Janus kinase inhibitors therapy in idiopathic inflammatory myopathies: a case series

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Abstract

Objective

To evaluate the clinical response of Janus kinase inhibitors (JAKi) across subtypes of idiopathic inflammatory myopathies (IIM) in a cohort of patients with refractory disease.

Methods

We conducted a retrospective analysis of all adult IIM patients treated with JAKi at our centre. Treatment response was assessed based on changes in muscle strength, serum biomarkers of muscle damage and inflammation, pulmonary function, radiological evolution of interstitial lung disease (ILD) and corticosteroid dosage.

Results

Ten IIM patients who were previously or currently receiving JAKi therapy were identified. Six patients were female and the mean age was 52.7 years (standard deviation [SD] 13.91). Anti-synthetase syndrome was the most common subtype (n=5, 50%). At baseline, median manual muscle test 8 score was 136 (interquartile range [IQR] 25.5) and, after therapy, was 147 (IQR 8), representing a statistically significant increase ($p<0.05$). Corticosteroid dose reduction was also statistically significant ($p<0.05$), with the median daily dose decreasing from 10mg to 2.5mg. Additionally, four patients were able to discontinue corticosteroid therapy. In six patients with ILD, diffusion capacity for carbon monoxide improved significantly ($p<0.01$), from 68.33% (IQR 19.31) to 93% (IQR 7.27). No significant changes were observed in serum inflammatory markers, creatine kinase, forced expiratory volume first second or forced vital capacity.

Conclusion

JAKi therapy appears to be clinically effective, well tolerated, and safe in patients with refractory IIM, with a particular benefit in ILD. The steroid sparing effect was also a major outcome. Future prospective and controlled studies are warranted to confirm these preliminary results and better define the therapeutic potential of JAKi in IIM.

Key words

myositis, Janus kinase inhibitors, dermatomyositis, anti-synthetase syndrome

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Introduction

Idiopathic inflammatory myopathies (IIM) are a group of multisystemic autoimmune diseases that most frequently share the feature of immune-mediated muscle injury (1). Progress in the treatment of IIM has been hindered by several factors, including limited understanding of disease pathogenesis, the rarity of these conditions, heterogeneous clinical phenotypes and the paucity of randomised clinical trials (1-3).

Type I and type II cytokine receptors signal through a small group of tyrosine kinases, known as Janus kinase (JAK) family. Upon cytokine binding, activation of these receptors triggers JAK signalling, which recruits the signal transducer and activator of transcription (STAT) proteins, that translocate to the nucleus and modulate gene transcription. Interferons (IFNs) constitute a key subfamily of cytokines, which includes type I (IFNα and IFNβ), type II (IFNγ) and type III (IFNλ). The IFNs bind to type II cytokine receptors. The pathogenic role of IFNs has been clearly demonstrated in monogenic type I interferonopathies, which are characterised by constitutive activation of the type I IFN signalling pathway (4).

The role of interferons in the pathophysiology of several immune-mediated disorders has been well established. In IIM, although the pathogenesis of the disease is poorly understood, several studies have suggested that IFNs may play an important role. Muscle biopsies from patients with dermatomyositis (DM) have shown activation of interferon pathways, supported by the presence of plasmacytoid dendritic cells, which produce significant amounts of type I IFNs. In contrast, muscle biopsies from patients with anti-synthetase syndrome (ASS) revealed more prominent activation of type II IFNs, accompanied by a Th1 phenotype with elevated levels of IFNγ in the bronchoalveolar lavage fluid. Inclusion body myositis (IBM) has also been associated with type II interferon activation. In immune-mediated necrotising myopathy (IMNM), however, IFN does not appear to play a central role (5).

