JAK inhibitors in the treatment of adult patients with juvenile idiopathic arthritis: a retrospective monocentric experience

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Abstract

Objective

This study aims to evaluate the efficacy and safety of JAK inhibitors (JAKi) in a monocentric cohort of adult patients with juvenile idiopathic arthritis (JIA).

Methods

Patients attending a rheumatology transition clinic were retrospectively included in case of: i) JIA diagnosis according to current classification criteria (1); ii) age ≥18 years and iii) treatment with JAKi for at least 3 months.

Results

Seventeen adult patients with JIA were treated with JAKi (as first JAKi, 9 patients (52.9%) received tofacitinib and 8 (47.1%) baricitinib). At 3 months after JAKi initiation, 8 patients (47%) achieved a response and 4 patients (23.5%) achieved disease remission (3 patients with baricitinib and 1 with tofacitinib, 37.5% vs. 16.7%, p=0.294). None of those with systemic JIA and enthesitis-related arthritis obtained remission; the remission rate at 3 months was higher, although not significantly, in the oligoarticular subset compared to the polyarticular subset (37.5% vs. 20%). Patients with ≤1 active joint involvement at JAKi start had a higher remission rate (50% vs. 22.2%). Subjects who achieved remission on JAKi had a significantly lower pre-treatment DAS28-CRP compared to those with still active disease (p=0.010, Mann-Whitney U=4). A pre-treatment DAS28-CRP <3.76 predicted response to JAKi with 100% sensitivity and 84.6% specificity (p=0.023). The remission rate was lower among patients who had been treated with ≥2 biological drugs before JAKi start (9% vs. 66.7%; p=0.05). One patient in concomitant treatment with leflunomide developed severe arterial hypertension.

Conclusion

JAKi may represent an effective and safe treatment option for adult JIA patients with low/moderate disease activity, particularly in case of oligoarticular involvement.

Key-words

juvenile idiopathic arthritis, JAK inhibitors, remission, uveitis

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Introduction

The therapeutic approach to patients with juvenile idiopathic arthritis (JIA) aims at preventing joint damage and the resulting irreversible functional impairment (1). Disease course may be highly polymorphic, but almost invariably patients with JIA, the most common rheumatic condition presenting in childhood, require treatment to achieve clinical remission, such as systemic and intraarticular corticosteroids, conventional disease-modifying anti-rheumatic drugs (cDMARDs,) or the more recent biologic drugs, each targeting a single cytokine (bDMARDs) (2). Even though the introduction of bDMARDs revolutionised JIA treatment, in at least half of the cases childhood-onset arthritis can persist into adulthood (3). In the course of a longstanding disease journey from early childhood to advanced age, there still exist several criticisms in the management of adults with JIA, despite the enriched therapeutic armamentarium (4). Some patients have drug-resistant arthritis with primary therapeutic failures, others secondarily cease to respond, while additional subjects experience side effects or develop contraindications to available drugs (5). These criticisms well explain why the quest for novel pharmacological targets has been constantly pursued: emerging mechanisms of action might enable clinical remission in higher rates of patients, with minimisation of personal disease burden and consistent socioeconomic advantages. Pharmacological compounds targeting Janus kinase (JAK), a family of 4 cytoplasmic tyrosine kinases that mediate intracellular signal transduction upon recruitment by more than 50 cytokines receptors, are among the most recently marketed in rheumatology. These JAK inhibitors (JAKi) act as competitive antagonists of the ATP-binding site of different JAK, leading to the suppression of downstream STAT (JAK-signal transducer and activator of transcription) cascade thus resulting in immunomodulatory effects (6). To date, 5 JAKi, orally available small molecules categorised as targeted synthetic DMARDs (tsDMARDs), have gained approval by different agencies for the treatment of rheumatologic conditions: baricitinib, filgotinib, peficitinib, tofacitinib, and upadacitinib, each with a peculiar selectivity for the 4 kinases (7). While evidence of JAKi efficacy in children with JIA has been steadily growing, with even a trial demonstrating the efficacy of tofacitinib in polyarticular course JIA, very scarce data are available about the use of JAKi in adult patients with longstanding JIA (8).

The aim of this study was thus to evaluate the efficacy and safety of baricitinib and tofacitinib in a monocentric cohort of adult patients with JIA.

