# The efficacy of bariticinib in real-world patients with refractory or severe juvenile dermatomyositis:a monocentric retrospective study

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**Case Report**

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## Abstract

# Objective

To evaluate the efficacy and safety of low dose baricitinib in children with refractory or severe juvenile dermatomyositis(JDM) in a real-world setting.

# Methods

A monocentric retrospective real-world study was conducted, in which fourteen refractory and one severe newly diagnosed JDM patients were included. These patients were all treated by low dose baricitinib (below the recommended dose) combined with corticosteroids and or immunosuppressive agents. Clinical data were collected at the baseline and 4, 12, 24 weeks after baricitinib implication. Treatment response (complete response, CR, Partial response, PR and non-response,NR) was evaluated using both the Paediatric Rheumatology International Trials Organization (PRINTO) remission criteria and skin Disease Activity Score (DAS). All the adverse events (AEs) were recorded.

# Results

After baricitinib treatment, all 15 patients showed improvement of skin involvement, including 14 patients with recurrent skin rashes and one newly diagnosed JDM. Calcinosis stabilized in two patients (2/3) and partially regressed in one. Four patients (4/15) had interstitial lung disease (ILD), which normalized in one, improved in two and stabilized in one. One patient complicated with macrophage activation syndrome (MAS) achieved clinical remission. CR was achieved in 3/15 patients, ranging from 4 to 12 weeks after baricitinib initiation. Five patients (5/15) got PR 4 to 24 weeks after baricitinib use. Daily steroid dosage was decreased from 0.632 mg/kg to 0.357 mg/kg (P = 0.043) at 24 weeks in all responders. However, there was no statistically difference in muscle improvement. One patient was stopped using baricitinib because of varicella zoster virus infection, while no other serious side effect was observed in this study.

# Conclusion

Low dose baricitinib had efficacy and was safe to applied in refractory or severe JDM patients, especially for recurrent skin rashes. Baricitinib may also be helpful for JDM complicated with ILD and MAS.

## Introduction

Juvenile dermatomyositis (JDM) is an autoimmune disease characterized by inflammation of both the skin and muscles. Typical skin signs were Gottron papules, heliotrope rashes and nailfold capillary changes. Other organs may also be involved in JDM, including lungs, heart and gastrointestinal tract,

leading to poor outcome of this disease. The pathogenesis of this disease is poorly understood which constraints targeted therapy drugs applying in JDM. Although the prognosis of JDM has been remarkably improved by corticosteroids(CS) combine with disease modifying antirheumatic drugs (DMARDs), there still have 20% patients who become refractory JDM or even unresponsive to the above therapy[1].Other therapies such as intravenous immunoglobulin, rituximab, etanercept and adalimumab have yielded some promising results[2–5], but they are only beneficial in some of the refractory cases. Persistent skin lesions and calcinosis remain as the treatment challenge to rheumatologists. Recent studies have shown that interferons (IFNs) play a central role in the pathogenesis of both juvenile and adult dermatomyositis.[6, 7] Elevated IFN-response gene signature has been found in the blood, muscle and skin of dermatomyositis patients[8–10]. In treatment naive JDM patients, serum IFN-α activity was positively correlated with serum muscle enzymes[9]. Activation of IFNs results in reduction of myogenin expression and up-regulation of atrophy-associated genes[11]. Based on these findings, clinicians proposed IFN pathway inhibition as a mechanism based treatment for dermatomyositis. Janus kinase(JAK)-signal transducer and activator of transcription (STAT) pathway plays a key role in cytokine transduces signals, JAK inhibitors undergo competitive ATP binding to interfere and downregulate type I and II cytokine signaling ,including IFNs signal. Actually, JAK inhibitors, such as tofacitinib, ruxolitinib and baricitinib had been reported to be used in JDM patients[12–20],which has shown efficacy in skin lesions, muscle weakness and amyopathic dermatomyositis-associated interstitial lung disease[12].However, data on use of bairicitinib in JDM is limited[16],the efficacy and safety are still unclear. Here we reported a series of refractory and new-onset severe JDM patient who had received baricitinib to evaluate it efficacy and safety in a real-world setting.

