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Use of JAK Inhibitors in Dermatomyositis: A Systematic Literature Review

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Abstract

Dermatomyositis (DM) is an idiopathic inflammatory myopathy that commonly manifests with proximal muscle weakness and is associated with extramuscular pathology including characteristic skin lesions such as Gottron's papules and heliotrope rash, as well as lung, gastrointestinal, joint, and cardiac involvement. Systemic corticosteroids are a cornerstone of therapy, and more recently intravenous immunoglobulin (IVIG; OCTAGAM®) has been approved by the US Food and Drug Administration for the treatment of adults with DM. Both steroids and IVIG represent nonspecific anti-inflammatory therapy, and more targeted approaches are lacking. Transcriptomics has identified upregulation of interferon (IFN)–regulated genes as key features of both adult DM and juvenile DM (JDM). Accordingly, blocking IFN signaling through inhibition of the Janus kinase (JAK) pathway represents a potential treatment option for DM. Placebo-controlled trial data assessing the use of JAK inhibitors for the treatment of DM are limited; as such, a systematic literature review was undertaken to assess the evidence of JAK inhibitors in the treatment of patients with DM. Terms related to DM and JAK inhibitors were searched using PubMed, Embase, Web of Science, Scopus, and Dimensions to identify peer-reviewed publications reporting patients with DM who were treated with a JAK inhibitor. Baseline demographics, clinical characteristics, and treatment outcome data were extracted. A total of 48 publications reporting 145 unique patients (adult DM, n=84; JDM, n=61) were identified. Among cases of adult DM, 61 of 84 (73%) had refractory skin disease at baseline, and all (61 of 61) reported improvement in cutaneous symptoms. Of patients with adult DM, 16 of 84 (19%) had refractory muscle disease at baseline, and all (16 of 16) reported improvement in muscle symptoms. In patients with adult DM complicated by interstitial lung disease (ILD; n=33), 31 (94%) patients improved with JAK inhibitor treatment. Among cases of JDM with refractory skin disease at baseline (60 of 61), most patients (57 of 60; 95%) showed improvements in skin symptoms after JAK inhibitor treatment. Of patients with JDM with refractory muscle disease at baseline (36 of 61), most (30 of 36; 83%) reported improvement in muscle symptoms. Four patients with JDM and ILD experienced improvement in lung disease activity following treatment with a JAK

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Author Contributions

JJP and **LCS** contributed to the writing and reviewing of the manuscript and approved the final version. **GL** and **AG** were responsible for data extraction and analysis. **GL**, **AG**, **PNM**, and **MPP** contributed to study design, manuscript review, and approved of the final version.

inhibitor. Among both DM and JDM cases, all patients (17 with DM and 16 with JDM) who had elevated serum IFN and/or IFN-stimulated gene expression at baseline showed reduction in IFN or IFN gene expression. Although the conclusions that can be drawn from this analysis are limited because of the differences in assessments used across publications, overall treatment of patients with DM or JDM with a JAK inhibitor was associated with significant improvement of a wide range of DM manifestations, including skin lesions, muscle weakness, and ILD. Our systematic literature review suggests that JAK inhibitors may be a viable treatment option for DM/JDM, and randomized controlled trials are necessary to confirm these findings.

Keywords

Baricitinib; Brepocitinib; Dermatomyositis; Idiopathic Inflammatory Myopathies; JAK; Janus Kinase Inhibitor; Juvenile Dermatomyositis; Myositis; Ruxolitinib; Tofacitinib

Introduction

Dermatomyositis (DM) is a rare idiopathic autoimmune disease associated with muscle and skin inflammation that can lead to significant morbidity and mortality (1). Patients with DM are frequently treated off-label with immunosuppressive agents, and only in the past year has the US Food and Drug Administration approved intravenous immunoglobulin (IVIG; OCTAGAM®) to treat DM in adults. There is an urgent, unmet need to develop additional disease-modifying treatments for DM.

In both adult DM and juvenile DM (JDM), transcriptomic analyses demonstrate an upregulation of interferon (IFN)–regulated genes (2-4). In particular, in myocytes of patients with DM, robust expression of both type I IFN– and type II IFN–inducible genes correlates with expression of genes associated with inflammation and regeneration (5). Given the substantial evidence demonstrating the importance of IFN-regulated genes in DM and the obligate role of Janus kinases (JAKs) in IFN signal transduction (6), JAK inhibitors have been used therapeutically. The various approved and investigational JAK inhibitors have distinct pharmacologic activity at the four human JAK isoforms (JAK1–3, tyrosine kinase 2 [TYK2]), and several are known to potently inhibit JAK1 and/or TYK2 and accordingly inhibit types I and II IFN signaling (7).

The first report of DM responsive to a JAK inhibitor, ruxolitinib, was in 2014, of a 72-year-old woman with recalcitrant DM and myelofibrosis (8). Although there was controversy about whether the treatment of her underlying myelofibrosis contributed to the remission of her DM (9,10), a subsequent case report and a case series demonstrated the efficacy of a JAK inhibitor in treating refractory skin disease (11,12). More recently, a proof-of-concept study of tofacitinib in refractory DM also showed safety and efficacy as measured by the validated American College of Rheumatology and European League Against Rheumatism (ACR/EULAR) Myositis Response Criteria (13). This study required washout of other immunosuppressive agents, thereby highlighting the therapeutic potential of JAK inhibitors as monotherapy in refractory skin-predominant disease. Beyond the treatment of skin-predominant disease, JAK inhibitors have also been reported to be efficacious in myositis-associated interstitial lung disease (ILD), in particular melanoma differentiation-associated 5 (MDA5)–associated ILD (14).