Patients and methods

Patients were consecutively included in this retrospective cohort study in case of: i) JIA diagnosis formulated according to ILAR criteria (9); ii) age >18 years; iii) persistence of disease activity into adulthood and iv) treatment with JAKi for at least 3 months. Patients were recruited at the outpatient transition clinic in the rheumatology department of ASST G. Pini - CTO in Milan, Italy; at our institution, the transition clinic follows patients with paediatric-onset rheumatic diseases from the transition into adult care onwards. Patients were further classified in disease categories according to ILAR criteria: oligoarticular, polyarticular, enthesitis-related arthritis (ERA), psoriatic and systemic JIA (9). Disease activity was assessed using Disease Activity Score (DAS) based on 28 joint (DAS28-CRP). DAS28-CRP is calculated from four components: number of tender joints (TJC), number of swollen joints (SJC), visual analogue scale (VAS) score of the patient's global health (GH), and C reactive protein (CRP, mg/dL) using the following formula: $DAS28\text{-}CRP=0.56*\sqrt{(TJC28)}+0.28*\sqrt{(SJC28)}+0.014*GH+0.36*\ln(CRP+1)+0.96$ (10). DAS28-CRP was assessed at JAKi initiation and discontinuation and at 3, 6 and 12 months during medical visits. Disease activity status was defined upon DAS28-CRP scores as follows: remission (DAS28-CRP<2.6), low ($2.6 \leq$DAS28-CRP< 3.2), moderate ($3.2 \geq$DAS28-CRP≤ 5.1) and high disease activity (DAS28-CRP>5.1). Response to JAKi

Table I. Demographics and clinical features at initiation of first JAKi of included subjects stratified upon disease subset.

	O-JIA (n=8)	P-JIA (n=5)	ERA (n=2)	S-JIA (n=2)	Whole cohort (n=17)	*p*-value
Age at JIA onset, median (IQR)	4.5 (9)	13 (6)	15 (1)	10 (6)	10 (13)	0.323
Age at JIA diagnosis, median (IQR)	4.5 (10)	14 (8)	15 (1)	10 (6)	11 (13)	0.385
Age at starting treatment with JAKi, median (IQR)	28.8 (6.7)	26 (12)	40.8 (1.8)	37 (10)	31 (13.6)	0.338
Gender, F % (n)	75% (6)	100% (5)	100% (2)	50% (1)	83.4% (14)	0.356
ANA positivity, % (n)	75% (6)	60% (3)	50% (1)	/	58.8% (10)	N.C.
Uveitis, % (n)	50% (4)	20% (1)	/	/	29.4 (5)	N.C.
Comorbidities, % (n)	50% (4)	40% (2)	/	/	35.2 (6)	N.C.
Disease duration at JAKi start in years, median (IQR)	27.1 (11.2)	18 (3)	26.25 (1.2)	28 (4)	25 (11.3)	0.622
DAS28-CRP at starting treatment with JAKi, median (IQR)	3.76 (1.07)	5 (1)	4.86 (0.25)	3.0 (1)	4 (1.57)	0.275
Active joints at starting treatment with JAKi, median (IQR)	1.5 (2)	2 (3)	2.5 (1)	1 (2)	2 (1)	0.282
Pre-JAKi cDMARDs, median (IQR)	1 (1.0)	1.0 (1.0)	1.0 (1.0)	0 (0.0)	1 (1.0)	0.215
Pre-JAKi bDMARDs, median (IQR)	2.5 (2.25)	3 (2)	5 (1)	2 (2)	2 (2)	0.195
Ongoing MTX, % (n) Median dose (IQR)	12.5% (1) 15 mg/wk	60% (3) 10 mg/wk	50% (1) 7.5 mg/wk	50% (1) 7.5 mg/wk	35.2 (6) 15 mg/wk	0.316
Ongoing LEF, % (n)	25% (2)	20% (1)	/	/	17.6% (3)	N.C.
Ongoing oral glucocorticoids, % (n) Median dose (IQR)	/	40% (2) 10 mg/day	100% (2) 5 mg/day	/	23.5% (4) 11.25 mg/day	N.C.

ANA: anti-nuclear antibodies; bDMARD: disease-modifying anti-rheumatic drugs; cDMARD: conventional disease-modifying anti-rheumatic drug; ERA: enthesitis-related arthritis; F: female; n: number; IQR: interquartile range; JIA: juvenile idiopathic arthritis; JAKi: janus kinase inhibitor; LEF: leflunomide; MTX: methotrexate; N.C.: not calculated; O-JIA: oligoarticular juvenile idiopathic arthritis; P-JIA: polyarticular juvenile idiopathic arthritis; PsA: psoriatic arthritis; S-JIA: systemic juvenile idiopathic arthritis; wk: week.

was defined as a DAS28-CRP change of at least 0.6. Disease flares were defined as an increase in DAS28-CRP above 1.2 (11).

