Janus kinase inhibitor significantly improved rash and muscle strength in juvenile dermatomyositis

Juvenile dermatomyositis (JDM) is a rare systemic autoimmune vasculopathy characterised by weakness in proximal muscles and pathognomonic skin rashes.[1] Clinically, some patients are refractory to any available treatments or became steroids dependent.[2] The adverse reactions of long-term use of steroids are severe; therefore, more effective and safer medications are urgently needed. JAK inhibitors (JAKi) can reduce interferon (IFN)-induced STAT1 phosphorylation and block the JAK-STAT pathway, demonstrating a therapeutic potential of inflammation control in JDM.[3] The successful uses of JAKi were reported in adult dermatomyositis (DM) and two patients with JDM.[3–5] Here, we want to share the JAKi using experiences of 25 refractory JDM cases who were diagnosed and classified according to Bohan and Peter's criteria and treated between November 2017 and May 2019. Written informed consents were obtained from the guardians of all patients before starting the treatment.

Among 25 cases, 44% (11/25) patients were female, the mean age of onset was 4.6±3.3 years and the mean age to start add-on JAKi treatment was 7.2±4.0 years. The mean disease course of the 25 JDM patients before JAKi treatment is 21.0 months (range: 14.0–36.5). All cases are refractory JDMs, including 32% (8/25) ineffective patients and 68% (17/25) glucocorticoid-dependent cases. After routine treatment fails, they received JAKi for 3–18 months as an off-label use. In subsequent JAKi treatment, 28% (7/25) used tofacitinib, and 72% (18/25) used ruxolitinib. In patients of <25 kg (n=11), the initial dosage was 2.5 mg twice daily, and in patients of ≥25 kg (n=14), the initial dosage was 5 mg twice daily, and one patient required the maximum dosage of 7.5 mg twice daily.

The 25 patients were followed for a median of 7.0 months (range: 3–21 months). Ninety-six per cent (24/25) had rash when

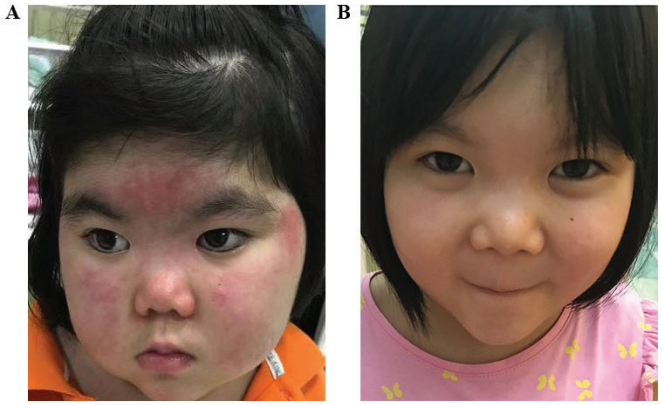

Figure 1 A typical case of a girl >25 kg who received an initial dose of 5 mg twice daily of Janus kinase inhibitor (JAKi) but required the maximum dose of 7.5 mg twice daily. She received this dose for 6 months, and the dose was gradually tapered. In the meantime, glucocorticoids were also tapered, and the patient showed an increased growth rate. (A) The typical skin lesions before treatment with JAKi. (B) Those lesions had mostly disappeared after treatment.

JAKi was added, and all showed improved rashes, including 66.7% (16/24) cases of complete resolution. In patients with rash, rashes started to improve after 1.0 (0.6–2.0) weeks of JAKi and showed obvious improvement after 2.5 (2.0–4.0) weeks of JAKi. No clinically observable rash could be seen after 12.0 (8.0–24.0) weeks of JAKi. The Cutaneous Assessment Tool Binary Method score decreased dramatically from 7.0 (3.0–10.0) to 0.0 (0.0–1.0) ($p<0.001$). figure 1 shows a girl with a long-term refractory rash that disappeared after gradually increasing the JAKi dose to 7.5 mg twice daily. Up to the last follow-up in August 2019, 28% (7/25) patients discontinued glucocorticoids including this girl. There is currently only one case relapsed, the rash disappeared after 8 weeks of JAKi but recurred 4 weeks later and JAKi was stopped at 12 weeks.