## Methods

# Patients

We retrospectively reviewed 16 cases with JDM who received baricitinib between July 2019 and July 2021. All patients were from Children's Hospital of Zhejiang University School of Medicine. Fourteen refractory and one new-onset severe patients were included. One patient was excluded because of short course ( less than 4 weeks ) of medication using. The average age at disease onset of JDM was 8 years old. The female to male ratio was 3:1. The mean time to initiate baricitinib therapy was 22.87 months (range from 0 to 84 months) after diagnosis (Table 1). We collected the patients' clinical data at the baseline and 4, 12, and 24 weeks after baricitinib implication. Informed consents were obtained from parents before using baricitinib.The study was approved by the Ethics Committee of Children's Hospital of Zhejiang University School of Medicine. (IRB approval no. 2019-IRB-154)

Inclusion criteria were: (i) diagnosis of JDM, according to the Bohan and Peter classification[21] (ii) all patients with JDM received baricitinib (iii) follow-up at least 24 weeks after the initiation of baricitinib. Exclusion criteria: (i) myositis overlapping with other autoimmune diseases (ii) evidence of any other acute or chronic infectious diseases, history of tuberculosis or mycobacterial infections (iii) history of any malignancy of any organ system (iiii) baricitinib treatment course less than 4 weeks.

Refractory JDM was defined by active disease despite a 12 weeks of steroids and with or without one other first line immunosuppressive agents (e.g. methotrexate, mycophenolate mofetil, or azathioprine) or have demonstrated significant toxicity or intolerance to above therapies[22].Severe JDM was defined as disease progressed rapidly and/or involved other organs, including the lungs, heart, and gastrointestinal tract, leading to a poor prognosis. Low dose baricitinib was defined as below the recommended dose which based on weight and renal function[23].

# Efficacy evaluation of baricitinib in JDM

Muscle strength was assessed using the Childhood Myositis Assessment Scale (CMAS, range 0–52) and the Manual Muscle Testing (MMT) scale (range 0–80). Severe muscle involvement was defined by CMAS score ≤ 15 or MMT score ≤ 30. Skin disease activity using the skin DAS (range 0–9). Complete Response (CR) was defined by both the PRINTO criteria (at least three of the four following criteria have to be met: creatine kinase ≤ 150 U/l, CMAS ≥ 48, MMT ≥ 78, and Physician visual analogue scale (VAS) ≤ 2cm (range,1-10cm) and inactive skin DAS (score ≤ 1/9 without cutaneous ulcerations or erythema). Partial response (PR) was defined as an improvement of the muscle and/or skin score assessed by MMT/CMAS and skin DAS, respectively, allow tapering of steroids dosage of at least 50% of the initial dosage at 6 months after baricitinib introduction, without adding a new immunosuppressive medicine. The outcome was counted as proportion of patients achieving CR/PR during 24 weeks after baricitinib implication.

# Adverse events

Occurrence of adverse events (AEs) and serious AEs (SAEs) were monitored and reported in a standardized manner using the Common Terminology Criteria Adverse Events version 4.0.

# Statistical analysis

Statistical analyses were performed using IBM SPSS statistics 25. Data from week 4, week 12 and week 24 were compared with baseline using Wilcoxon rank-sum test.The continuous variables were presented as the medians with interquartile range (IQR) or mean with Standard deviation (SD). The categorical variables were presented as the number of patients and percentages.

## Results

1. The clinical features of JDM patients before baricitinib therapy

All 16 patients had skin involvement, in which 14 patients had recurrent skin rashes and 3 patients had calcinosis. one patient was diagnosed as clinically amyopathic dermatomyositis (CADM). The median (IQR) skin DAS score was 6.00 (5.00,7.75) before baricitinib therapy (Table 1). Six of 16 patients had muscle involvement at the entry. Median (IQR) CMAS score or median (IQR) MMT score were 50.00 (41.75,2.00) or 78.00 (73.25,80.00), respectively. Two patients had severe muscle weakness who had CMAS score ≤ 15. (Table 1). Four patients had interstitial lung disease (ILD), and one patients developed MAS in early stage of disease. The daily median dosage of corticosteroid at entry point of the study was 0.73mg/kg.

