficacy was reported in a case series of the use of adalimumab and infliximab (TNFα blockades), and also in an International study of B cell depletion by rituximab (anti-CD20) [39, 40]. However, there is a need for more targeted treatments and methods to identify patients who will require these.

Several more recent emerging biologic therapies for the treatment of IIM have been reported including; belimumab, abatacept, bimagrumab, spiponimod, apremilast, gevokizumab, eculizumab and basiliximab (Table 2) [41–48]. Sifalimumab, a fully human immunoglobulin G1 κ anti-IFNα monoclonal antibody that binds to and neutralizes the majority of IFN-α subtypes, is an important candidate therapeutic due to the wealth of evidence of the strong IFN signature identified in myositis [11, 12, 50–55]. A phase 1b clinical trial of sifalimumab in adult patients with dermatomyositis (DM) and polymyositis (PM), used outcome measures of IFN gene signature suppression against disease improvement. Initial results suggested that targeting the IFN pathway with sifalimumab showed more neutralisation of IFN gene expression in patients that had greater improvement of disease, but blockade of the type I IFN receptor (IFNAR) may offer superior clinical benefit [49]. Beyond the therapeutics highlighted in Table 2 there are potential new therapies for the treatment of IIM including JAK inhibitors to target the IFN pathway.

**Interferon: mechanisms in autoimmune disease**

While the interferon family are a group of molecules central to the anti-viral responses, many autoimmune

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**Table 1 JDM disease features**

| Epidemiology                      | Median age of onset (IQR): 6.3 (3.8–9.6) years [1] |
|-----------------------------------|-----------------------------------------------------|
| Incidence:                        | 7.98 cases/million/year [2]                          |
| Prevalence:                       | 14/100,000 [2]                                      |
| Sex distribution (F:M):           | 2:1:1 [3]                                           |
| Clinical features                 |                                                     |
| Muscle weakness                   | Most patients                                       |
| Cutaneous manifestations          | 30–70% [3]                                          |
| Calcinosis                        | 12–47% [4, 5]                                       |
| Lipodystrophy                     | 8–14% [6]                                           |
| Interstitial lung disease         | 8–19% [7]                                           |
| Myocardial involvement            | Common, non-specific [8]                            |
| Vasculopathy                      | Most patients, central to pathogenesis [9]         |
| Autoantibodies                    |                                                     |
| MSA 49% + ve for MSA              | - Transcriptional intermediary factor 1 (TIF-1γ) 22–29% |
|                                  | - Nuclear matrix protein 2 (NXP2) 23–25%            |
|                                  | - Aminoacyl tRNA synthetase (ASA) 2–4%              |
|                                  | - Signal recognition particle (SRP) < 2%            |
|                                  | - 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) < 1% |
|                                  | - Nucleosome-remodelling deacetylase complex (Mi-2) 4–10% |
|                                  | - Small ubiquitin-like modifier activating enzyme (SAE) < 1% |
|                                  | - Melanoma differentiation associated gene 5 (MDAS) 7–38% [10] |
| Pathogenesis                      |                                                     |
| Type I IFN signature              | Muscle, blood [11, 12]                              |
| Mononuclear cells                 | Muscle [15]                                         |
| FOXP3+ regulatory T cells         | Increased in muscle [16]                            |
| pDCs                              | Increased in muscle/skin [17]                       |
| Myogenic pre-cursor cells         | Increased source of IFN in muscle [18, 19]         |
| Mast cells                        | Increased in skin [20]                              |
| Natural killer cells              | Decreased in blood [21]                             |
| Cytokines                         |                                                     |
| Blood:                            | Increased IRF-4, IL-6, IL-17F, IL-23A, IL-21, GATA3, IL-1β |
| Muscle:                           | Increased GATA3, IL-13, STAT5B [22]                 |
diseases also have an aberrant interferon response. Gene activation is the main mechanism for the interferon anti-viral response, but interferons are also integral to intra-cellular signalling in the immune system (Additional file 1: Supplementary Fig. 1 [56]). Many autoimmune diseases have been found to have an up-regulated IFN type I signature, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and myositis [11, 50, 51, 57–59]. The IFN type I comprise of thirteen types including IFN-α, IFN-β, IFN-κ, IFN-ω and IFN-ν; these bind to a common receptor, IFN-α receptor (IFNAR), but the differences in induction of cellular responses is poorly defined [60]. There are three proposed mechanisms. The first is that plasmacytoid dendritic cells (pDCs) are activated by endogenous IFN inducers to produce IFN-α [61]. The second is that genes

