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BRIEF REPORT

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# JAK inhibitors in refractory dermatomyositis: A case series

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## Abstract

This retrospective cohort study assessed the efficacy and safety of Janus kinase (JAK) inhibitors, tofacitinib and baricitinib, in 14 patients with refractory dermatomyositis (DM), a multisystemic autoimmune disorder with limited therapeutic options. Results demonstrated a significant median decrease of 21 points and a 76% reduction in the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) scores, along with a complete resolution of muscular symptoms in 64% of the patients. JAK inhibitors were effective in managing refractory DM across various subtypes with mild and manageable adverse events.

**KEYWORDS**

baricitinib, dermatomyositis, JAK inhibitors, juvenile, refractory, tofacitinib

## INTRODUCTION

Dermatomyositis (DM) is a rare systemic autoimmune disorder characterized by muscle inflammation and skin involvement, resulting in substantial morbidity and mortality.[1] Current treatment options, including corticosteroids, intravenous immunoglobulins, antimalarials and immunosuppressants, have limitations, leaving a subset of patients uncontrolled or reliant on high corticosteroid doses.[1] As such, there is a need for more targeted, safe and effective disease-modifying strategies for DM.

Transcriptomic analyses in both adult and juvenile DM have revealed a pivotal role of type I interferon (IFN-I) pathway in the pathogenesis and maintenance of the disease.[2] The emergence of Janus kinases (JAKs) as crucial mediators in IFN signal transduction positions JAK inhibitors as therapeutic agents able to reduce serum IFN

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and/or IFN stimulated gene expression,[2] and thus, change the course of the disease.

Recent studies have revealed the efficacy of JAK inhibitors in managing a spectrum of DM manifestations, including cutaneous symptoms, myositis and interstitial lung disease (ILD).[2–4] Most case series involve concomitant treatment with corticosteroids or immunosuppressant drugs. Tofacitinib, a JAK1 and JAK3 inhibitor, showed promising results as monotherapy for recalcitrant cutaneous manifestations, as evidenced by a recent proof-of-concept study.[5] However, a comprehensive understanding of the efficacy and safety of JAK inhibitors across diverse patient subsets is required to determine if JAK inhibitors are potential candidates in every clinical setting.

This study aims to assess the effectiveness and safety of JAK inhibitors in a real-world setting for refractory DM patients, including different patient subsets.

## MATERIALS AND METHODS

This retrospective cohort study evaluated the clinical outcomes of patients with DM who received treatment with JAK inhibitors in a real-world setting. The study included patients with DM being treated with JAK inhibitors between January 2020 and July 2023 in a tertiary care hospital in Barcelona, Spain. Patients were followed up until March 2024, with a median follow-up period of 30 months.

Inclusion criteria were individuals diagnosed with DM or juvenile dermatomyositis (JDM), based on clinical presentation, cutaneous biopsy and serological examinations. Patients were required to have received JAK inhibitor treatment for at least 2 months due to refractory disease, defined as a lack of disease control after at least two distinct lines of systemic therapy, including corticosteroids.

The primary outcome measure was the change in the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) score.[6] Changes in Manual Muscle Testing (MMT) grading system, subjective improvements in other manifestations and adverse events were also assessed. The statistical analysis was performed using SPSS software. The Wilcoxon signed-rank test was employed to assess the significance of changes in CDASI and MMT scores from baseline to post-treatment. $p$-values $<0.05$ were considered statistically significant. Approval for the administration of JAK inhibitors was granted by the Pharmacy Commission of our hospital. Ethical considerations and patient confidentiality were maintained throughout the study.