A complete ophthalmological evaluation, including best-corrected visual acuity (BCVA) assessment on standard ETDRS letters, slit-lamp biomicroscopy, intraocular pressure (IOP) assessment and dilated fundus evaluation, was performed at baseline and during follow-up visits. Fluorescein angiography, indocyanine green angiography and optical coherence tomography (OCT) were performed when appropriate in case of posterior pole involvement. Uveitis response to JAKi was defined as a two-step decrease in inflammation score (anterior chamber cells) or a decrease to zero between baseline and 3 months of treatment, according to SUN criteria (12). Partial response was defined as a one-step improvement in inflammation score.

Erythrocyte sedimentation rate (ESR) was assessed by Wintrobe method and values above 12 mm/hour were regarded as increased; CRP was tested by colorimetric-enzymatic assay with a cut-off level at 0.5 mg/dL. Anti-nuclear antibodies (ANA) were tested in serum samples at indirect immunofluorescence on HEp-2 cells and positivity was defined at a titre ≥1:80.

If clinically required, accurate assessment of joint disease activity was performed by musculoskeletal ultra sound using a dedicated device (13).

Data were extracted from a local registry of patients with inflammatory arthritides (authorisation 150/2002; Gaetano Pini Institute Ethics Committee); patients provided written informed consent.

Sample size

To estimate the size of patients representative of subjects with active JIA in adulthood, the following formula was applied: n = (Z2 x P x (1 - P))/e2, where: Z = value from standard normal distribution corresponding to desired confidence level (Z=1.96 for 95% CI); P is expected true proportion; e is desired precision (half desired confidence interval [CI] width). The following values were considered: e=0.05; *p*=0.25. According to the data from a large Canadian cohort, approximately one quarter of patients with JIA reaches adulthood with active disease despite treatment (14). We considered n=3731, given that JIA has an incidence of 6.34/100.000 per year in Italy of 60:100.000, with an overall Italian population of 58.851.000. It follows n=16 with an apparent precision of 0.01.

Statistical analysis

Continuous data were expressed as median (interquartile range [IQR]) and categorical data as percentages. The association between categorical variables was assessed by chi-squared or Fisher exact tests as appropriate; Mann-Whitney test was applied to compare continuous variables between subgroups of patients. Wilcoxon signed rank test was applied to evaluate clinical variables before and after JAKi treatment; Mc Nemar's test was performed to compare disease activity status before and after JAKi treatment. DAS28-CRP scores over follow-up were compared within the same subject by Friedman's test. Univariate logistic regression analyses were performed. ROC curves were drawn to identify the DAS28-CRP value with the highest predictive role for response and remission upon JAKi treatment. Univariate survival analysis was performed with Kaplan-Meier method; differences between

survival curves were evaluated by log-rank. *p*-values <0.05 were regarded as significant. Statistical analysis was performed using Prism v. 6.

Results

From February 2018 to December 2022, 17 patients fulfilling inclusion criteria were initiated on JAKi and thus were included in this study. Of these, 7 patients (41.2%) were treated with tofacitinib 5 mg twice daily (Xeljanz®, Pfizer, NY, USA) while 8 subjects (47.1%) received baricitinib 4 mg daily (Olumiant®, Eli-Lilly/Incyte, EN, USA); two subjects received both agents sequentially. The demographics and clinical features at initiation of first JAKi of included subjects stratified upon disease subset are detailed in Table I. Most patients had oligoarticular JIA (47%) and half of the patients had persistent oligoarticular form; polyarticular JIA represented the second most prevalent disease subset (29%) with only one subject being rheumatoid factor (RF) positive. All patients had longstanding JIA, with median disease duration of 25 years; most patients (12, 70.6%) had moderate/high disease activity at the time of initiating JAKi.

Nine patients (52.9%) received JAKi in association with a cDMARD; 2 patients with polyarticular JIA were also treated with oral corticosteroids. Most patients had a refractory disease, as 12 subjects (70.6%) had been treated with at least 2 different bDMARDs and 6 (35.3%) had switched 4 or more biologicals.