## 2.1 Bariticinib treatment of refractory or severe JDM

As shown in Table 2,the enrolled patients received baricitinib at a dose of 1–2 mg once or twice daily. In addition to treatment with baricitinib, patients also received CS (n = 12), intravenous methylprednisolone (IVMP, n = 3), intravenous immune globulin (IVIG, n = 8) and/or other biologic agent at the same time (Table 1). The duration of baricitinib treatment was from 3 months to 22 months.(Table 2). The median duration of follow-up was 15.7 months (range from 6 to 22 months,Table 2). Baricitinib was discontinued in one patient (P2) because of insufficient efficacy

## 2.2 Baricitinib had efficacy in children with refractory or severe JDM

CR was achieved in 3/15 patients during 4 to 12 weeks after baricitinib initiation, it was sustained after a median duration of follow-up of 15.7 months. 5/15 patients met PR ranging from 4 to 24 weeks. Eight patients were classified as non-responders (NR) within 24 weeks of observation. All responders (n = 8,CR/PR) with a median (IQR) skin DAS score of 6.00 (5.00-7.75) at study entry were improved to 1.00 (0.00,5.50) by 24 weeks (P = 0.001). The median (IQR) CMAS score of all enrolled patients was 50.00 (41.75,52.00), which is indicative of only very mild muscle weakness at study entry. one patient had a CMAS score of < 15 at entry who demonstrated 15-point improvement at 4 weeks. Calcinosis stabilized in two patients (P2, P12) and partially regressed in one (P3). ILD normalized in one of four (P9) patients, improved in two (P4,P14) and stabilized in one ( P5). One MAS was cured after baricitinib combined with IVMP, IVIG,tocilizumab and baricitinib. .

## 2.3 Baricitinib was helpful for tapering steroids and/or immunosuppressive agents dosage

The daily steroid dose decreased from a median dosage of 0.632 mg at baricitinib introduction (range 0.227–1.000) to 0.357 mg (range 0.224–0.500, P = 0.043 ) at 24 weeks in all responders. Four (50%) of the 8 responders were able to taper or remove immunosuppressive medication during 24 weeks.

## 2.4 Baricitinib was overall well-tolerated and safe

There were twenty AEs occurred in six patients in this study (Table 3). One patient who had herpes zoster infection required hospitalization and discontinuation of baricitinib temporarily.

# Discussion

There has been increasing evidence documenting the critical role of type I IFNs in the development of JDM. Baricitinib, a JAK1/JAK2 inhibitor, interfering with I IFNs expression or signaling have already shown favourable results with baricitinib in refractory or sever newly JDM[16, 17, 24].

In this study, patients with cutaneous manifestations were improved markedly after baricitinib therapy. Significant improvement was noted at week 4 in skin DAS(P = 0.008). It was consistent with previous

cases report that indicated baricitinib was clinically beneficial to skin lesions[16, 17, 24]. A case serials reported that 4 refractory JDM with baricitinib also showed skin disease improvement by week 4[16]. Voyer and his colleague reported a new-onset case with severe skin ulcerations got CR after 1.7 months of baricitinib initiation[14].Calcification is a therapeutic challenge in JDM. Data was limited in the treatment of JAKi in calcification, one paper displayed that only partially regressed was observed in a case who had JDM complicated with calcification.[25, 26]. In our study, only partially regressed in one (1/3) patient with calcification in this study. Baricitinib may show good efficacy in the treatment of calcification if expanded the observation duration.

Previous study showed JAK inhibitor can restore muscle strength, significance improvement was observed after short usage[14, 27, 28]. In our study, one patient with severe muscle weakness was improved markedly (CMAS 15 to 30) upon baricitinib at 4 weeks of treatment. However, possible reason was that most patients enrolled in this study had mild muscle involvement.