| Biologic | Mechanism | Clinical trial type | Clinical trial number | Patient group | Outcome |
|----------|-----------|---------------------|-----------------------|---------------|---------|
| rituximab [30] | Monoclonal anti-CD20 antibody that depletes B cells | Randomized, double-blind, placebo-phase trial | NCT001061 84 | JDM and DM | Higher proportion of JDM (87%) patients treated with rituximab met the definition of improvement more quickly compared to adult DM (78%) |
| belimumab | Anti-B cell activating factor (BAFF) monoclonal antibody | Multicentre double-blind, placebo-controlled trial | NCT0234 7891 | Refractory IIM | Evaluating the efficacy and safety |
| abatacept | Modified fully human soluble recombinant protein that consists of cytotoxic T cell lymphocyte antigen-4 (CTLA4) fused with Fc region of human IgG1 | Intervventional clinical trial | NCT02594 735 NCT03215 927 NCT029716 83 | Refractory JDM Myositis-associated ILD IIM | Clinical improvement Evaluate efficacy and safety |
| bimagrumab [41, 42] | Human recombinant monoclonal anti-ACVR2B activin type 2 receptor antibody | Phase IIb/III double-blind, placebo-controlled multicentre study Phase IIb/III Study | NCT019252 09 CBYM33 882203 | IBM/IIM | Improvement in muscle volume and strength |
| spiponimod | Oral selective sphingosine-1-phosphate receptor modulator, acts by preventing the migration of lymphocytes to inflammatory sites and therefore reducing inflammation | Multicentre, phase 2, double-blind, randomized, controlled trial | NCT020292 74 NCT0114 8810 | IIM | International Myositis Assessment Study (IMACS) definition of improvement |
| apremilast [44] | Phosphodiesterase-4(PDE-4) inhibitor, reduces the expression of pro-inflammatory cytokines by increasing cyclic adenosine monophosphate | Open-label, single-centre study Phase two, open-label, single group assignment, interventional study | NCT011405 03, NCT0352 9955 | DM | 30% reduction in the cutaneous disease activity and severity index (CQDAS) Safety, efficacy and clinical response |
| gevokizumab | Humanised IgG2 monoclonal antibody against human IL-1β | Proof-of-concept, randomized, double-blind, placebo-controlled trial | EudraCT number: 2012–005772-34 | IIM | Prematurely terminated therefore limited results |
| eculizumab [46, 47] | Monoclonal humanised antibody against terminal complement components | Randomized, double-blind, placebo-controlled pilot study Phase two, randomized, placebo-controlled, third-party-blind study | NCT000055 71 | IIM DM | Improvement of global physician score for cutaneous disease Evaluation of safety and efficacy, results pending. |
| basiliximab [48] | IL-2R chimeric monoclonal antibody; blocks IL-2 receptor on the surface of activated T-cells | Open-label, randomized, parallel assignment without masking, phase-2, single center study | NCT031 92657 | Amyopathic dermatomyositis (CADM) patients with interstitial pneumonia | Primary outcome measure is survival at 52 weeks |
| sifalimumab [49] | anti-IFNα monoclonal antibody | Double-blind, phase 1b multicentre randomised control trial | NCT00533 091 | DM and PM | Neutralisation of IFN gene signature suppression against disease improvement |
associated with autoimmune disease risk, lie within the IFN type I signalling pathway that in turn effect the production and response of IFN-α. IFN-regulatory factor (IRF) 5 was identified as a SLE risk gene as it has increased expression and is activated in SLE patients [62–64]. Other autoimmune diseases have specific risk genes that associate with the IFN signature [65]. The third mechanism proposes that regulation and control of plasmacytoid dendritic cells (pDC) and the expression of interferon regulatory genes (IRG) is not functioning correctly [61]. A decrease in reactive oxygen species (ROS) production from monocytes can lead to enhanced autoimmunity. In addition there is a predominant STAT1 signature in ROS deficient disease [66]. The relative contribution of these three mechanisms may differ between autoimmune disease, severity and patient.

**Role of interferons in myositis**

The most abundant IFN type I are IFN-α and IFN-β. The IFNs bind to the IFN-α receptor (IFNAR) and activate the Janus kinase (JAK)-signal transducer and transcription (STAT) pathway that in turn lead to the transcription of IFN-stimulated genes (ISGs) [67, 68]. The over production of IFN in the blood and muscle is an abnormality in the pathogenesis of dermatomyositis [13, 14, 69]. The release of IFN type I leads to immune cell activation and vasculopathy. A major source of IFN type I is from plasmacytoid dendritic cells (pDC) after activation by either self-DNA or viral nucleic acid [70, 71]. Plasmacytoid dendritic cells (pDC) have been identified in JDM muscle, but IFN type I is difficult to detect in serum due to limits of sensitivity of existing assays until recently [11, 72]. The Simoa assay developed by Rodero et al. can detect IFN-α at differential levels and determine cellular sources measured from lysed cell subsets [57]. Using this assay IFN-α levels were significantly increased in sera from a JDM cohort compared to a healthy cohort [57, 73].