JAK inhibitors (JAKi) are orally administered agents that target JAK proteins and modulate downstream intracellular signalling. These drugs have been approved as effective treatment options for a range of immune-mediated diseases, including rheumatoid arthritis, spondylarthritis, psoriasis, psoriatic arthritis, atopic dermatitis, alopecia areata and inflammatory bowel disease, as well as for hematologic conditions such as myelofibrosis, polycythaemia vera and graft-versus-host disease. The selectivity of each JAKi dictates its specific effects on distinct inflammatory pathways. First-generation therapies, such as tofacitinib, baricitinib, ruxolitinib and peficitinib, inhibit multiple members of the JAK family, whereas next-generation JAKi, like upadacitinib and filgotinib, are more selective for JAK 1 (4, 6).

IIM are a group of disorders with a limited therapeutic armamentarium, with intravenous immunoglobulin (IVIg) being the only on-label drug approved for the treatment of refractory DM (3). JAKi were first introduced for use in IIM in 2014, and since then, numerous case series have highlighted their efficacy in managing refractory skin manifestations of DM. A recent systematic review about the use of JAKi in DM, including juvenile dermatomyositis and anti-melanoma differentiation-associated protein 5 (anti-MDA5) autoantibody-positive amyopathic dermatomyositis (ADM), demonstrated that JAKi treatment was associated with significant improvements in skin lesions, muscle weakness, interstitial lung disease (ILD), and calcinosis (7). A retrospective case series involving 10 patients with refractory DM and ASS treated with upadacitinib showed improvements in cutaneous disease activity, although it failed to evaluate the impact on muscle strength, as only one patient had muscle weakness at baseline (8). In a recent prospective cohort study of patients with DM and ASS, tofacitinib treatment led to significant reductions in disease activity, as assessed by the Myositis Disease Activity Assessment Tool (9).

Most of recently published cases of JAKi therapy in IIM have primarily focused on the dermatomyositis subtype. However, the pathophysiology of other

IIM subtypes, apart from IMNM, appears to support a potentially beneficial therapeutic effect of this drug class. In this study, we report a case series of 10 patients with IIM (other than DM) who were treated with a JAKi. Our aim was to assess the treatment response across various IIM subtypes in a cohort of patients with refractory disease. A beneficial effect was documented, particularly in muscle strength and lung functional performance.

Methods

We conducted a retrospective analysis of all adult patients diagnosed with IIM treated with JAK inhibitors at the Clinical Immunology Unit of Santo António's Hospital in Porto. Patients' medical records were used to obtain medical histories, laboratory analyses, imaging studies, respiratory function tests and histological results. IIM diagnoses were based on the European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) criteria. The subtypes of IIM were defined according to the recent classification proposed by Betteridge et al which has been widely adopted by clinicians worldwide (1). The decision to initiate off-label JAKi therapy was made by a panel of immunology experts and subsequently approved by the Hospital's Pharmacy and Therapeutic Commission. JAKi therapy was proposed for patients with refractory disease, defined as a lack of response to at least two immunosuppressive drugs, at their maximal tolerated dosage, associated with the inability of weaning glucocorticoid therapy for a minimum of three months. Three different JAK inhibitors were prescribed, including baricitinib, tofacitinib, and upadacitinib at daily oral doses of 4 mg, 10 mg and 15 mg, respectively. Muscle strength was evaluated using the Manual Muscle Test 8 (MMT 8). Clinical and laboratory assessments were conducted at baseline and between 3 to 6 months after the initiation of JAKi therapy. Respiratory function tests, including the measurement of diffusing capacity for carbon monoxide (DLCO), and high-resolution computed tomography (HRCT) were performed in patients with interstitial lung disease, with evaluations conducted at baseline and between 6 months to one year after treatment initiation. Assessment of HRCT changes was qualitative, and radiologists' reports did not include a specific classification. Data was collected between January 2017 and December 2024.

Statistical analysis was performed using GraphPad Prism (Prism 10 for Windows, version 10.4.1, November 2024). Qualitative data were presented as numbers and percentages, while quantitative data were expressed as means and standard deviations (SDs) or medians and interquartile ranges (IQRs). Normality was assessed using the Shapiro-Wilk test. Paired comparisons were conducted using the *t*-test and the Wilcoxon signed-rank test. The threshold for statistical significance was set at a *p*-value <0.05.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Santo António's Hospital in Porto, Portugal.