## RESULTS

Fourteen patients diagnosed with DM were included in this case series (Table S1). Baseline characteristics and demographics are summarized in Table 1. The patient cohort

**TABLE 1** Baseline and demographic characteristics.

| Items | $N=14$ |
|---|---|
| Gender | |
| Female | 10 (71%) |
| Male | 4 (29%) |
| Age, years | 57.5 (19–68) |
| DM subtype | |
| Classic | 8 (57%) |
| Amyopathic | 3 (21%) |
| Juvenile | 2 (14%) |
| Paraneoplastic | 1 (7%) |
| Manifestations | |
| Dermatologic | 14 (100%) |
| Calcinosis | 2 (14%) |
| Baseline CDASI | 29.0 (18–56) |
| Constitutional | 11 (79%) |
| Muscle | 11 (79%) |
| Baseline MMT | 4.0 (2–5) |
| Lung (ILD) | 2 (14%) |
| Laryngeal | 1 (7%) |
| Antibody profile | |
| Anti- TIF1γ | 7 (50%) |
| Anti- MDA5 | 4 (29%) |
| Anti- Ro52 | 3 (21%) |
| Anti- Mi2 | 2 (14%) |
| Anti- NXP2 | 2 (14%) |
| Anti- PL7 | 2 (14%) |
| Anti- RNP | 1 (7%) |
| Previous therapies[a] | |
| Systemic steroids | 14 (100%) |
| Median dose (mg/d) | 10 (0–30) |
| Classic IS | 11 (79%) |
| 0 | 3 (21%) |
| 1 | 10 (71%) |
| 2 | 1 (7%) |
| IVIG | 6 (43%) |
| Antimalarials | 2 (14%) |

*Note*: Continuous data are presented as median (range). Categorical data are presented as number and percentage.

Abbreviations: CDASI, Cutaneous Dermatomyositis Disease Area and Severity Index; DM; dermatomyositis; ILD, interstitial lung disease; IS, immunosuppressants; IVIG, intravenous immunoglobulins; MMT, Manual Muscle Testing.

[a]Including only those therapies used immediately before the initiation of JAK inhibitor treatment.

contained diverse DM subtypes, with classic DM accounting for 57%, followed by amyopathic (21%), juvenile (14%) and paraneoplastic (7%). Cutaneous lesions were observed in all patients, including two cases with calcinosis. Other affected systems included the musculoskeletal (79%), pulmonary (14%) and the larynx (7%). Anti-TIF1γ was the antibody that tested positive most frequently (50% of patients). In the therapeutic plan immediately prior to the initiation of JAK inhibitors, patients were prescribed a median dosage of 10 mg of prednisone, and 79% were being treated with at least one immunosuppressant. JAK inhibitors employed in this series were tofacitinib (93%) and baricitinib (7%), at initial doses of 5 mg bid and 4 mg daily, respectively. One case treated with tofacitinib had received prior treatment with ruxolitinib, but this was changed due to a refractory dyslipidaemia. The results revealed significant global improvements within a median timeframe of 2 months (range: 1–6 months). In terms of cutaneous manifestations, there was a median reduction from 29 CDASI points to 8 points, resulting in a median 76% decrease in CDASI scores compared to the baseline ($p < 0.001$).

Complete resolution of cutaneous manifestations was observed in 29% of patients. One patient did not exhibit any response, and there were two cases of secondary failure. One of the two patients with calcinosis demonstrated a significant response to JAK inhibitors along with topical corticosteroids. Muscular manifestations displayed complete resolution in 64% of cases, defined by lack of muscular symptoms, normalization of MMT grading system and muscle enzymes. The median MMT in all muscular groups analysed increased from 4/5 to 5/5 points ($p = 0.013$). One of the two patients with pulmonary involvement showed a mild improvement in pulmonary function test results and radiological findings. The other patient reached radiological and clinical stabilization with the addition of antifibrotic therapy. Patients with no prior history of pulmonary manifestations did not develop them while undergoing treatment with JAK inhibitors. Complete resolution of laryngeal symptoms was observed in the patient presenting this manifestation (Table 2). Only 7% of patients being treated with classic immunosuppressants were required to maintain them concomitant with JAK inhibitors. Moreover, JAK inhibitors allowed the gradual reduction of oral prednisone dosage. Starting on an average dose of 13.9 mg/day of prednisone, at the end of the follow-up period, the dose had decreased to 5.2 mg/day.