Response to JAKi at 3 months

The introduction of JAKi did not allow dose tapering in any of the 4 patients on glucocorticoids; 3 patients required intra-articular knee injection of steroids over JAKi treatment due to active arthritis. In six patients (35.4%), JAKi allowed a better disease control leading to a shift in disease activity status; in 10 subjects (58.8%), disease activity remained stable whereas in a single patient (5.8%) disease activity increased leading to a shift in disease activity status. Overall, disease activity status did not change significantly with the introduction of JAKi (*p*=0.130). DAS28-CRP scores at 3 months of JAKi initiation were significantly lower compared to those registered at baseline (median at baseline 3.99 [IQR 1.8], after 3 months of JAKi treatment 3.52 [IQR 3.74]; *p*=0.041, median change -0.55 [IQR -2.54]). Conversely, the number of active joints, ESR and CRP values did not change significantly after the introduction of JAKi (*p*=0.143, *p*=0.132 and *p*=0.148, respectively).

At 3 months, a response to JAKi was registered in 8 patients (47%, Table II) while disease flared in a single patient; 8 subjects (47%) reached a low disease activity. The response rate at 3 months was higher – although not significantly – for baricitinib: 5 patients achieving remission had been treated with baricitinib and 3 with tofacitinib (62.5% *vs*. 33.3%, *p*=0.229). None of the patients with ERA responded to JAKi at 3 months; the response rate was similar in the remaining subsets (50% in oligoarticular and systemic JIA, 60% in the polyarticular subset; *p*=0.931). All but one of the 4 patients with oligoarticular JIA responding to JAKi had the persistent form. Although age at disease onset and disease duration were similar between patients achieving response and those not (*p*=0.761 and *p*=0.941), patients responding to JAKi were significantly younger at JIA onset than subjects without response at 3 months. Concomitant treatment with methotrexate, leflunomide or both did not significantly affect the response rate (response rate in treated *vs*. untreated patients 37.5% and 33.3%, *p*=0.857; 25% and 11.1%, *p*=0.453 and 62.5% *vs*. 44.4%, p=0.456, respectively).

There was no difference in the number of bDMARDs received before JAKi between subjects with response and those without (*p*=0.334). Patients

Table II. Demographics and clinical features of included subjects stratified upon response at 3 months of treatment with JAKi.

	Response (n=8)	No response (n=9)	*p*-value
Age at JIA onset, median (IQR)	10 (6.75)	14 (14)	**0.009**
Age at JIA diagnosis, median (IQR)	10 (7.75)	14 (14)	**0.035**
Age at starting treatment with JAKi, median (IQR)	29 (15.34)	30.5 (12.15)	0.865
Gender, F % (n)	87.5% (7)	77.8% (7)	0.600
ANA positivity, % (n)	62.5% (5)	55.6% (5)	0.772
Uveitis, % (n)	12.5% (1)	44.4% (4)	0.149
Comorbidities, % (n)	37.5% (3)	44.4% (4)	0.772
Disease duration at starting JAKi treatment (years), median (IQR)	22.1 (10.09)	25.4 (13.49)	0.470
DAS28-CRP at starting treatment with JAKi, median (IQR)	3.45 (1.16)	4.7 (0.99)	0.594
Active joints at starting treatment with JAKi, median (IQR)	1.5 (1.25)	2.0 (0)	0.931
Pre-JAKi bDMARDs, median (IQR)	2.5 (3.25)	3 (1.0)	0.610
Ongoing MTX, % (n) Median dose (IQR)	37.5% (3) 15 mg/wk	33.3% (3) 10 mg/wk	0.999
Ongoing LEF, % (n)	25% (2) 20 mg/day	11.1% (1) 20 mg/day	0.999
Ongoing oral glucocorticoids, % (n) Median dose (IQR)	12.5% (1)	11.1% (3)	N.C.
Duration of treatment with JAKi (days) median (IQR)	722.5 (895)	99 (119)	**<0.001**
Active joints at 3 months of JAKi, median (IQR)	0 (1)	1 (2)	0.150

ANA: anti-nuclear antibodies; bDMARD: disease-modifying anti-rheumatic drugs; cDMARD: conventional disease-modifying anti-rheumatic drug; ERA: enthesitis-related arthritis; F: female; IQR: interquartile range; JIA: juvenile idiopathic arthritis; JAKi: janus kinase inhibitor; LEF: leflunomide; MTX: methotrexate; N.C.: not calculated; n: number; O-JIA: oligoarticular juvenile idiopathic arthritis; P-JIA: polyarticular juvenile idiopathic arthritis; PsA: psoriatic arthritis; S-JIA: systemic juvenile idiopathic arthritis; wk: week.