JDM patients with ILD are often refractory to therapy. It was found that patients with anti-MDA5 antibodies positive were more prone to develop ILD[12, 26, 29–31][32, 33]. Four patients with ILD in our series had different MSAs (Table 1), an anti-PL-7-positive patient showed complete remission in images under the treatment of baricitinib. However, small size of our cohort makes it hard to distinguish which type of MSAs is an indication for the use of baricitinib.

It is reported that interference with IFN α/β expression or signaling following JAK/STAT inhibition may control catastrophic hyperinflammation in MAS[34, 35].With comprehensive treatment that including IVMP, IVIG, tocilizumab and baricitinib, one patient effectively tackle the cytokine storm to get disease remission, which showed the possibility of baricitinib treatment of MAS in the real world.

Consistent with previous study, bariticinib maybe helpful for tapering the dose of steroid and other immunosuppressive medicine. In some case reports, JAK inhibitor may be beneficial when used alone[20]. In this study,daily corticosteroids were decreased from 0.632mg/kg/day at the entry of study, to 0.357mg/kg/day ($P = 0.043$). Half of these patients were able to reduce or remove other immunosuppressive medications.

Due to high price and off-label drug use, patients received dose of baricitinib from 1mg to 4mg per day, which is lower than other studies[16, 36]. It was cost-effective to got response in 8/15 patients during 24 weeks usage in this study.

Bariticinib was reported as well-tolerated and safe in previous study[27][16]. In our study, the most common AE was mild respiratory infection (Table 3). One patient infected with herpes zoster had to temporarily suspended using of Bariticinib.

Our study has limitations as a single-centre study with small sample size and short observation period. It was carried out in a routine clinical practice situation, the effects of basic and combined medications

may influence the truly efficacy of bariticinib. In addition, we did not measure the concentration of interferon-αprotein made it unable to assess changes of in interferon expression in a molecular level.

# Conclusion

This research indicated that low dose of baricitinib combined with other immunosuppressants or biologics had efficacy in refractory or severe patients with JDM, especially in recurrent skin rashes. But it had limited efficacy in calcinosis and muscle weakness. It may be helpful for alleviating severe complication such as ILD and MAS, but evidence was weak due to limited cases enrolled in this study. Bariticinib maybe helpful for tapering the dose of steroid and other immunosuppressive medicine. There was no serious side effects observed in this study, except for varicella zoster virus infection occurred in one patient. More cases and multicentre clinical trials are needed to identify the precise therapeutic effect in JDM .

# Abbreviations

JDM:Juvenile dermatomyositis; DMARDs:disease modifying antirheumatic drugs;

IFNs:interferons; JAK:Janus kinase; STAT: signal transducer and activator of transcription; CMAS: Childhood Myositis Assessment Scale; MMT: Manual Muscle Testing;VAS:visual analogue scale ; AEs:adverse events; SAEs:serious;CR:Complete Response; PR:Partial response; NR:non-responders; IQR:interquartile range;SD: Standard deviation; ILD:interstitial lung disease; IVMP:intravenous methylprednisolone; IVIG:intravenous immune globulin; CS:corticosteroids; MSAs:Myositis specific autoantibodies;

# Declarations

## Ethics approval and consent to participate

The study has obtained approval from the Clinical Research Ethics Committee of Children's Hospital, Zhejiang University School of Medicine (IRB approval no. 2019-IRB-154).

### Consent for publication

All patients and their parents provided written informed consent for their data to be used in analyses and reported.

### Availability of data and materials

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

### Competing interests

The authors have no funding and conflicts of interest to disclose.


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### Authors' contributions

ZLW was responsible of the collection of clinical information, statistical analyses, figures, data interpretation and manuscript preparation. QZ was responsible for critical review of the statistical analyses and the manuscript. XSX was assist in collecting clinical information. MPL is the project leader of the study; she is involved in the conceptualization of the project, the study design and preparation of the manuscript. All authors read and approved the final manuscript.


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