Table I. Demographic, clinical and serological parameters.

Variable	Value
Number of patients, n	10
Age, mean (SD), years	52.7 (13.91)
Age at diagnosis, mean (SD), years	45.8 (16.30)
Female, n (%)	6 (60)
Disease duration, median (IQR), months	74 (39.75)
Expert classification subtype, n (%)	
Anti-synthetase syndrome	5 (50)
Inclusion body myositis	2 (20)
Dermatomyositis	1 (10)
Amyopathic dermatomyositis	1 (10)
Overlap myositis	1 (10)
Myositis specific and associated autoantibodies, n (%)	
Jo-1 + Ro52	4 (40)
Seronegative	2 (20)
MDA5 + SRP + Ro52	1 (10)
Ku + Ro52	1 (10)
cN-1A + Ro52	1 (10)
Mi2	1 (10)
Organ-specific manifestations, n (%)	
Muscular	9 (90)
Articular	8 (80)
Cutaneous	7 (70)
Pulmonary	6 (60)
Cardiac	1 (10)
Vascular	1 (10)

IQR: interquartile range; SD: standard deviation.

Results

In our cohort, we identified 10 patients with IIM who had either previously received or were currently receiving JAKi therapy (Table I). The mean disease duration was 74 months, and most patients were diagnosed at our hospital. The most common classification subtype was ASS (n=5, 50%), followed by IBM (n=2, 20%), DM (n=1, 10%), ADM (n=1, 10%) and overlap myositis (n=1, 10%). Myositis-specific and associated antibodies were consistent with the classification subtype in most cases, except for two seronegative patients, whose clinical diagnoses were supported by biopsy results. Muscular involvement was the most frequent organ-specific manifestation (n=9, 90%), followed by articular (n=8, 80%), cutaneous (n=7, 70%), pulmonary (n=6, 60%), and, in a small subset of patients, cardiac (n=1, 10%) and vascular (n=1, 10%).

The most used JAKi was baricitinib (n=7, 70%), followed by tofacitinib and upadacitinib. As of December 2024, the median treatment duration with a JAKi was 34.5 months. All patients were considered refractory, having previously received first-line therapies, including glucocorticoids or conventional DMARDs, before the initiation of JAKi therapy, with a median of four different drugs

Table II. Previous and current therapies and adverse reactions.

Variable	Value
JAKi drug, n (%)	
Baricitinib	7 (70)
Tofacitinib	2 (20)
Upadacitinib	1 (10)
Treatment duration with JAKi, median (IQR), months	34.5 (30.25)
Minimum treatment time with JAKi, months	1
Maximum treatment time with JAKi, months	46
Previous therapies, n (%)	
Prednisolone	9 (90)
Rituximab	7 (70)
Azathioprine	6 (60)
Mycophenolate mofetil	4 (40)
Intravenous immunoglobulin	4 (40)
Methotrexate	4 (40)
Tacrolimus	3 (30)
Cyclophosphamide	2 (20)
Secukinumab	1 (10)
Number of previous therapies, median (IQR)	4 (2)
Current therapy, n (%)	
JAKi combined therapy, n (%)	6 (60)
Prednisolone	4
Azathioprine	2
Rituximab	2
Mycophenolate mofetil	1
Methotrexate	1
Tacrolimus	1
Intravenous immunoglobulin	1
JAKi monotherapy, n (%)	2 (20)
Other therapies, n (%)	2 (20)
Mycophenolate mofetil	2
Prednisolone	1
Azathioprine	1
Methotrexate	1
Intravenous immunoglobulin	1
Suspended JAKi, n (%)	2 (20)
Adverse reaction: diverticulitis, n (%)	1 (10)
Lack of response, n (%)	1 (10)

IQR: interquartile range; JAKi: Janus kinase inhibitor.