Due to the difficulties in measuring IFN directly, gene expression is often used as a marker of the activation of the IFN type I pathway. An IFN score was developed to encompass a selection of the IFN response genes, IFI27, IFI44L, IFIT1, ISG15, RSAD2 and SIGLEC1, these are measured by quantitative reverse transcription polymerase chain reaction (qPCR) [74]. Other studies have also measured expression of additional genes including ISG15 ubiquitin-like modifier (GIP2), and interferon regulatory factor 7 (IRF7) [51, 71]. Variations of this score have been used to correlate with disease in multiple studies [53, 75, 76]. A signature of 43 genes was elevated in myositis compared to controls [14]. A positive correlation has been shown between an IFN score (6 genes) compared to serum IFN-α levels (n = 24, R² = 0.620, p = 0.0004) taken from JDM patients [57]. The type II IFN signature also correlates to disease activity in JDM and other chemokines [77]. This suggests that as a whole the IFN family are upregulated in the context of JDM and adult DM. The clinical trial of sifalimumab in DM/PM showed suppression of the IFN gene signature in blood and muscle tissue of the IIM patient cohort. Patients with 15% or greater improvement from baseline manual muscle testing scores (MMT8) showed greater neutralisation of the interferon gene signature than patients with less than 15% improvement [49]. This trial highlights the potential for the therapeutic targeting of interferon in DM and JDM.

Another indirect measure is the IFN-driven protein signature which may include measurement of levels of monocyte chemoattractant protein 1 (MCP-1), monocyte chemoattractant protein 2 (MCP-2), interferon gamma-induced protein 10 (IP-10), tumour necrosis factor receptor II (TNFRII), galectin 9 and chemokine (C-XC motif) ligand 9 (CXCL9). These proteins, measured in serum, significantly correlated with disease activity in JDM [22, 78–80]. Chemokines and cytokines have shown to correlate with the IFN signature in peripheral blood mononuclear cells. A study in JDM showed an expansion of peripheral blood naïve immature B cells, skewed to an inflammatory profile, in early disease, that correlated with an IFN type I score taken from RNA-seq analysis of B cells and downstream IFN proteins [81].

Circulating endothelial cells (CEC) have been detected in peripheral blood and associated with vascular injury [82]. An in vitro study has shown that IFN type I treatment of HUVECs impaired endothelial cell function, with significant reduction of tubule formation when HUVECs were cultured with IFN type I + VEGF and anti-IP10 [83]. A recent study in JDM, identified higher CEC in both active and definite inactive disease (JDM n = 90; median 96(IQR 40–192) cell/ml compared to controls n = 79; median 12(IQR 8–24) cells/ml, p = 0.0001). They also showed a strong correlation with other markers of vascular injury including endothelial microparticles and galectin-9 [9]. Another study showed that CEC correlated with extra muscular disease activity but not muscular damage [84]. In JDM, CEC may prove to be a useful biomarker for underlying disease pathology.

Key sites of inflammation in JDM are the muscle and skin. Both muscle and skin tissue biopsy material can provide valuable insights to our understanding of an individual JDM patients disease [85–88]. These tissue samples are the key to understanding the pathophysiology of disease at the tissue site. IFN type I and other cytokines have been detected within the inflamed muscle [89]. The IFN proteins (IFN-α, β, γ) themselves have been detected in muscle, but also the IFN-stimulated proteins ISG15, MxA and class I MHC [90–92]. Higher levels of
ISG15 were quantified in JDM muscle tissue compared to non-JDM [93]. Markers of disease activity and muscle damage have been shown to correlate with the expression of MxA in the muscle tissue [94, 95]. Research has been carried out to identify the direct effects that IFN type I has on muscle tissue types. Muscle atrophy and loss of myogenin has been detected on muscle myotubes, reduced junctions and capillary growth on endothelium [96]. A recent study has shown that these effects have been blocked in vitro by the JAK inhibitor Ruxolitinib [97]. These findings build a picture of the interferonopathy at both the tissue site and the peripheral blood.

**The JAK-STAT pathway – a therapeutic target**

When IFN binds to its respective receptor, IFN-R, on the cell surface membrane, this in turn activates the signalling cascade inducing the Janus kinase-signal transducers and activators of transcription (JAK-STAT) pathway [98, 99] (Fig. 1). The JAK-STAT pathway consists of JAK1–3, TYK2, and STAT1–6, of these JAK1 and TYK2 are directly activated by IFN type 1 proteins. This signalling cascade triggers the receptor-associated JAK to phosphorylate the receptor and other JAKs [100]. If specific tyrosine motifs are phosphorylated in the cytokine receptor, then a docking-site for STATs is opened enabling further phosphorylation of STATs. When STATs are phosphorylated they dimerize through their Src homology domain-2 (SH2) domains, this allows them to translocate to the nucleus and activate specific genes [101]. An individual receptor is made up of several subunits, each is associated with a specific JAK. Therefore, each receptor chain can have more or less specificity to an individual JAK. The JAK-STAT pathway could offer a potential target for the blockade of the transcription of IFN genes [100].