Given the promising therapeutic potential of JAK inhibitors in DM, the purpose of this systematic literature review is to examine the evidence available for JAK inhibitor use in this disease. Although adult-onset DM and JDM have clinical similarities, there are also notable distinctions, including markedly diminished malignancy risk and increased calcinosis in JDM compared with adult-onset DM (15); thus, we report findings for the two diseases separately.

Methods

Search Strategy

The systematic literature review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A comprehensive electronic search strategy of databases—including PubMed, Embase, Web of Science, Scopus, and Dimensions—was performed August 18–20, 2021, with the terms ((“dermatomyositis” OR “myositis” OR “inflammatory myopathy” OR “inflammatory myopathies”) AND (“JAK” OR “janus kinase” OR “tofacitinib” OR “baricitinib” OR “ruxolitinib” OR “upadacitinib” OR “filgotinib”)) queried for the title, abstract, or keywords. The same terms and delimiters were also queried in published abstracts between 2012 and 2021 from the following congress proceedings: ACR, EULAR, Paediatric Rheumatology European Society, Asia-Pacific League of Associations for Rheumatology, and Pan-American League of Rheumatology Associations. For each identified publication, citations both within and of that paper were reviewed.

Articles and conference abstracts were eligible for inclusion if they were primary publications of patients with DM or JDM who were treated with JAK inhibitors. All study designs (ie, case reports, case series, retrospective studies, observational studies, randomized controlled trials) were eligible for inclusion. Publications were excluded if they did not document patient clinical characteristics, prior and/or concomitant therapies, or outcomes following treatment with JAK inhibitors. Review articles and nonprimary case reports were also excluded. Publications were included even if individual patients were subsequently included in another primary publication (eg, case reports that were also included in a retrospective study), to compile all relevant data for each patient. Patients documented in multiple publications were only counted once as unique patients. We identified unique reports (ie, individual peer-reviewed article or congress proceeding), unique analyses (ie, all reports that possibly or likely presented the same patient in multiple publications such as patients included in a study that were also included in a case report), and unique patients (ie, individual patients, counted from only one report), and for clarity we present results as unique patients.

Data Extraction and Assessments

One researcher (GL) reviewed search results and extracted data from each identified publication, and another researcher (AG) reviewed search results and extracted data from a random 10% of all identified publications to ensure consistency, as done in a similarly performed analysis (16). Discrepancies were resolved by consensus. From included publications, the following information was extracted: study type and follow-up time, JAK inhibitor used, number of patients, patient baseline demographics and clinical characteristics, symptoms, treatment history, concomitant medications, and treatment outcomes, IFN signature, muscle enzyme (creatine kinase [CK], aldolase) levels, and myositis-specific and myositis-associated autoantibodies (MSAs, MAAs). Efficacy outcomes included Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity score (scale 0–100; higher score indicating more severe disease), total improvement score (TIS), and individual core set measures (CSMs) of the TIS such as manual muscle testing (MMT-8; scale 0–150, respectively; higher scores indicating greater strength). Data were also extracted on serum IFN or IFN-regulated gene expression. For publications reporting JDM cases, data were also extracted for the Childhood Myositis Activity Score (CMAS; scale 0–52; higher scores indicating greater muscle strength) and Global Disease Activity Score (DAS; total 0–20 consisting of skin DAS [0–9] and muscle DAS [0–11]). In patients with ILD, data were extracted for diffusing capacity for carbon monoxide (DLCO%) and forced vital capacity (FVC%). The above parameters were extracted from text, tables, figures, and/or supplementary materials depending on the information reported in each publication. If relevant data with discrete numeric values (eg, CDASI scores, individual CSMs, TIS) were only provided in chart form, WebPlotDigitizer was used to extract numeric values from the images (17). Extraction of safety-related data was beyond the scope of this review.

Risk of Bias Assessment

Risk of bias was assessed using the National Institutes of Health (NIH) quality assessment tool for case series studies (18). One researcher (GL) rated each study as low, high, or unclear risk of bias, and a second researcher (AG) assessed 10% of the identified publications to ensure consistency. Discrepancies were resolved by consensus.

Results

Publications Search Overview

The literature search yielded a total of 749 records (Figure 1), 313 of which were unique records screened for eligibility. Of these, 265 did not meet inclusion criteria. This resulted in 48 records published between December 2014 and August 2021. From these publications, individual patients were reported in unique reports (n = 39; clinical trials, retrospective studies, case series, or case reports), included in multiple publications of a study (eg, STIR primary study and long-term analysis), or reported in a case series and likely included in a larger study (eg, a retrospective study that includes patients previously described in a case study). Data were extracted from reports of 145 individual patients with adult DM or JDM. Of these, 34 publications reported DM in 84 unique adult patients, and 15 reported JDM in 61 unique pediatric patients (one report included patients with adult DM and JDM (19)). In 16 publications (12 adult DM, 4 JDM), 33 patients with DM and 10 patients with JDM were primarily treated for DM-ILD. The characteristics of included studies are presented in Supplemental Table 1 for publications on adult DM and Supplemental Table 2 for publications on JDM.