Efficacy remained consistent across different DM and patient subgroups, albeit with no response observed in the sole patient with paraneoplastic DM, who prematurely discontinued the JAK inhibitor treatment due to concerns about potential side effects. Five patients discontinued treatment, due to a lack of substantial clinical improvement, secondary failure, adverse events and a voluntary decision. Dosage adjustments were made based on clinical evolution. Seven patients

**TABLE 2** JAK inhibitors in refractory Dermatomyositis. Treatment and outcomes.

| Item | *N* = 14 |
|---|---|
| Treatment | |
| Tofacitinib | 13 (93%) |
| Baricitinib[a] | 1 (7%) |
| Concomitant treatments with JAK inhibitors (at the end of follow-up) | |
| Systemic steroids | 8 (57%) |
| Median dose (mg/d) | 5 (0–20) |
| IVIG | 5 (36%) |
| Antimalarials | 3 (21%) |
| Plasmapheresis | 1 (7%) |
| Methotrexate | 1 (7%) |
| JAK inhibitor interruption | |
| No | 9 (64%) |
| Yes | 5 (36%) |
| Median time to interruption, months | 6 (2–45) |
| Causes | |
| Voluntary withdrawal | 1 (20%) |
| Lack of substantial improvement | 3 (60%) |
| Secondary failure | 2 (40%) |
| Adverse events | 2 (40%) |
| Next line of treatment used | |
| Maintenance of other systemic therapies | 2 (40%) |
| Anifrolumab | 1 (20%) |
| Lost to follow-up (baricitinib proposed) | 1 (20%) |
| Rituximab | 1 (20%) |
| Efficacy | |
| Median time to improvement, months | 2 (1–6) |
| Cutaneous manifestations | |
| Complete resolution | 4 (29%) |
| Significant response | 7 (50%) |
| Secondary failure | 2 (14%) |
| No response | 1 (7%) |
| Post-therapy CDASI | 8.0 (0–35) |
| Calcinosis | |
| Significant response | 1 (50%) |
| No response | 1 (50%) |
| Muscle manifestations | |
| Complete resolution | 7 (64%) |
| Partial response | 3 (27%) |
| No response | 1 (9%) |
| Post-therapy MMT | 5.0 (3–5) |
| Pulmonary manifestations | |
| Mild response | 1 (50%) |
| Stabilization | 1 (50%) |
| Laryngeal manifestations | |
| Complete resolution | 1 (100%) |

**TABLE 2** (Continued)

| Item | *N* = 14 |
|---|---|
| Adverse events | |
| None | 9 (64%) |
| Yes | 5 (36%) |
| Herpes zoster | 1 (7%) |
| Dyslipidaemia | 1 (7%) |
| Headache | 1 (7%) |
| Weakness | 1 (7%) |
| Diarrhoea | 2 (14%) |

*Note*: Data regarding JAK inhibitor treatment and other concomitant therapies, their efficacy and safety profile. Continuous data are presented as median (range). Categorical data are presented as number and percentage.

Abbreviations: bid, 'bis in die' (twice daily); CDASI, Cutaneous Dermatomyositis Disease Area and Severity Index; ILD, interstitial lung disease; IVIG, intravenous immunoglobulins; MMT, Manual Muscle Testing; tid, 'ter in die' (three times a day).

[a]One patient had previously received ruxolitinib 5 mg bid (24 months) and 5 mg tid (3 months).

required an increase of tofacitinib to 5 mg tid or 10 mg bid, due to partial improvement in skin manifestations, calcinosis refractoriness or the occurrence of a flare-up.

Non-serious events were experienced by 36% of patients, in alignment with the established side effect profile of JAK inhibitors. A single case of herpes zoster needed a dose reduction of tofacitinib. Two cases of mild adverse events (headache and diarrhoea), coupled with inadequate improvement with JAK inhibitors, prompted the withdrawal of JAK inhibitor treatment.

## DISCUSSION

This case series contributes to explore the potential efficacy and safety of JAK inhibitors in managing diverse clinical subtypes of refractory DM. The results further reinforce the growing evidence supporting the use of JAK inhibitors in addressing various manifestations of the disease.