**JAK inhibition**

JAKs are constructed from four domains made of seven homologous regions (JH1–7) (Fig. 2). To date JAK inhibitors (JAK-inhibitors) have generally targeted the JH1 domain. JH1 is the active catalytic phosphotransferase domain and competes with adenosine triphosphate at the catalytic site [102]. JH2 is a pseudokinase domain that supresses ligand-independent kinase activity, the mode of action is direct interaction with JH1 and activation of ligand-induced JAK [103]. Deucravacitinib is an example of a JAK inhibitor that targets the JH2 pseudokinase domain [104, 105]. JH3/4 have a primary role in stabilising the structure of the enzyme. JH5–7 associate JAKs with their cognate receptors [106]. There have been multiple JAK-inhibitors that have been or are in development. These can be defined in two categories; first-generation or next-generation JAK-inhibitors [100]. The first-generation exert pan-inhibition on all four of the JAKs, these include; tofacitinib, ruxolitinib, baricitinib, and oclacitinib [107]. The next-generation of JAK-inhibitors are more specific in their target blockade, these include; fedratinib, momelotinib, and pacritinib [108]. This specificity should help with disease targeted treatment and reduce associated side-effects.
Inhibition of TYK2 is an example of a more specific next-generation Jakinib. TYK2 has been associated with several autoimmune conditions including; RA, JIA, SLE, type 1 diabetes and MS [109–114]. A GWAS analysis of IIM in Caucasian individuals identified that a non-synonymous SNP rs2304256 in TYK2 was associated with DM, IIM but not PM (Bonferroni correction $p = 0.17$, [115]. In a study of a Chinese Han population, analysis of TYK2 SNPs associated with DM and PM excluded TYK2 rs2304256 as it deviated from the Hardy-Weinberg equilibrium (HWE) in healthy controls [116]. This SNP is in the protein FERM (4.1 protein, erzin, radixin, moesin) domain, mediating interaction with JAK and microtubule interacting protein1, this is thought to be increased in DM. Examples of TYK2 inhibitors trialled in psoriasis include; brepocitinib, BMS-986165 and PF-06826647 [117]. TYK2 is just one proposed target for inhibition in IIM.

**JAK inhibitor use in IIM – clinical trials**

For the potential treatment of autoimmune conditions, multiple JAK inhibitors have been developed, trialled or approved [104, 107]. In adults the metabolism, pharmacokinetics and efficacy of JAK-inhibitors are highlighted in Additional file 1: Supplementary Table 1. Clinical trials are ongoing to determine the safety and efficacy of the use of multiple JAK-inhibitors as a therapy for treatment-resistant adult IIM. In addition to their small open-label, proof-of-concept study of tofacitinib in 10 treatment-resistant DM patients (6 were anti-TIF1-γ positive), Paik et al. are carrying out a larger randomised controlled trial, with results pending (NCT03002649). Initial results from 10 participants showed they all met the primary outcome DOI at 12 weeks, 5 of 10 (50%) had moderate improvement and 5 of 10 (50%) had minimal improvement according to the 2016 ACR/EULAR myositis response criteria. The secondary outcome showed a significant change in CDASI disease activity score (mean average $28 \pm 15.4$ (baseline) vs. $9.5 \pm 8.5$ (12 weeks), $p = 0.0005$). There was also a trend towards a reduction of CXCL9/10 in serum and STAT1 signalling in 3 of 9 skin biopsies [118]. Another case report of 3 patients with refractory DM and calcinosis treated with tofacitinib showed an improvement of their calcinosis after 12 weeks (3 months) on treatment [119]. There is little know about the pathology of calcinosis but if JAK-inhibitors are effective then the JAK-STAT pathway may play a role in the underlying mechanism. Chen et al. are conducting a single centre, open-label clinical study of the use of tofacitinib in myopathic dermatomyositis-associated ILD (Chinese Clinical Trial Registry number, ChiCTR-180016,629). Initial results showed that 26 week (6-month) survival after onset of ILD was significantly higher in the prospective group (18 of 18, 100%) compared to the historical controls (25 of 32, 78%, $p = 0.04$), more conclusive results are pending [120]. Another ongoing study of the use of Baricitinib in adult IIM, is the MYOJAK study, a phase II, multicentre, randomised treatment delayed-start trial to receive active treatment (Baricitinib) or delayed-start after 13 weeks (NCT04208464). These trials are currently only including adult IIM patients of which have different clinical features to that of juvenile disease. Children have distinct developmental and physiological differences to adults, as such it is important to test the pharmokinetics and formulation of any given drug in the appropriate age populations.