Of patients with adult DM, 64 patients (76%) were female. Of patients with JDM, 34 (56%) were female; sex was not reported for one patient. Of patients with DM, 67 were treated with tofacitinib, eight with baricitinib, and nine with ruxolitinib; of patients with JDM, 19 were treated with tofacitinib, eight with baricitinib, 27 with ruxolitinib, and seven with baricitinib or ruxolitinib (specific JAK inhibitor for each patient not reported in one study). Most patients (92% DM, 100% JDM) received concomitant therapies while initiating JAK inhibitor treatment. These were typically the standard-of-care agents, including corticosteroids, immunosuppressants (eg, methotrexate, azathioprine), and IVIG. All patients with DM had documented prior therapy, and 66/84 were initiated on JAK inhibitor treatment owing to refractory cutaneous or muscle disease, ILD, and/or other symptoms. Prior therapy for most patients (83/84) included corticosteroids (Supplemental Table 3). Of patients with refractory DM who were receiving corticosteroids when JAK inhibitor therapy was initiated, 90% (43/48) were able to taper or discontinue corticosteroid therapy. Among patients with JDM, 60/61 presented with refractory disease (as assessed by the investigator), and specific prior therapy was reported for 27 of 61 patients. The most common prior therapy was corticosteroids (27/27; Supplemental Table 3). Of patients with JDM, concomitant steroid therapy was reported for 47 patients. Of these patients, 23 tapered or discontinued corticosteroid therapy; the remaining studies reporting concomitant corticosteroid use did not report changes to corticosteroid therapy during JAK inhibitor therapy.

Overall, treatment with a JAK inhibitor significantly improved or resolved symptoms of disease for patients with DM and JDM with cutaneous or muscle disease or with ILD (Supplemental Table 4).

JAK Inhibition in Adult Dermatomyositis

Cutaneous Disease—A total of 28 publications included 61 patients with DM who had refractory cutaneous disease (Table 1). All patients (61/61) improved with JAK inhibitor treatment. In the 24 unique patients for whom individual pre- and post-treatment CDASI scores (scale 0–100) were reported, all 24 patients showed improvements (lowering of scores). Among these patients, baseline CDASI scores ranged from 12–57 (8,11,19-24). In studies that reported score changes after 4–12 weeks of JAK inhibitor use, improvements ranged from 2–41 points from baseline, with posttreatment CDASI scores ranging from 0–15 (8,19-23). Patients continued to experience improvement in CDASI scores in studies with long-term follow-up of JAK inhibitor treatment (20–96 weeks) (21-23).

Three analyses in 5 publications reported mean scores, accounting for 29 patients (some with individual scores reported in separate analyses as described above). In the open-label STIR trial of tofacitinib in 10 adult patients with refractory DM, mean CDASI score at baseline was 28 and at week 12 was 9.5 (13,25). At week 96 of the STIR long-term extension trial, the mean score reported for seven patients was 4.71 (26). In a case series of 12 patients treated with either baricitinib or ruxolitinib, the mean baseline CDASI score was 31 and by week 12 was 16; 11 of 12 patients showed clinically significant improvement with JAK inhibitor treatment, defined as a >5-point improvement in CDASI score (27). Mean CDASI was further reduced to a score of 8 after long-term (~50 weeks) follow-up of these 12 patients. Another case series reported 7 patients treated with tofacitinib, with mean improvement in CDASI score of 13 points (28).

Among the 14 publications that indicated an outcome related to refractory cutaneous symptoms but did not report pre- and posttreatment CDASI scores, 21 of 21 patients improved after treatment with a JAK inhibitor (12,29-40). In one study of five patients with cutaneous disease in addition to rapidly progressive ILD, skin symptoms of heliotrope rash, Gottron's papules, and erythema improved with JAK inhibitor treatment, although two patients later died (see ILD section) (14).

Muscle Disease—A total of 14 publications included 16 patients presenting with refractory muscle disease (Table 2). Patients treated with a JAK inhibitor displayed significant improvements in muscle strength. Of the 16 adult patients, 15 (93.8%) had patient- or clinician-reported improvement, decreased edema on magnetic resonance imaging, and/or improvement in muscle strength measurements (ie, MMT-8, Medical Research Council Muscle Scale [MRC]); one study did not report outcomes specific to muscle disease. The STIR open-label trial reported one patient with adult DM involving active, refractory muscle disease (13). This patient had a baseline MMT-8 score (scale 0–150) of 127 that improved to 136 at week 12 of treatment with a JAK inhibitor. In another study, one patient demonstrated improved arm abductor strength measured by handheld dynamometry; scores improved from 4-/5 to 5-/5 (12). MRC scoring (scale 0–5) was used in two patients with muscle disease; scores improved from a baseline of 3/5 to 4/5 in both patients (20).

Interstitial Lung Disease—In 12 publications, 33 unique adult patients had DM-ILD, 32 of whom were seropositive for anti-MDA5 antibodies, including many with poor prognostic factors (eg, hyperferritinemia). Most patients (32/33) were treated with tofacitinib, and one was treated with ruxolitinib. Overall, 31 patients (94%) improved with JAK inhibitor treatment. In an open-label trial of tofacitinib in 18 patients with DM-ILD who were anti-MDA5-Ab positive, a 100% 6-month survival rate was reported vs 78% of historical controls (41). In a patient who was negative for anti-MDA5 antibodies but positive for anti-Jo1 and antinuclear antibodies, treatment with tofacitinib was also effective (42). In a case series of patients with DM-ILD and poor prognostic factors (pertaining to serum ferritin levels and lung opacity unresponsive to triple therapy) who received triple therapy (glucocorticoid pulse therapy followed by prednisolone, cyclophosphamide, and cyclosporine A) and tofacitinib (n=5), three patients recovered and two patients died within 2 months of combination therapy (due to respiratory failure [one patient] and liver failure subsequent to bacterial infection, respiratory failure, and shock [one patient]). In comparison, six patients receiving only triple therapy (historical controls) died within 2 months (14). Baseline FVC% or DLCO% measurements were reported for 23 patients with DM-ILD, and improvements, although not explicitly quantified in all cases, were noted in all 23 patients treated with JAK inhibitors (23,33,38,41-43).