Table III. Demographics and clinical features of included subjects stratified upon remission at 3 months of treatment with JAKi.

	Remission (n=4)	No remission (n=13)	*p*-value
Age at JIA onset, median (IQR)	11.5 (7.5)	10 (14)	0.583
Age at JIA diagnosis, median (IQR)	12.5 (9)	10 (14)	0.425
Age at starting treatment with JAKi, median (IQR)	28.8 (20.9)	30.5 (14.4)	0.785
Gender, F % (n)	75% (3)	84.6% (11)	0.659
ANA positivity, % (n)	25% (1)	61.5% (8)	0.200
Uveitis, % (n)	25% (1)	30.8% (4)	0.824
Comorbidities, % (n)	25% (1)	85.7% (6)	0.452
Disease duration at starting JAKi treatment (years), median (IQR)	24.2 (15.5)	25.1 (12.5)	0.999
DAS28-CRP at starting treatment with JAKi, median (IQR)	2.79 (1.53)	4.54 (1.09)	**0.022**
Active joints at starting treatment with JAKi, median (IQR)	1.5 (1.75)	2.0 (1.5)	0.397
Pre-JAKi bDMARDs, median (IQR)	0 (1.5)	3 (1.5)	**0.008**
Ongoing MTX, % (n)	25% (1)	38.5% (5)	0.999
Median dose (IQR)	15 mg/wk	10 mg/wk	
Ongoing LEF, % (n)	25% (1) 20 mg/day	15.4% (2) 20 mg/day	0.999
Ongoing oral glucocorticoids, % (n) Median dose (IQR)	-	30.8% (4) 11.25 mg/day	N.C.
Duration of treatment with JAKi (days) median (IQR)	723.0 (1111.2)	208.0 (166.5)	**0.060**
Active joints at JAKi discontinuation, median (IQR)	0 (0)	2 (2)	**0.048**

ANA: anti-nuclear antibodies; bDMARD: disease-modifying anti-rheumatic drugs; cDMARD: conventional disease-modifying anti-rheumatic drug; ERA: enthesitis-related arthritis; F: female; IQR: interquartile range; JIA: juvenile idiopathic arthritis; JAKi: janus kinase inhibitor; LEF: leflunomide; MTX: methotrexate; N.C.: not calculated; n: number; O-JIA: oligoarticular juvenile idiopathic arthritis; P-JIA: polyarticular juvenile idiopathic arthritis; PsA: psoriatic arthritis; S-JIA: systemic juvenile idiopathic arthritis; wk: week.

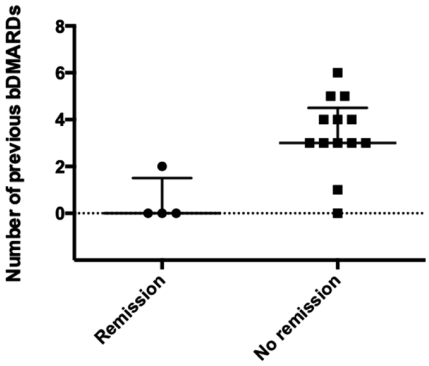

Fig. 1. Number of previous biological DMARDs in patients obtaining remission and those not obtaining remission after 3 months of treatment with JAKi.

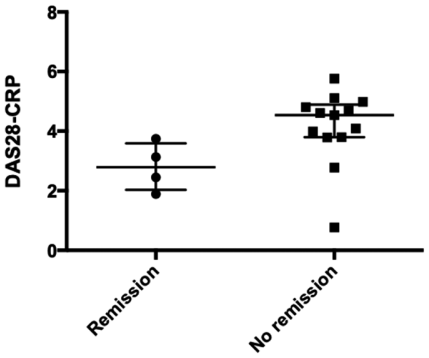

Fig. 2. Pre-treatment DAS28-CRP levels in patients obtaining remission and those not obtaining remission after 3 months of treatment with JAKi.

with 2 or more active joint involvement at JAKi start had a significantly lower response rate (77.8% *vs*. 12.5%; p=0.007, χ^2=7.24). Patients with large joint involvement were more prone to respond to JAKi treatment (p=0.029), while no difference in the response rate emerged in case of small joint involvement (p=0.149). Subjects who responded to JAKi had a significantly lower pre-treatment DAS28-CRP compared to those who did not (median DAS28-CRP (IQR) 3.43 (1.5) and 4.70 (1.8), respectively; p=0.020, Mann-Whitney U=12). A pre-treatment DAS28-CRP <3.79 predicted response to JAKi with 75% sensitivity and 88.9% specificity (AUC 0.83, p=0.020, 95% CI 0.61–1.05). Starting JAKi treatment in case of DAS28-CRP below 3.79 conferred an odds ratio (OR) for response at 3 months of 13.3 (95% CI 1.7–166.5, p=0.027).