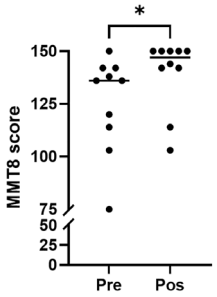

Fig. 1. Manual Muscle Testing 8 (MMT8) score before and after JAKi therapy. MMT8 includes the sum of muscle strength of 5 proximal muscle groups bilaterally, 2 distal muscle groups bilaterally and one axial muscle. The potential range is 0 to 150 and maximum score corresponds to normal muscle strength.
p=0.031 (*).

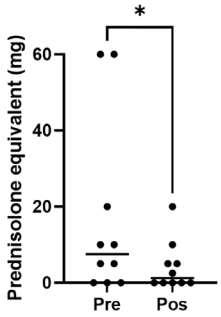

Fig. 2. Prednisolone equivalent dose before and after JAKi therapy. Prednisolone equivalent corresponds to the conversion dose of the glucocorticoid taken by the patient to prednisolone to allow for a comparison between all patients.
p=0.031 (*).

administered (Table II). Considering the median disease duration of 74 months, there was an interval of 39.5 months during which alternative therapies were attempted to induce remission.

Patients were divided into three treatment groups: those receiving a JAKi in combination with other immunosuppressants, those receiving a JAKi alone, and those receiving immunosuppressants other than a JAKi. The latter group consisted of two patients who discontinued JAKi therapy. The first patient experienced an adverse reaction, acute diverticulitis, and the medication was discontinued after one month of treatment. The second patient showed no clinical response after two months of therapy and, given the severity of muscle weakness, treatment was switched to abatacept.

To evaluate the clinical effect of JAKi therapy on IIM patients, we compared the MMT8 score before and after the initiation of treatment. A statistically significant increase in the MMT8 score was observed following treatment (Fig. 1).

We assessed the impact of JAKi therapy on the maintenance dose of prednisolone equivalents (PE). A statistically significant reduction in PE dose was observed following JAKi initiation (Fig. 2). The median daily dose decreased from 10mg to 2.5mg, and all patients were receiving doses equal or inferior to 20mg. Notably, four patients were able to discontinue corticosteroids completely.

To evaluate the impact of JAKi therapy on systemic inflammatory markers, we analysed the variation of ferritin, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Ferritin levels were available for only eight patients. No statistically significant differences were observed in these parameters after treatment (Figs. 3, 4, 5).

We also examined whether there was a variation in creatine kinase levels following the initiation of JAKi therapy, but no statistically significant difference was found (Fig. 6).

In six patients with pulmonary involvement, we further evaluated the changes in DLCO, forced expiratory volume in first second (FEV_1) and forced vital capacity (FVC). A statistically significant increase in DLCO was observed following JAKi therapy (Fig. 7), while no significant changes were noted in FEV_1 and FVC (Figs. 8, 9).

Thoracic CT-scans of these six patients, before and after JAKi therapy, were described as stable in four patients, better in one patient and worsened in one patient. The most common findings were peripheral ground glass opacities,

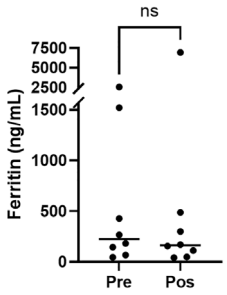

Fig. 3. Ferritin levels before and after JAKi therapy.
p=0.672 (ns: non-significant).

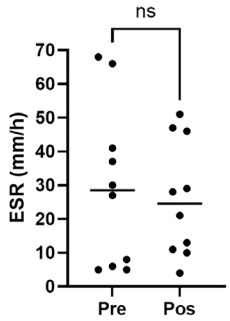

Fig. 4. Erythrocyte sedimentation rate levels before and after JAKi therapy.
ESR: erythrocyte sedimentation rate. *p*=0.558 (ns).