Calcinosis and Arthralgia—There were six cases of adults with calcinosis reported in four publications, all of which improved after treatment with a JAK inhibitor (13,22,23). In a case series of three patients with calcinosis from the STIR open-label study, improvement in calcinosis was noted on imaging after 3 months of treatment (24). Two of these patients were positive for antinuclear matrix protein 2 (NXP2) antibodies, and the third was positive for anti-transcription intermediary factor 1 γ (TIF1-γ) antibodies.

Arthralgia improved with JAK inhibitor treatment in all cases for which outcomes (either subjective or objective) for arthralgia were reported (12,23,30,32,34,36,37,40).

IFN Gene Signature—In the five studies reporting data for 17 unique adult patients in which serum IFN levels and/or IFN-stimulated gene expression were measured, all 17 patients showed reduction in IFN or IFN gene signature with JAK inhibitor treatment (13,20,32,33,35).

Laboratory Parameters—Although not all patients were surveyed for autoantibodies, antibody testing was reported in 69 patients with DM. Of these patients, 63 (91%) were seropositive for at least one MSA or MAA. Of MSAs, 20 patients were positive for anti–TIF1-γ, 33 for anti-MDA5, four for anti-NXP2, three for anti-Mi2, four for anti-small ubiquitin like modifier activating enzyme heterodimer (SAE), and one for anti-Jo1 antibodies. Of MAAs, 12 patients were positive for anti-Ro (−52 or −60) antibodies. Six patients were MSA/MAA negative. Other antibodies that were reported included antinuclear antibody (ANA; for which six patients were positive), rheumatoid factor (two patients), and anti–cyclic citrullinated peptide (two patients).

In four studies, CK levels were reported for four unique patients. Baseline CK (range, 354–4112 U/L) improved with JAK inhibitor therapy (range, 32–308 U/L) (20,21,37). One case (baseline CK, 535 U/L) reported levels as normal after therapy (44).

Total Improvement Score—In the STIR trial, all 10 patients achieved the ACR/EULAR criteria for at least minimal improvement (TIS ≥20) after 12 weeks of tofacitinib treatment, and five of the 10 patients achieved at least moderate improvement (TIS ≥40) (13,25,26). In the long-term extension study of up to 96 weeks, six of seven patients demonstrated at least minimal improvement on the TIS (26).

Juvenile Dermatomyositis

Cutaneous Disease—Of the 61 unique patients with JDM, 60 had active cutaneous disease (Table 3). Of these patients, 57 had significant improvement in skin symptoms after JAK inhibitor treatment. One patient (1.6%) had initial improvement but experienced relapse of skin rash after 8 weeks of treatment with a JAK inhibitor.

CDASI scores (pre- and post-JAK inhibitor treatment) were reported for eight patients with JDM (19,45,46). At baseline, CDASI scores ranged from 20–53. After treatment with a JAK inhibitor, improvements ranged from 7–27 points from baseline after 4–12 weeks, 9–34 points from baseline after 52 weeks, and 14–36 points from baseline after 72 weeks. Skin DAS (scale 0–9) or modified skin DAS (scale 0–5) scores were reported for 14 patients

(47-50). Baseline skin DAS scores ranged from 2–8, and posttreatment initiation scores ranged from 0–8. Eight patients had complete resolution (0 on skin DAS; 57%), and two had scores that did not improve (14%) (47,49,50). One patient with a baseline modified skin DAS score of 5 improved to a score of 1 (48).

Muscle Disease—A total of 36 patients with JDM from 10 analyses (11 publications) had active, refractory muscle disease (Table 4). Overall, improvement with JAK inhibitor treatment was reported in 30 patients (83%). Pre- and posttreatment muscle activity scores (MMT-8, Muscle DAS, or CMAS) were available for 25 patients with muscle disease (45-48,50-54). Of these 25 patients, seven (28%) did not show objective improvements in muscle disease with JAK inhibitor therapy. Three of the seven patients were reported in a retrospective study of patients treated with ruxolitinib or tofacitinib (55) in which 7/10 patients had muscle improvement as measured by the CMAS (mean CMAS scores: baseline, 24.9; posttreatment, 38.2). Of the three patients from this study with CMAS scores that were unchanged from baseline after treatment, two reported qualitative improvements in fatigue and activity tolerance; the third patient was not evaluated using CMAS before treatment owing to joint involvement (55). In a retrospective study in which nine patients had JDM with muscle involvement and were treated with ruxolitinib or baricitinib, four achieved complete responses (by MMT-8 and CMAS) (49). However, three patients experienced muscle relapse after partially responding, one patient with partial response discontinued owing to insufficient efficacy, and one patient was considered a nonresponder (49).

Of the patients with muscle disease who had objective muscle activity responses to JAK inhibitor treatment, baseline MMT-8 ranged from 108–142 (45,46), and baseline CMAS ranged from 0–46 (47-52,54). MMT-8 scores improved by 25–26 points from baseline after 12 weeks of treatment with a JAK inhibitor (45); in patients with longer-term use, scores improved by 7–39 points (45,46). With long-term JAK inhibitor use (12–31 months), CMAS scores improved by 18–41 points from baseline (54).