**Evidence for the use of JAK inhibitors in JDM**

There have been several reports and case series which support the need to pursue testing JAK-inhibitors for the future therapeutic use in juvenile DM (Table 3). The potential for Ruxolitinib was shown in a report of compassionate treatment for a case of severe vasculopathic refractory JDM. The thirteen year old patient presented with severe disease and was admitted to ICU after 3 weeks of diagnosis with multi-symptom, systemic disease. Over a period of 78 weeks (18 months) the patient was poorly controlled with combination therapy, and developed lower limb oedema and diffuse fascia calcinosis. The IFN type I signature was investigated, which showed IFN-α serum levels and IFN score were increased compared to controls, this was also the case with constitutive phosphorylation of STAT1/3 in T-cells and monocytes.

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**Fig. 2** JAK domains and homologous regions. JAKs are constructed from four domains made of seven homologous regions (JH1–7)
From these results the patient was taken off MMF, rituximab infusions were stopped, and switched to Ruxolitinib (10 mg BD) with Prednisolone. After 2 table there was a noted improvement in disease activity scores and no reported adverse events. During the 52 weeks (12 months) of Ruxolitinib treatment the IFN measures did not normalise, but there was decreased STAT 1 phosphorylation in T cells \[121\].
Positive results were seen in a compassionate case of the use of the Jakinib, Baricitinib for an eleven year old male with a seven year history of refractory JDM positive for anti-TIF1-γ and anti-Ro52 autoantibodies. When Baricitinib therapy was started clear improvement of disease was recorded. The IFN biomarkers, IFN type I signature and STAT1 phosphorylation in T cells and monocytes, decreased to comparative levels seen in controls. Also observed was a marked decrease of CEC. To note this was a singular, very severe case, however for the first time in seven years prednisolone could be tapered down, progression of calcinosis was halted and the disease improved as a whole [122]. Further prospective studies need to be carried out to investigate the safety and efficacy of Baricitinib for the use in the treatment of JDM.

A report of 2 patients with anti-MDA5 AB+ JDM with uncontrolled disease were treated with tofacitinib. Disease activity scores decreased within 26 weeks (6 months) following the start of tofacitinib therapy; IFN score, STAT1 phosphorylation of T-cells and monocytes decreased. This report shows evidence that tofacitinib improves JDM at an immunopathogenic level [123]. Another recent report of 3 cases of refractory JDM showed that 26 weeks (6 months) of treatment with tofacitinib was tolerated and the patients responded well to the treatment. Comparing 0–26 weeks (0–6 months) on treatment there were significant improvements in physician global VAS (p < 0.001), manual muscle testing-8 (MMT) (p = 0.002), child myositis assessment scale (CMAS) (p = 0.006), C-HAQ (p < 0.001) and DAS (p = 0.002). This set of case reports showed that tofacitinib treatment improved signs and symptoms of JDM and could be a promising treatment option [124].

A recent retrospective study included nine refractory and one new-onset JDM patients treated with ruxolitinib (n = 7) or baricitinib (n = 3). At 26 weeks (6 months) of follow up five of the ten patients (three Ruxolitinib and two Baricitinib) had reached clinically inactive disease (CID). In these patients the mean daily dose of steroids decreased from 1.1 mg/kg (range 0.35–2) to 0.1 (range, 0–0.3, p = 0.008). Serum IFN-α levels normalised 26 weeks (6 months) after the start of treatment in all patients [125].

A larger case series of refractory JDM patients, 8/25 (35%) treatment was ineffective and 17/25 (68%) glucocorticoid dependant, were treated with tofacitinib 7/25 (28%) or ruxolitinib 18/25 (72%). All 25 patients were followed up for a median of 30 weeks (7 months) (range = 3–21 months). 24/25 (96%) of patients had improvement of their rash of which 16/24 (66.7%) the rash completely resolved. The cutaneous assessment tool binary method score significantly decreased (7.0(3.0–10.0) to 0.0(0.0–1.0) p < 0.001). As a measure of muscle activity 7/25 (28%) of patients showed an improvement of CMAS score (from 18.6 ± 15.0 to 35.7 ± 6.3, p = 0.018). As of follow-up in August 2019 7/25 (28%) of patients had discontinued glucocorticoids. This case series has shown promise for the use of both drugs especially to improve skin disease [126].