Additionally, 10/25 (40%) patients had decreased muscle strength, and 4% (1/25) had continuous high levels of muscle enzymes. After treatment, seven cases improved in childhood myositis assessment scale (CMAS) score (from 18.6±15.0 to 35.7±6.3, $p=0.018$). Two patients did not change in CMAS score (pretreatment/post-treatment score=47) but reported improvement in fatigue and activity tolerance. One patient was unevaluable for CMAS score before JAKi treatment due to joint contracture. As for biochemical indicators, CK and/or LDH were abnormal in 12 patients when JAKi was added. Median CK levels were normal before and after treatment. LDH decreased from 361.5 (306.3–463.3) U/L to 291.0 (275.8–394.8) U/L ($p=0.034$) in 12 patients, but two patients showed LDH increase, from 340 to 395 U/L and from 307 to 420 U/L, respectively. More details of patients' clinical characters and index changes are in the online supplemental material. During our observation period, no increase in the infection rates with Epstein-Barr virus, cytomegalovirus, varicella-zoster virus and tuberculosis occurred as reported by another study.[6] No thromboembolic event was observed as well.

This is the first case series study summarising the JAKi treatment on patients with refractory JDM. In our observation, JAKi improved refractory rash and muscle involvement, helped to reduce or stop glucocorticoid and no obvious side effects were found. Therefore, our study suggested that JAKi might be an idea choice in children with refractory JDM.

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Competing interests None declared.

Patient consent for publication Parental/guardian consent obtained.

Ethics approval According to the off-lable principle, written informed consents of receiving JAKi treatment were obtained from the guardians of all patients before starting the treatment. The study was approved by the ethics committee of the Capital Institute of Pediatrics (SHERLL2019065).

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REFERENCES

1 Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975;292:344–7.
2 Bellutti Enders F, Bader-Meunier B, Baildam E, *et al*. Consensus-Based recommendations for the management of juvenile dermatomyositis. *Ann Rheum Dis* 2017;76:329–40.

3 Oddis CV, Reed AM, Aggarwal R, *et al*. Rituximab in the treatment of refractory adult and juvenile dermatomyositis and adult polymyositis: a randomized, placebo-phase trial. *Arthritis Rheum* 2013;65:314–24.
4 Papadopoulou C, Hong Y, Omoyinmi E, *et al*. Janus kinase 1/2 inhibition with baricitinib in the treatment of juvenile dermatomyositis. *Brain* 2019;142:e8
5 Aeschlimann FA, Frémond M-L, Duffy D, *et al*. A child with severe juvenile dermatomyositis treated with ruxolitinib. *Brain* 2018;141:e80.
6 You H, Xu D, Zhao J, *et al*. Jak inhibitors: prospects in connective tissue diseases. *Clin Rev Allergy Immunol* 2020;28.

Diagnostic and classification criteria

JDM was diagnosed and categorized according to Bohan and Peter's criteria. The inclusion criteria were: 1) ≤18 years of age; 2) refractory JDM, defined as patients with no clinical improvement following treatment with combined therapy of glucocorticoids and over two kinds of immunosuppressant or biological agents; or recurrence during the tapering of glucocorticoids dosage; or relapse of JDM symptoms within 3 months after discontinuation of glucocorticoids [1]; and 3) treated with JAKi. The exclusion criteria were: 1) other chronic or inflammatory diseases; 2) ongoing infection; or 3) severe gastrointestinal tract involvement.