Interstitial Lung Disease—In four publications, 10 patients had JDM-ILD, and four were anti-MDA5 positive (46,50,54,55). Of the 10 patients with ILD, all experienced improvement in lung disease activity with JAK inhibitor treatment (46,50). Four patients had individual DLCO% reported (all baseline DLCO% ≤60%); one patient improved from 55% to 96%, whereas three patients experienced smaller improvements (posttreatment DLCO%, 60%–75%). No outcomes specific to ILD were reported in the remaining two studies (six patients) (54,55).

Calcinosis—Calcinosis was reported in eight patients with JDM, seven of whom experienced improvement in calcinosis following JAK inhibitor treatment (46,48,49,52,53,56).

IFN Gene Signature—In six analyses, 18 patients had elevated serum IFN or IFN-stimulated gene expression; in all patients for whom posttreatment measurements were taken (n=16), IFN levels or gene signatures were decreased following JAK inhibitor treatment (45-49,51).

Laboratory Parameters—Antibody testing was reported for 56 patients, 11 of whom were MSA-/MAA-negative. Of MSAs, six patients were positive for anti–TIF1-γ antibodies, six for anti-MDA5, 24 for anti-NXP2, one for anti-Mi2, one for anti-Jo1, and one for anti-PL7. Of MAAs, one patient was positive for anti-Ku antibodies, one for anti–U1-RNP, and 11 for anti-Ro (−60 and/or −52). A total of 14 patients also tested positive for ANA.

CK and aldolase levels were reported for four and two patients, respectively. Two patients with baseline CK levels of 403 and 1797 U/L decreased to 61 and 70 to 109 U/L, respectively, after JAK inhibitor treatment (48,50); two patients with baseline CK levels of 640 and 1440 U/L were reported as normal after treatment (52). Aldolase levels of two patients decreased from 9.6 to 7 U/L and 10.1 to 4.9 U/L (46).

Risk of Bias

Risk of bias, assessed using an NIH quality assessment tool for case series studies, was found to be low for all eight open-label trials included. Of the 40 remaining case series, case reports, and observational or retrospective studies identified, risk of bias was assessed to be low for 31 reports; 9 reports had unclear risk of bias.

Discussion

JAK inhibitors add to the growing armamentarium of potential therapeutic options for adult DM and JDM and have emerged as a potential treatment for refractory DM following the demonstrated disease-modifying effects of JAK inhibition in rheumatic diseases (57,58). The patients reported in the publications in this systematic literature review displayed persistent refractory symptoms and did not see improvement with several first- and second-line treatments (eg, methotrexate, mycophenolate, azathioprine), including corticosteroids and other immunomodulatory agents such as IVIG. Outcome assessments varied; however, our review demonstrates that treatment with a JAK inhibitor was associated with a wide range of significantly improved or resolved DM manifestations, including skin lesions, muscle weakness, ILD, and calcinosis. Clinical efficacy in patients with DM was seen with similar daily JAK inhibitor doses used in other autoimmune diseases (Supplemental Tables 1 and 2; (59-61).

Our findings highlight that clinical improvement was most striking in adult patients with pronounced skin symptoms. When included as an outcome measure, CDASI scores improved by a mean of 19 points overall across studies of patients with DM and JDM (8,13,19-23,26,27,45,46). Improvements after treatment with a JAK inhibitor were reported for most cases of muscle disease in adults with DM, and most were described as an increase in muscle strength. Patients with JDM had a mean improvement in MMT-8 scores of 24.9 points, highlighting improvement in muscle strength in children. Overall, the composite assessment of improvement in JDM as measured by the CMAS also demonstrated a clinically significant improvement of 16 points (a 1.5- to 3-point change in CMAS can be considered clinically meaningful for patients with JDM (62)).

Patients with DM have dysregulation of the type I IFN pathway (3), which is mediated through JAK1 and TYK2 activation (6). Among the studies that reported IFN levels or IFN-regulated gene expression after JAK inhibitor initiation, all showed that the clinical response corresponded with the downregulation of IFN activity, providing further evidence that JAK inhibitors may similarly benefit patients with DM by decreasing type I IFN signaling.

Although most patients were on concomitant immunosuppression, an open-label proof-of-concept study demonstrated that JAK inhibitor monotherapy was efficacious (13). Furthermore, most patients with DM were able to taper or discontinue concomitant corticosteroid therapy while on JAK inhibitor therapy, further supporting the therapeutic potential of JAK inhibitors in DM.

No JAK inhibitor is currently indicated for DM/JDM, limiting their clinical use. JAK inhibitors currently approved for autoimmune diseases are baricitinib (JAK1/2 inhibitor), upadacitinib (JAK1 inhibitor), and tofacitinib (JAK1/2/3 inhibitor) (Supplemental Table 5). In addition to the approved drugs that target JAK1 and/or JAK2, several drugs that target other members of the JAK family are in development. TYK2 inhibitors, such as deucravacitinib (TYK2) and brepocitinib (JAK1/TYK2), may be especially of interest for mediating IFN signaling. Randomized controlled trials are needed to further elucidate the therapeutic utility of JAK inhibition in DM and JDM.

Although this study is the most comprehensive systematic review on JAK inhibitor therapy and DM to date, it is not without limitations. The studies included are heterogeneous, often with differing outcome measures; thus, direct comparison of results is difficult. If a publication included patients that were likely included in another publication (ie, from a larger analysis or from an ongoing trial), the patients from the publication in question were not included in the count of unique patients, and therefore the number of unique patients may be underrepresented. Evaluation of safety-related data was beyond the scope of this review.