The response patterns observed in this case series align with existing literature. We observed a remarkable and sustained improvement in cutaneous and muscular manifestations with a median decrease of 21 points in the CDASI score and a median increase of 0.25 points in the MMT grading system. In a systematic review including 145 patients with DM and juvenile DM (JDM) treated with JAK inhibitors alongside other therapies, 83%–100% of the patients improved in terms of skin and muscle refractory symptoms, ILD and calcinosis, with an average improvement of 19 points in CDASI scores.[2] More recent case series also yielded similarly positive results, and allowed corticosteroid dose tapering.[3,4]

Similarly to adult DM, JDM is also characterized by the hyperactivation of the IFN-I signalling system. Studies in 15 JDM patients revealed a strong correlation between elevated IFN I scores and disease activity, suggesting IFN I-score as a potential biomarker.[7] In a review of 195 JDM patients treated with JAK inhibitors, baricitinib showed 92.7% improvement rate, followed by tofacitinib (89.7%) and ruxolitinib (69.2%). Although adverse events were common, they were mostly mild, with upper respiratory tract infections being predominant.[8]

Despite the high occurrence of cases with antibodies profiles strongly associated to paraneoplastic dermatomyositis in our series (with 50% testing positive for TIF1γ antibody and 14% for NXP2 antibody), a complete neoplasia screening following current guidelines and a meticulous follow-up only revealed a case of paraneoplastic DM, consisting in a patient with a prior diagnosis of breast cancer. The management of paraneoplastic DM is challenging, often displaying lower responsiveness to pharmacological interventions.[9] Unfortunately, our ability to precisely evaluate the effectiveness within this subset was limited by the voluntary withdrawal of the only patient from the study. Future research efforts should focus on the exploration of patient subgroups that might benefit most from JAK inhibitor therapy.

In our case series, among the five patients who interrupted treatment with JAK inhibitors, one patient refused to start new systemic drugs, and another patient maintained her treatment with subcutaneous methotrexate due to acceptable disease control. Of the remaining three patients, baricitinib was proposed for one but was lost to follow-up; and the other two patients have already shown improvement with anifrolumab and rituximab. There is a paucity of publications regarding options for JAK inhibitor-refractory cases. Switching from a JAK inhibitor to another, though uncertain in effectiveness, could be considered in cases with partial improvement, given the differing affinities of baricitinib and tofacitinib for JAK isoforms. Moreover, variances in the ability of JAK inhibitors to reverse IFN-I induced genetic changes in myoblasts from patients with JDM, imply distinct action profiles for each drug.[10] In our series, a patient under ruxolitinib had been switched to tofacitinib for refractory dyslipidaemia, maintaining acceptable disease control with normalization of cholesterol levels. Rituximab, a monoclonal antibody against CD20 antigen, has shown promising results in refractory DM and JDM, with significant improvement in muscular and cutaneous manifestations. Antagonists of IFN-I receptor have also shown potential in suppressing IFN expression and improving muscular manifestations. Other options such as intravenous immunoglobulins and tocilizumab (IL-6 antagonist) can be considered in refractory cases.[11]

Adverse events observed in our case were consistent with known profiles of JAK inhibitors, remaining predominantly non-serious and manageable. However, serious infections and thromboembolic events have been

reported in other case series.[3,4] Though we did not observe any internal malignancy attributed to JAK inhibitors, the risk of malignancies in DM is inherently increased, and a detrimental effect of JAK inhibition on carcinogenesis has been demonstrated,[12] underscoring the necessity for close follow-up for potential malignancies.

Our study has several limitations, including the relatively small sample size, the heterogeneity of patients and JAK inhibitors and dosages used, and the retrospective design. The inclusion of concomitant therapies may have influenced the apparent efficacy of JAK inhibitors, demanding careful interpretation.

## CONCLUSION

JAK inhibitors hold a promising potential in the management of refractory DM symptoms. Our case series contributes to shaping evidence-based strategies for treating this multisystemic autoimmune disorder. Further extensive, long-term series are required to identify predictors of treatment response and assess the sustained efficacy of JAK inhibitors and their safety profile over extended periods.

### AUTHOR CONTRIBUTIONS

We declare that all authors have contributed significantly to the work.

### ACKNOWLEDGEMENTS

None.

### CONFLICT OF INTEREST STATEMENT

None declared.

### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### ETHICS STATEMENT

Approval for the administration of these drugs was granted by the Pharmacy Commission of our hospital in all instances, and written informed consent was obtained from all patients. All patient data in our retrospective case series were anonymized, ensuring privacy and confidentiality without involving identifiable subjects.

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### SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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