Recently data has been published from a compassionate use study (NCT01724580) for the treatment of JDM with Baricitinib. Four JDM patients with chronically active disease were assessed at regular intervals over a 24-week period. There was significant improvement in clinical scores from 4-weeks (Physicians Global Assessment, Pt Global activity and CDASI activity score) and down-regulation of IRG score (28 genes) and serum IP-10. In CD4+ and CD8+ T Cells there were lower levels IFN-α stimulated pSTAT1 and interleukin-2 (IL-2) stimulated pSTAT5 IC50. In CD4+ T cells and CD19+ B cells there were lower levels of IL-10 stimulated pSTAT3 IC50s [127].

Overall, these reports provide more supportive evidence for the use of JAK-inhibitors in JDM, but these are limited case studies with the use of several distinct JAK-inhibitors. Along with specific clinical trials of the use of JAK-inhibitors in the treatment of JDM, there is a need for standardised outcome measures for both clinical and pathological disease improvement.

The future of JAK inhibitors

Clinical trials currently only include adult IIM patients. Successful results from these trials and validation of the case studies in JDM should be translatable to trials and treatment in juvenile disease. There are multiple JAK-inhibitors that are being trialled as potential new therapeutics for adult IIM, but these differ in their JAK targets and pharmokinetics. JAK-inhibitors provide one step further towards more targeted treatment beyond IFN blockade. It is vital to continue to investigate the exact pathogenic mechanism of the JAK/STAT pathway in IIM. If a more specific target can be found then a refined JAK-inhibitor can be developed for clinical trial in juvenile disease.

Concluding remarks

There is a wealth of information and evidence for the potential use of JAK-inhibitors as a therapy for JDM. There is a desperate need for therapeutics that target defined pathogenic pathways in JDM. The IFN pathway is a clear point of target. JAK-inhibitors appear to be promising, but there is still the question of safety and efficacy for the use in JDM. The choice of agent will need careful consideration before choice of trials of first generation pan-JAK-inhibitors or next-generation JAK specific inhibitors. An international collaborative approach, or novel trial design for disease trials, may be required in order to achieve clear evidence of efficacy.
Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12969-021-00637-8.

Additional file 1: Supplementary Figure 1 The role of type I IFN and the interaction with other cytokines in the immune system.

Additional file 2: Supplementary Table 1 Metabolism, pharmacokinetics and efficacy of JAK-inhibitors.

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Authors’ contributions

MGLlW (wrote and prepared manuscript), CTD (review and edit), CP (review and edit), DE (review and edit), LRW (review and edit). The author(s) read and approved the final manuscript.

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References

1. Martin N, Krol P, Smith S, Murray K, Piklington 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. https://doi.org/10.1093/rheumatology/keq261.

2. Meyer A, Meyer N, Schaeffer M, Gottenberg JE, Gery B, Sibilia J. Incidence and prevalence of inflammatory myopathies: a systematic review. Rheumatol. 2015;54(1):50–63.

3. Ramanan AV, Feldman BM. Clinical features and outcomes of juvenile dermatomyositis and other childhood onset myositis syndromes. Rheum Dis Clin N Am. 2002;28(4):833–57. https://doi.org/10.1016/s0889-8577(02)00024-8.

4. Fisher RE, Liang MG, Fuhlbregge 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. https://doi.org/10.1067/mjd.2002.121196.

5. Huber AM, Lang B, LeBlanc CMA, Birdi N, Bolaria RK, Malleson P, et al. Juvenile dermatomyositis and other childhood onset myositis syndromes. Rheum Dis Clin N Am. 2002;28(4):833–57. https://doi.org/10.1016/s0889-8577(02)00024-8.

6. Huemer C, Kitson H, Malleson PN, Sanderson S, Huemer M, Cabral DA, et al. Lipodystrophy in patients with juvenile dermatomyositis - evaluation of clinical and metabolic abnormalities. J Rheumatol. 2001;28(3):610–5.

7. Morinishi Y, Ok-Ishi T, Kabuki T, Joh K. Juvenile dermatomyositis: clinical and metabolic abnormalities. J Rheumatol. 2001;28(3):610–5.

8. Tikkanen MI, Koivula M, Hietala K, Lipponen K, Kaila J. Increased presence of FOXP3+ regulatory T cells in inflamed muscle of children with juvenile dermatomyositis. Arthritis Rheum. 2000;43(3):541–68. https://doi.org/10.1002/1529-0131(200003)43.0:3<541::AID-ANR9>3.0.CO;2-T.

9. Betteridge Z, McHugh N. Myositis-specific autoantibodies: an important tool for diagnosis of myositis. J Intern Med. 2016;280(1):18–23. https://doi.org/10.1111/joim.12451.