Supplementary Table 1. Characteristics of the patients

	N=25
Female	11 (44%)
Ethnic group (Han/Minority)	24/1
Age at disease onset (years)	4.6±3.3
Age at starting JAKi (years)	7.2±4.0
Age at the end of follow-up (years)	7.9±4.0
Diagnosis (JDM/CADM)	23/2
Refractory	
No response to GC+IA$^{>2}$/BA	8 (32%)
Relapse†	17 (68%)
Other diagnoses	
Cataract	3 (12%)
Compression fracture	1 (4%)
Hypertension	1 (4%)
Interstitial lung disease	4 (16%)
Joint contracture	1 (4%)
Symptoms at disease onset	
Rash‡	24 (96%)
Heliotrope rash	22 (88%)
Malar/facial erythema	24 (96%)
Gottron's sign	18 (72%)
Skin ulcer	10 (40%)
Muscle weakness	17 (68%)

Dysphagia/hoarseness/drinking cough/low voice	8 (32%)
Fever	6 (24%)
Maximum CK (U/L)	594 (276-1203)
Maximum LDH (U/L)	548 (389-660)
Myositis-specific antibodies (MSA)	
Negative¶	14 (56%)
Anti-NXP2 Positive	8 (32%)
Anti-MDA5 Positive	1 (4%)
Anti-JO-1 Positive	1 (4%)
Anti-PL-7 Positive	1 (4%)
Anti KU Positive	1 (4%)
ANA positive	6 (24%)
Anti-Ro-52 positive	5 (20%)
Therapy before JAKi started	
GC+IA$^{<=2}$	9 (36%)
GC+IA$^{>2}$	7 (28%)
GC+IA+IVIG	4 (16%)
GC+IA+IVIG+BA	3 (12%)
GC+IA+IVIG+plasma exchange/ASCT	2 (8%)
Therapy when JAKi started	
GC	3 (12%)
IA$^{<=2}$	2 (8%)
GC+IA$^{<=2}$	15 (60%)
GC+IA$^{>2}$	1 (4%)
GC+IA$^{<=2}$+IVIG	3 (12%)
GC+IA$^{<=2}$+BA	1 (4%)
Disease course of JDM before JAKi treatment (months)	21.0 (14.0-36.5)
JAKi, <25 kg, 2.5 mg bid	11 (44%)
JAKi, ≥25 kg, 5 mg bid	14 (56%)
Ruxolitinib	18 (72%)
Tofacitinib	7 (28%)
Follow up (months)	7 (4.0-12.0)

Continuous data are presented as mean ± SD or median (interquartile range). Category data are presented as number and percentage.

JAKi: Janus-kinase inhibitor; JDM: juvenile dermatomyositis; CADM: clinically amyopathic dermatomyositis; CK: creatinine kinase; LDH: lactate dehydrogenase; NXP2: nuclear matrix protein 2; MDA5: melanoma differentiation-associated gene 5; ANA: antinuclear antibodies; GC: glucocorticoids; IA: immunosuppressive agents; $IA^{<=2}$: two or fewer types of IA; $A^{>2}$: more than two types of IA; IVIG: intravenous immunoglobulins; BA: biological agents.

† Relapsing: manifestations recur during GC dosage reduction or within 3 months after GC withdrawal.

‡ Rash: Heliotrope rash; Malar/facial erythema; Gottron's sign.

¶ In six patients, the antibodies were tested after treatment in other hospitals.

Supplementary Table 2. Disease activity markers before and after JAK inhibitor treatment

	n	Before JAKi	After JAKi	P
CAT-BM activity score	25	7.0 (3.0-10.0)	0.0 (0.0-1.0)	<0.001*
CAT-BM damage score	25	0.0 (0.0-1.0)	0.0 (0.0-1.0)	--
CMAS	10	24.9±18.0	38.2±7.4	0.023*
CK (U/L)	12	107.5 (79.8-177.8)	124.0 (61.0-178.8)	0.814
LDH (U/L)	12	306.3 (361.5-463.3)	275.8 (291.0-394.8)	0.034*
SF (ng/mL)	25	81.2 (55.4-113.0)	64.3 (37.2-98.2)	0.010*
Hospitalizations in 6 months	12	2.5 (1.0-4.8)	0.0 (0.0-2.8)	0.028*

Continuous data are presented as mean ± SD or median (interquartile range). Category data are presented as number and percentage.

CAT-BM: Cutaneous Assessment Tool Binary Method; CMAS: Childhood Myositis Assessment Scale; CK: creatinine kinase; LDH: lactate dehydrogenase; SF: serum ferritin.

* Significantly statistic difference, P<0.05.