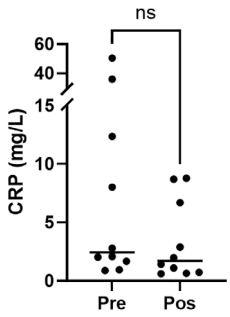

Fig. 5. C-reactive protein levels before and after JAKi therapy.
CRP: C-reactive protein. *p*=0.106 (ns).

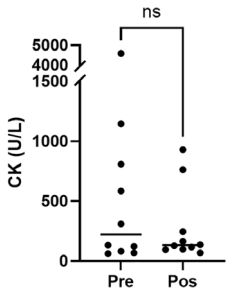

Fig. 6. Creatine kinase levels before and after JAKi therapy.
CK: creatine kinase. *p*=0.492 (ns).

bronchiectasis and subpleural reticulation, with two patients showing mild lung fibrosis.

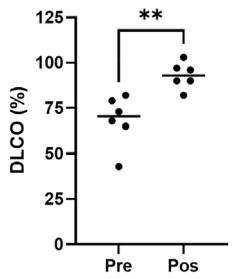

Fig. 7. Diffusing capacity for carbon monoxide before and after JAKi therapy.
DLCO: diffusing capacity for carbon monoxide. *p*=0.006 (**).

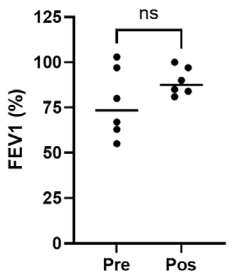

Fig. 8. Forced expiratory volume in first second before and after JAKi therapy.
FEV_1: forced expiratory volume in first second. *p*=0.092 (ns).

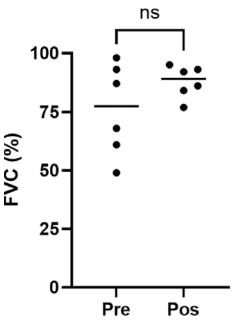

Fig. 9. Forced vital capacity before and after JAKi therapy.
FVC: Forced vital capacity. *p*=0.103 (ns).

All treatment response results are summarised in Table III.

Discussion

IIM represents a heterogeneous group of rare immune-mediated disorders for which therapeutic options remain off-label and guided by strategies applied to other systemic autoimmune diseases and, as such, very limited. Evidence regarding second-line treatment is variable and sometimes conflicting (10). Glucocorticoids alone were the cornerstone of initial therapy for induction of remission until recently. However, evidence for an early relapse on steroids tapering, along with their long-term adverse effects and the potential to induce steroid-related myopathy, has led experts to recommend the addition of another immunosuppressor from the diagnosis. Consequently, attaining steroid-free remission is considered a major therapeutic goal. Current recommendations support the use of conventional DMARDs, including tacrolimus, azathioprine, methotrexate and mycophenolate mofetil, in patients with mild to moderate disease activity. In more severe or treatment-resistant cases other immunosuppressants may be required, such as cyclophosphamide, rituximab, IVIg or abatacept. Although JAKi are being increasingly employed in the management of refractory IIM, the insufficient body of evidence has precluded a formal recommendation so far.

Our cohort comprised ten patients with refractory distinct subtypes of IIM, including DM, anti-MDA-5 autoantibody positive ADM, ASS, overlap myositis and IBM. The primary goal was to evaluate the therapeutic impact of JAKi across this heterogenous group, thereby contributing to the limited evidence available, which predominantly focuses on classical dermatomyositis.

All patients except one presented with muscle weakness at baseline, prior to the initiation of JAKi therapy. Therefore, we were capable to assess the drug's efficacy on muscle involvement. A statistically significant improvement in muscle strength was observed, as reflected by an increase in the median MMT8 score from 136 to 147, indicating a potentially favourable therapeutic response. This effect has previously been described in a systematic review of DM patients treated with a JAKi, which included 16 patients with refractory muscle involvement (7). Another retrospective cohort study failed to demonstrate a statistically significant improvement in muscle strength, although most patients in that cohort had already experienced recovery of muscle function with prior immunosuppressive therapy (11).