Our systematic review demonstrated that treatment with a JAK inhibitor was associated with reduced IFN markers and improved or resolved symptoms of DM and JDM, including skin, muscle, and lung disease. There is a need for carefully designed randomized controlled trials to confirm the role of JAK inhibition in these encouraging findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest

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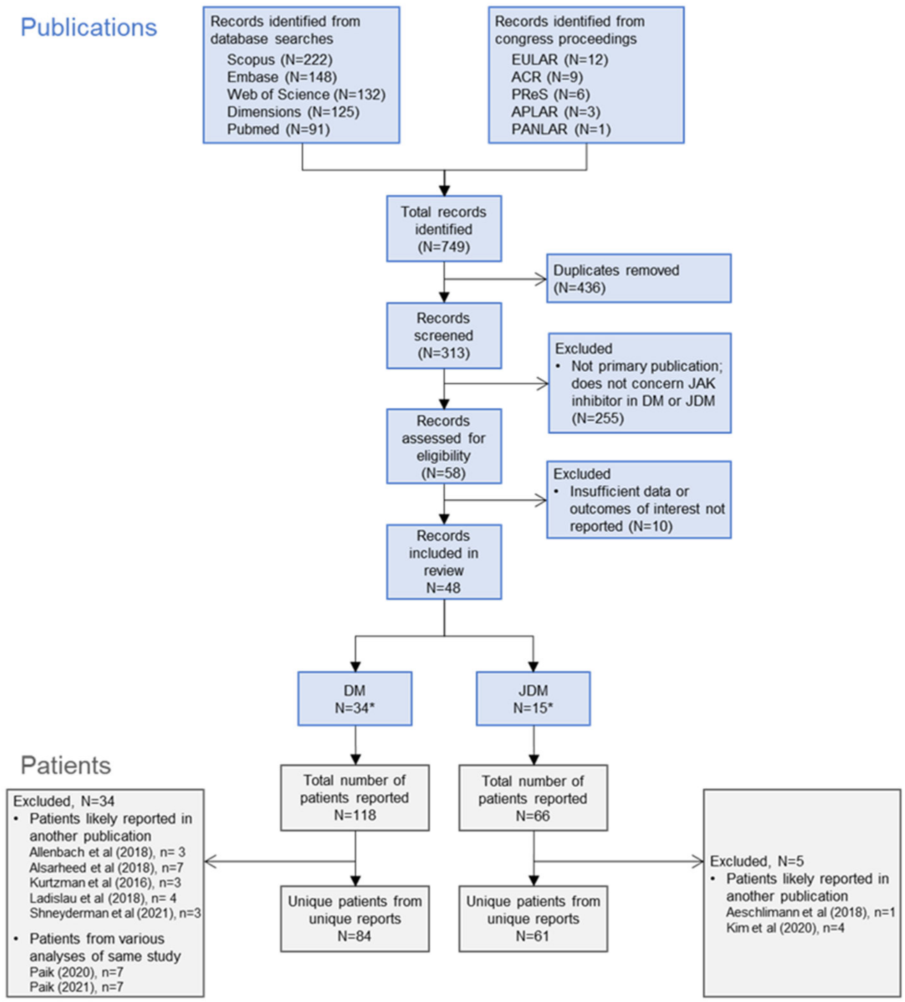

Figure 1.

Systematic literature review search strategy and article attrition. ACR, American College of Rheumatology; APLAR, Asia-Pacific League of Associations for Rheumatology; DM, dermatomyositis; EULAR, European League Against Rheumatism; JAK, Janus kinase; JDM, juvenile dermatomyositis; PANLAR, Pan-American League of Rheumatology Associations; PReS, Paediatric Rheumatology European Society. *1 report included patients with DM and JDM (19).

Table 1.

Publications of Adult DM That Report Efficacy of JAK Inhibitors on Skin Disease

Publication	N	Time to Outcome	Baseline CDASI Assessment	Posttreatment or Change in CDASI Assessment	Other Clinical Improvements
Hornung et al (2014) (8)	1	2 months	12	0	–
Paik and Christopher-Stine (2017) (12)	1	2–6 months	NR	NR	Improvement in cutaneous symptoms within 2 months; prednisone tapered without worsening of skin lesions
Hornig et al (2018) (33)	1	2 months	NR	NR	Improved skin condition at 2 months
Kurasawa et al (2018) (14)	5	12 months	NR	NR	Skin rash improved within 30 days for all 3 surviving patients
Landon-Cardinal et al (2019) (27)	12	3, 11.6 ± 6.8 months	Mean, 31	Mean, 16 (3 months); 8 (11.6 months)	At 3 months, 11/12 patients had >5-point improvement in CDASI score
Allenbach et al (2018) (63)*	3	3 months	NR	NR	Improvement in skin lesions
Ladislau et al (2018) (20)*	4	3 months	Mean, 34.3	Mean, 12.8	All patients had improved facial rash
Moghadam-Kia et al (2019) (37)	4	3–6 months	NR	NR	All patients had improvement in skin lesions or rash
Wendel et al (2019) (23)	2	12–28 weeks	25†	10 at 12 weeks, 3 at 28 weeks†	Rapid improvement in skin lesions
Delvino et al (2020) (30)	1	3–12 months	NR	NR	Rapid and significant improvement in cutaneous lesions by 3 months
Fetter et al (2020) (31)	1	4 months	NR	NR	Noticeable improvement in skin condition after 4 months; hair regrowth on scalp and eyebrows
Fischer et al (2020) (32)	1	8 months	NR	NR	Improvement of skin lesions
Ishikawa et al (2020) (34)	1	6–12 months	NR	NR	Gradual improvement of skin lesions
Jalles et al (2020) (35)	1	4 months	NR	NR	Clinical remission of skin disease after 4 months
Navarro-Navarro et al (2020) (21)	2	4–20 weeks	Mean, 19.5	Mean, 4	Both patients had cutaneous response within 4 weeks
Riggle et al (2020) (22)	4	6 months	Mean, 16.5	Mean, 5.3	All patients had significant improvement of cutaneous disease activity and pruritus
Shinjo and de Souza (2020) (39)	1	2 months	NR	NR	Skin lesions significantly improved within 3–4 weeks
Williams and McKinney (2020) (40)	1	6 months	NR	NR	Substantial improvement in rash
Crespo Cruz et al (2021) (29)	1	Up to 7 months	NR	NR	All skin lesions significantly improved and complete resolution of pruritus
Jasmine et al (2021) (36)	1	2 months	NR	NR	No recurrence of rash after 2 months
Min et al (2021) (19)	9	1–2 months	Mean, 27.2	Mean, 9.2	All patients had clinically significant improvement in pruritus if present; all patients had CDASI improvement of ≥11 points