10. Greenberg SA, Pinkus JL, Pinkus GS, Burleson T, Sanoudou D, Tawil R, et al. Type I interferon pathway in adult and juvenile dermatomyositis and other childhood-onset myositis syndromes. Arthritis Rheum. 2007;56(11):3784–92. https://doi.org/10.1002/art.22820.

11. Baechler EC, Bilgic H, Feldman BM. Cardiac findings in children with juvenile Dermatomyositis at disease presentation. Pediatr Rheumatol Online J. 2017;15(1):54.

12. Greenberg SA, Pinkus JL, Pinkus GS, Burleson T, Sanoudou D, Tawil R, et al. Interferon-alpha/beta-mediated innate immune mechanisms in dermatomyositis. Ann Neurol. 2003;53(5):664–78.

13. Walsh RJ, Kong SW, Yao Y, Jallal B, Kiefer PA, Pinkus JL, et al. Type I interferon-inducible gene expression in blood is present and reflects disease activity in dermatomyositis and polymyositis. Arthritis Rheum. 2007;56(11):3784–92.

14. Baechler EC, Bauer JW, Slattery CA, Ottmann WA, Espe KJ, Novitzke J, et al. An interferon signature in the peripheral blood of dermatomyositis patients is associated with disease activity. Mol Med. 2007;13(1–2):59–68.

15. McDouall RM, Dunn MJ, Dubowitz V. Nature of the mononuclear infiltrate and the mechanism of muscle damage in juvenile dermatomyositis and Duchenne muscular dystrophy. J Neurol Sci. 1990;99(2–3):199–217. https://doi.org/10.1016/0022-510X(90)90156-H.

16. Vercoulen Y, Bellutti Enders F, Meerdink J, Plantinga M, Elst EF, Varsani H, et al. Increased presence of FOXP3+ regulatory T cells in inflamed muscle of patients with active juvenile dermatomyositis compared to peripheral blood. PLoS One. 2014;9(8):e105333. https://doi.org/10.1371/journal.pone.0105333.
Allenbach Y, Leroux G, Suárez-Calvet X, Preusse C, Gallardo E, Hervier B, et al. Dermatomyositis with or without anti-melanoma differentiation-associated gene 5 antibodies common interferon signature but distinct NOD2 expression. Ann J Pathol. 2016;188(3):691–700. https://doi.org/10.1016/j.ajpath.2015.11.010.

Ladislaus L, Suárez-Calvet X, Toquet S, Landon-Cardinal O, Amelin D, Depp M, et al. JAK inhibitor improves type I interferon induced damage: proof of concept in dermatomyositis. Brain. 2018;141(6):1609–21. https://doi.org/10.1093/brain/awy105.

Coskun M, Salem M, Pedersen J, Nielsen OH. Involvement of JAK/STAT signaling in the pathogenesis of inflammatory bowel disease. Pharmacol Res. 2013;76(1–2):1–8. https://doi.org/10.1016/j.phrs.2013.06.007.

Gadina M, Le MT, Schwartz DM, Silvennoinen O, Nakayamada S, Yamaoka K, et al. Human tyrosine kinase 2 deficiency reveals its requisite roles in multiple cytokine signals involved in innate and acquired immunity. Immunity. 2006;25(5):745–55. https://doi.org/10.1016/j.immuni.2006.09.009.

Clark JD, Ranagan ME, Telliez JB. Discovery and development of Janus kinase (JAK) inhibitors for inflammatory diseases. J Med Chem. 2014;57(12):5023–38. https://doi.org/10.1021/jm5004140.

Hammarén HM, Ungureanu D, Grisoud J, Skoda RC, Hubbard SR, Silverton O. ATP binding to the pseudokinase domain of JAK2 is critical for pathogenic activation. Proc Natl Acad Sci U S A. 2015;112(15):4642–7. https://doi.org/10.1073/pnas.1423201112.

Spinelli FR, Meylan F, O'Shea JJ, Gadina M. JAK inhibitors: ten years after. Eur J Immunol. 2021;51(1):161–27. https://doi.org/10.1002/eji.202048922.

Liu C, Lin J, Langevine C, Smith D, U. J, Tokarz I, et al. Discovery of BM82602: a clinical Tyk2 inhibitor that binds to Tyk2 JH2. J Med Chem. 2021;64(1):67–94.

Babor JJ, Liu NP, Kenhavi NJ. JAK1 takes a FERM hold of type II cytokine receptors. Structure. 2016;24(6):840–6. https://doi.org/10.1016/j.str.2016.05.007.

Fragnoulis GE, McNieces KB, Siebert S, JAK-inhibitors. New players in the field of immune-mediated diseases, beyond rheumatoid arthritis. Rheumatol (Oxford). 2019;58:43–54.