Given the clinical relevance of glucocorticoid tapering in patients with IIM, we assessed the effect of JAKi therapy on the maintenance dose of prednisolone-equivalent corticoster-

Table III. Evaluation of response to JAKi therapy with comparison of mean/median values before and after starting treatment.

Parameter	Pre JAKi therapy	Post JAKi therapy	*p*-value
MMT8 score, median (IQR)	136 (±25.5)	147 (±8)	0.0312*
Prednisolone equivalent, mg, median (IQR)	10 (±15)	2.5 (±6.25)	0.0312*
Ferritin, ng/mL, median (IQR)	224 (±574.75)	163 (±250.5)	0.6719
Erythrocyte sedimentation rate, mm/h, mean (SD)	29.3 (±24.09)	26 (±17.12)	0.5577
C-reactive protein, mg/L, median (IQR)	2.44 (±9.53)	1.71 (±4.92)	0.1055
Creatine kinase, U/L, median (IQR)	224 (±574.75)	163 (±250.5)	0.4922
Diffusing capacity for carbon monoxide, %, mean (SD)	68.33 (±13.97)	93 (±7.27)	0.0058**
Forced expiratory volume first second, %, mean (SD)	77.5 (±19.31)	89.5 (±7.61)	0.0922
Forced vital capacity, %, mean (SD)	76 (±19.56)	87.83 (±6.79)	0.1030

IQR: interquartile range; MMT8: Manual Muscle Testing 8; SD: standard deviation.

oid. A statistically significant reduction was observed, with the median daily dose decreasing from 10mg to 2.5mg. These findings support prior observations suggesting that JAKi may be effective in sustaining remission while minimising or eliminating the need for long-term corticosteroid therapy (12).

The risk of ILD is particularly elevated in patients with ASS, anti-MDA-5 autoantibody positive ADM, and overlap myositis, particularly when associated with systemic sclerosis. In our cohort, six patients presented with IIM-associated ILD: four with ASS, one with anti-MDA5 antibody positive ADM and one patient with overlap myositis related to Sjögren's disease. Following treatment with JAKi, we observed a statistically significant improvement in DLCO, while FEV_1 and FVC showed non-significant changes. CT-scan findings remained stable for most patients. These results reflect a 6-month follow-up period, however longer-term effects will continue to be evaluated. Prior studies assessing the use of JAKi in IIM-associated ILD have primarily focused on patients with ADM. These studies reported improvements in FVC, DLCO and radiological findings, as well as a survival benefit at six and twelve months of follow-up (13, 14). In our study, the differential effect of JAKi on DLCO compared with FEV_1 and FVC warrants further discussion. Interpretation of pulmonary function tests in IIM is challenging because ILD, respiratory muscle weakness and pulmonary hypertension can coexist, all of which impair DLCO. The restrictive ventilatory pattern characterised by reduced FEV_1 and FVC with normal FEV_1/FVC ratio, reflects both ILD and respiratory muscle weakness (15). DLCO is the most important parameter for detecting changes in pulmonary function and the most frequently altered measure in IIM-related ILD (16). In our cohort, JAKi therapy improved DLCO, suggesting a preferential effect on gas diffusion across the alveolar-capillary interface, probably through attenuation of local inflammation, since all patients included with lung involvement had interstitial inflammatory disease and not a restrictive ventilatory pattern. As pure respiratory muscle involvement in IIM is rare, and these patients were not represented in the cohort, significant improvements in FEV_1 and FVC would be observed only if a substantial resolution of ILD had occurred in all patients.