Publication	N	Time to Outcome	Baseline CDASI Assessment	Posttreatment or Change in CDASI Assessment	Other Clinical Improvements
Alsarheed et al (2018) (28)[‡]	7	4–20 months	–	Mean change, 13	6/7 patients transitioned from moderate or severe cutaneous disease to mild disease as determined by CDASI scores; all patients had improvement in pruritis
Kurtzman et al (2016) (11)[‡]	3	4 weeks	Mean 28.3	Mean, 16.3	All patients had improvement in pruritus
Ohmura et al (2021) (38)	1	7.5 months	NR	NR	Significant improvement in skin lesions after 80 days; symptom-free after 7.5 months
Paik et al (2021a) (13)	10	12 weeks	Mean, 28	Mean, 9.5	Skin improvement evident as early as 4 weeks
Shneyderman et al (2021) (24)[§]	3	12 weeks	Mean 31.3	Mean, 8	–
Paik et al (2020) (25)[§]	7	42, 68 weeks	Mean, 25.4	Mean, 3.9 (at week 42); 5.4 (at week 68)	–
Paik et al (2021b) (26)[§]	7	96 weeks	Mean, 25.4	Mean, 4.7	–

CDASI, Cutaneous Dermatomyositis Disease Area and Severity Index; DM, dermatomyositis; NR, not reported.

[*] Some or all patients likely to have been reported in Landon-Cardinal et al (2019) (27).

[†] Reported for one patient.

[‡] Some or all patients likely to have been reported in Min et al (2021) (19).

[§] Patients reported in Paik et al (2021a) (13).

Table 2.

Publications of Adult DM That Report Efficacy of JAK Inhibitors in Muscle Disease Activity

Publication	N*	Time to Outcome	Baseline Muscle Strength Assessment	Posttreatment Muscle Strength Assessment	Other Clinical Improvements
Hornung et al (2014) (8)	1	2 months	NR	NR	Patient regained muscle strength
Paik and Christopher-Stine (2017) (12)	1	2–6 months	Handheld dynamometry, 4/5	Handheld dynamometry, 5/5	Muscle strength improved within 2 months; prednisone tapered at 2 months without worsening of muscle weakness
Allenbach et al (2018) (63)†	1	3 months			Muscle strength improved
Ladislau et al (2018) (20)†	2	3 months	Mean MRC, 3	Mean MRC, 5	Muscle strength improved
Moghadam-Kia et al (2019) (37)	1	6 months	NR	NR	Improved MMT at 6 months in patient with active muscle disease
Wendel et al (2019) (23)	1	12, 28 weeks	NR	NR	Muscle strength improved after 12 weeks
Delvino et al (2020) (30)	1	3–12 months	NR	NR	Subjective improvement in strength within 3 months, which was sustained at 12 months
Fetter et al (2020) (31)	1	4 months	NR	NR	Noticeable improvement in muscle strength
Jalles et al (2020) (35)	1	4 months	NR	NR	Patient regained muscle strength; clinical remission
Navarro-Navarro et al (2020) (21)	1	20 weeks	NR	NR	Subjective improvement in strength and fatigue; muscle enzymes returned to normal range
Williams and McKinney (2020) (40)	1	6 months	NR	NR	Patient experienced regained muscle strength
Min et al (2021) (19)	2 active, 2 mild	1–2 months	NR	NR	Resolution of muscle disease activity in patients with refractory muscle weakness; subjective improvement in strength and fatigue in patients with mild muscle weakness
Kurtzman et al (2016) (11)‡	2 mild	4 weeks	NR	NR	Subjective improvement in strength and fatigue
Paik et al (2021a) (13)	1	12 weeks	MMT-8, 127	MMT-8, 136	Evidence of edema on baseline muscle MRI, which improved by week 12

DM, dermatomyositis; MMT, manual muscle testing; MRC, Medical Research Council MMT Scale; MRI, magnetic resonance imaging; NR, not reported.

*Number of patients with active muscle disease; publication may have included additional patients without active muscle disease.

†Some or all patients likely to have been reported in another publication.