Patel AA, Odenike O. The next generation of JAK inhibitors: an update on Fedritadinib, Momelotonib, and Facitribin. Curr Hematol Malig Rep. 2020;15(6):409–18. https://doi.org/10.1007/s11999-020-00596-z.

Eyre S, Bowes J, Diogo D, Lee A, Barton A, Martin P, et al. High-density genetic mapping identifies new susceptibility loci for rheumatoid arthritis. Nat Genet. 2012;44(12):1336–40.

Hinks A, Martin MC, Cobb J, Comeau ME, Sudman M, Ainsworth HC, et al. Brief Report: The Genetic Profile of Rheumatoid Factor-Positive Polycartilaginous Juvenile Idiopathic Arthritis Resembles That of Adult Rheumatoid Arthritis. Arthritis Rheum. 2018;70(6):957–62.

Suarez-Gestal M, Calaza M, Endrefey E, Pullmann R, Ordi-Ros J, Domenico Sebastiani G, et al. Replication of recently identified systemic lupus erythematosus genetic associations: a case-control study. Arthritis Res Ther. 2009;11(3):1–9.

Wallace C, Smyth DJ, Maisuria-armr M, Walker NM, Todd JA. UKPMC funders group alters susceptibility to type 1 diabetes. Diabetes Res. 2010;82(1):1–13.

Mero IL, Lorentzen ÅR, Ban M, Smestad C, Celius EG, Arnesth JH, et al. A rare variant of the TYK2 gene is confirmed to be associated with multiple sclerosis. Eur J Hum Genet. 2010;18(4):502–4. https://doi.org/10.1038/ejhg.2009.195.

Papp K, Gordon K, Thaci D, Morita A, Gooderham M, Foley P, et al. Phase 2 trial of selective tyrosine kinase 2 inhibitor in psoriasis. N Engl J Med. 2018;379(14):1513–21. https://doi.org/10.1056/NEJMoa1806382.

Jani M, Massey J, Wedderburn LR, Vencovsky J, Danko K, Lundberg IE, et al. Genotyping of immune-related genetic variants identifies TYK2 as a novel associated locus for idiopathic inflammatory myopathies. Ann Rheum Dis. 2014;73(9):1750–2. https://doi.org/10.1136/annrheumdis-2014-205440.

Li L, Chen S, Wang Q, Wu C, Wen X, Yang F, et al. GLIS3 and TYK2 single nucleotide polymorphisms are not associated with dermatomyositis/polymermosis in Chinese Han population. Genet Test Mol Biomarkers. 2017;21(9):565–70. https://doi.org/10.1089/gtmb.2017.0059.

Nogueira M, Puig L, Torres J. JAK inhibitors for treatment of psoriasis: focus on selective TYK2 inhibitors. Drugs. 2020;80(4):341–52. https://doi.org/10.1007/s40265-020-01261-8.

Paik JJ, Casciola-Rosen L, Shin JY, Albadya J, Tinikou F, Leung DG, et al. Study of Tofacitinib in refractory dermatomyositis: an open-label pilot study of ten patients. Arthritis Rheum. 2021;73(5):858–65.

Shneyderman M, Ahlawat S, Christopher-Stine L, Paik J. Calcinosis in refractory dermatomyositis improves with tofacitinib monotherapy: a case series. Rheumatology. 2021;0:1–2.

Zhivenei C, Xiaodong Wang MD, M.D., Shuang Ye MD. Tofacitinib in Amyopathic dermatomyositis-associated interstitial lung disease. N Engl J Med. 2019;381(3):291–3. https://doi.org/10.1056/NEJMoa1900045.

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

Papadopouloou C, Hong Y, Omoyeni E, Brogan PA, Eleftheriou D. Janus kinase 1/2 inhibition with baricitinib in the treatment of juvenile dermatomyositis. Brain. 2019;142(3):E8.

Sabbagh S, De Jesus AA, Huang SJ, Kuehn HS, Kim H, Jung L, et al. Treatment of anti-MDA5 autoantibody-positive juvenile dermatomyositis using tofacitinib. Brain. 2019;142(11):E59. https://doi.org/10.1093/brain/awz293.

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. 2020;60(4):1–8. https://doi.org/10.1093/rheumatology/keaa558.

Le Voyer T, Guitaux 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. 2021;1–8.

Ong 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. Ann Rheum Dis. 2021;80(4):543–5. https://doi.org/10.1136/annrheumdis-2020-218582.

Kim H, Dill S, O'Brien M, Van L, Li X, Manuykan M, et al. Janus kinase (JAK) inhibitor with baricitinib in refractory juvenile dermatomyositis. Ann Rheum Dis. 2021;80(3):406–8. https://doi.org/10.1136/annrheumdis-2020-218690.

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