Laboratory markers of systemic inflammation, including ferritin, erythrocyte sedimentation rate and C-reactive protein, did not demonstrate significant changes following JAKi therapy. Similarly, serum creatine kinase (CK) levels did not show a statistically significant reduction, although a downward trend was noted. Importantly, the most relevant parameter to monitor during the treatment of IIM is muscle strength rather than serum enzymes levels. CK and other muscle enzymes are only indirect markers of muscle inflammation, and treatment goals should prioritise the recovery and maintenance of muscle strength over the normalisation of CK values (17). Moreover, normal CK levels do not exclude active myositis, although some correlations have been described between CK, MMT, and global disease activity assessments by both patients and physicians (18). Increasing evidence suggests that non-immune mechanisms also contribute to the pathophysiology of IIM, as several clinical observations, such as the dissociation between inflammation and muscle weakness and the incomplete response to potent immunosuppressants, cannot be fully explained by immune-mediated injury alone (3). Consequently, we hypothesise that JAKi may exert beneficial effects on overall muscle function through additional non-immune and non-inflammatory pathways, which may not directly translate into parallel changes in CK levels. Furthermore, all patients in our cohort had previously received immunosuppressive therapy, and most were being treated with a combination regimen. This therapeutic overlap complicates the interpretation of inflammatory markers and their relationship with clinical disease activity.

Most patients in our cohort received JAKi in combination with other immunosuppressants, therefore the isolated effect of JAKi monotherapy could not be evaluated based on our findings. Although a temporal association between the initiation of JAKi therapy and clinical improvement was observed, the potential contribution of other immunosuppressive agents cannot be excluded. Three different JAKi were used, however most patients (n=7, 70%) were treated with baricitinib. One patient who received upadacitinib experienced an early adverse event that precluded proper evaluation of treatment response. Consequently, all but one patient were treated with a pan-JAK inhibitor, either baricitinib or tofacitinib. Given the small sample size, no reliable statistical comparison between specific JAKi could be performed.

Adverse reactions were reported in only one patient, who had a prior history of colonic diverticulosis and developed an episode of acute diverticulitis without complications. No cases of serious infection or thromboembolic events were observed during the follow-up period.

The follow-up time varied according to the length of JAKi therapy, ranging from one to 46 months, with a median of 34.5 months. The small sample size limits the statistical power of the Wilcoxon signed-rank test, particularly when comparing patients with longer (≥36 months, n=5) and shorter treatment duration. Furthermore, in this analysis, we chose to evaluate outcomes only at 3 to 6 months after initiation of treatment, considering the speed of action of these drugs. Patients with extended follow-up were those who demonstrated a meaningful clinical response and therefore continued JAKi therapy until December 2024. A detailed analysis of time-dependent changes in clinical and functional outcomes will be addressed in future studies.

As a retrospective case series, our study has several inherent limitations that should be acknowledged. First, the absence of a control group precludes definitive conclusions regarding causality or the independent efficacy of JAKi therapy. Second, the potential for selection and information bias limits the generalisability of our findings, especially in the case of a rare and heterogenous group of diseases. Third, case-series are inherently descriptive and primarily serve as hypothesis-generating studies. The retrospective design, small sample size, and concomitant use of other immunosuppressants further limit statistical power and the ability to isolate treatment effects. Consequently, larger, prospective cohorts and controlled clinical trials are required to confirm these preliminary observations.

In our study, treatment of idiopathic inflammatory myopathies with a Janus kinase inhibitor was associated with improved muscle strength, a significant reduction in daily corticosteroid requirements, and, in patients with interstitial lung disease, an enhancement in diffusing capacity of the lungs for carbon monoxide. The therapy was well tolerated, with a favourable safety profile, and clinical benefits were observed across multiple IIM subtypes. We believe our findings contribute to the growing body of evidence supporting Janus kinase inhibitors in the management of idiopathic inflammatory myopathies, other than dermatomyositis subtype, and particularly in those patients with interstitial lung disease. Further prospective and controlled studies are warranted to confirm these preliminary results and better define this therapeutic potential.

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