‡Some or all patients likely to have been reported in Min et al (2021) (19).

Table 3.

Publications of JDM That Report Efficacy of JAK Inhibitors on Skin Disease

Publication	N	Time to Outcome	Baseline CDASI or Skin DAS Assessment	Posttreatment or Change in CDASI or Skin DAS Assessment	Other Clinical Improvements
Papadopoulou et al (2019) (48)	1	6 months	Modified skin DAS, 5	Modified skin DAS, 1	–
Sabbagh et al (2019) (46)	2	6, 12 months	Mean CDASI, 21	Mean CDASI, 9.5	–
El-Lateef (2020) (56)	1	6 months	NR	NR	Remission of skin lesions
Heinen et al (2020) (51)	1	7 months	NR	NR	Reduction in sternal rash
Kim et al (2020a) (45)	4	24, 72 weeks	CDASI mean, 42.5	CDASI mean, 26.3 (24 weeks); 17.8 (72 weeks)	Significant improvement in CDASI by week 4
Yu et al (2020) (50)	3	3, 6 months	Skin DAS mean, 4.7	Skin DAS mean, 1.7 (3 months); 0 (6 months)	Significant improvement in skin disease activity by 3 months; near complete resolution of Gottron's papules and heliotrope rash in one patient
Ding et al (2021) (55)	25*	3–18 months	NR	NR	All patients showed improvement in rashes within 1–2 weeks; no clinically observable rash present after 12 weeks; one patient experienced relapse of rash
Kostic et al (2021) (64)	2	5, 7 months	NR	NR	Partial or complete response within 5 or 7 months, respectively, by physician assessment
Le Voyer et al (2021) (49)	10	3–6 months	Skin DAS mean, 6.0	Skin DAS mean, 1 (6 months)†	–
Aeschliman et al (2018) (47)‡	1	2 months	Skin DAS, 4	Skin DAS, 0	
Zhou et al (2021) (53)	1	6, 17 months	NR	NR	Skin lesions fully resolved within 6 months (physician assessment)

CDASI, Cutaneous Dermatomyositis Disease Area and Severity Index; DAS, disease activity score; JDM, juvenile dermatomyositis; NR, not reported.

*1 patient did not have active cutaneous disease.

†Reported in patients with outcome data at 6 months.

‡Patient likely to have been reported in Le Voyer et al (2021) (49).

Table 4.

Muscle Disease Activity Results Among Publications of JDM That Report Muscle Symptom Outcomes

Publication	N*	Time to Outcome	Baseline Muscle Strength Assessment	Posttreatment Muscle Strength Assessment	Other Clinical Improvements
Papadopoulou et al (2019) (48)	1	6 months	MMT, 59 CMAS, 46	MMT, 70 CMAS, 50	Clinical improvement in muscle symptoms
Sabbagh et al (2019) (46)	2	6, 12 months	Mean MMT-8, 136 CMAS, 21†	MMT-8 (6 months), 148† MMT-8 (12 months), 149† CMAS, 49 (12 months)†	–
Heinen et al (2020) (51)	1	7 months	CMAS, 18	CMAS, 40	Increased muscle strength within 3 months; absence of inflammation in quadriceps on MRI
Kim et al (2020a) (45)	2	24, 72 weeks	Mean MMT-8, 112	Mean MMT-8, 138.5 (24 weeks); 146 (72 weeks)	Muscle improvement seen as early as week 4 with clinical improvement (per MMT-8) by week 8 and confirmed by MRI
Sozeri et al (2020) (52)	2	3 months	Mean CMAS, 30	Mean CMAS, 51	–
Yu et al (2020) (50)	3	3, 6 months	Mean MMT, 48.3 Mean CMAS, 30 Mean Muscle DAS, 7.3	Mean MMT, 69 (3 months); 79.3 (6 months) Mean CMAS, 45 (3 months); 50.3 (6 months) Mean Muscle DAS, 3 (3 months); 0.3 (6 months)	Significant improvement in muscle weakness by 3 months
Ding et al (2021) (55)	10	3–18 months	Mean CMAS, 24.9§	Mean CMAS, 38.2§	2 of 9 patients with CMAS assessment had no improvement but reported subjective improvement in fatigue and activity tolerance
Le Voyer et al (2021) (49)	9 active, 1 mild	3–6 months	Mean MMT, 53.5 Mean CMAS, 26.6	Mean MMT, 69 Mean CMAS, 40.4	4 of 9 patients had complete response; 5 of 9 had muscle relapse, were non-responders, or had insufficient efficacy
Aeschliman et al (2018) (47)‡	1	2 months	Mean MMT, 57 Mean CMAS, 47	Mean MMT, 79 Mean CMAS, 52	Resolution of muscle disease within 2 months
Wang et al (2021) (54)	5	12–31 months	Mean CMAS, 1.6	Mean CMAS, 33	–
Zhou et al (2021) (53)	1	6, 17 months	CMAS, 36	CMAS, 40 (6 months); 48 (17 months)	–

CMAS, Childhood Myositis Activity Score; DAS, disease activity score; JAK, Janus kinase; JDM, juvenile dermatomyositis; MMT, manual muscle testing; MRC, Medical Research Council MMT Scale; MRI, magnetic resonance imaging; NR, not reported.

*Number of patients with active muscle disease; publication may have included additional patients without active muscle disease.

†Score reported for one patient.

‡Patient likely to have been reported in Le Voyer et al (2021) (49).

§1 patient with baseline muscle weakness did not undergo CMAS assessment before initiating JAK inhibitor.