Remission at 3 months of JAKi treatment

At 3 months, 4 patients (23.5%) achieved disease remission on JAKi (Table III). No difference between the 2 agents emerged in terms of remission rate: 3 patients achieving remission had been treated with baricitinib and 1 with tofacitinib (37.5% *vs*. 16.7%, p=0.294). None of the patients with systemic JIA and ERA obtained remission; the remission rate at 3 months was higher, although not significantly, in the oligoarticular subset compared to the polyarticular subset (37.5% *vs*. 20%; p=1.0). All the 3 patients with oligoarticular JIA achieving remission had the persistent form. Disease duration and age at JAKi start were similar between patients achieving remission and those with still active disease (p=0.999 and p=0.785, respectively). Patients whose disease manifested between 5 and 10 years of age had a significantly lower probability of achieving remission on JAKi than subjects with age at onset below 5 or above 10 years (15.4% *vs*. 100%, p=0.015, χ^2=8.355). Concomitant treatment with methotrexate, leflunomide or both did not significantly affect the remission rate (remission rate in treated *versus* untreated patients 37.5% and 16.7%, p=1.0; 50 and 27.3%, p=1.0 and 50% *vs*. 22.2%, p=0.584, respectively).

The remission rate was lower among patients who had been treated with 2 or more bDMARDs before JAKi start (9% *vs*. 66.7%; p=0.052; Fig. 1). Patients that had failed treatment with any of the agents targeting tumour necrosis factor-α (anti-TNF-α) had a significantly lower chance of achieving remission with JAKi (75% *vs*. 7.6%, p=0.005, χ^2=7.702). No additional difference in the remission rate emerged between patients categorised upon previous treatment failure. Patients with

Table IV. Demographic features and treatment regimen of included patients with uveitis during treatment with JAKi.

Patient, sex, diagnosis	Age at JIA onset (years)	Age at uveitis onset (years)	Uveitis features	Uveitis complications at JAKi start	n. of bDMARD before JAKi	Active uveitis at JAKi start	JAKi	Systemic steroid during treatment with JAKi	cDMARD during treatment with JAKi	AC cells		Topical steroid (drops)		Follow-up time on JAKi (days)
										B	A	B	A	
1, M, O-JIA	1.85	2.24	Bilateral panuveitis	- Band keratopathy - Cataract - Posterior synechiae	4	Yes	Tofacitinib, Baricitinib	No	No	2+	0	4	0	335
2, F, O-JIA	0.95	1.20	Bilateral anterior uveitis	- Band keratopathy - Posterior synechiae	3	Yes	Baricitinib	No	No	3+	0	4	0	153
3, F, O-JIA	9.69	9.69	Bilateral panuveitis	- Band keratopathy - Cataract	2	No	Baricitinib	No	MTX	0	0	0	0	1552
4, F, O-JIA	1.75	1.75	Bilateral anterior uveitis	- Band keratopathy - Posterior synechiae	1	No	Tofacitinib	No	No	0	0	0	0	92
5, F, RF- P-JIA	0.19	1.52	Bilateral anterior uveitis	- Band keratopathy - Posterior synechiae	5	Yes	Baricitinib	Yes	MTX	2+	0	4	0	208

JIA: juvenile idiopathic arthritis; O-JIA: oligoarticular juvenile idiopathic arthritis; RF: rheumatoid factor; P-JIA: polyarticular juvenile idiopathic arthritis; F: female; M: male; JAKi: janus kinase inhibitor; N: number; bDMARD: disease-modifying anti-rheumatic drugs; cDMARD: conventional disease-modifying anti-rheumatic drug; MTX: methotrexate; B: before JAKi treatment; A: after JAKi treatment; AC: anterior chamber.

2 or more active joint involvement at JAKi start had a lower remission rate (50% *vs*. 22.2%; p=0.584). No difference in the remission rate emerged upon the involved joints at JAKi start and the articular disease pattern (large *versus* small joint involvement p=0.371). Subjects who achieved remission on JAKi had a significantly lower pre-treatment DAS28-CRP compared to those with still active disease (median DAS28-CRP (IQR) 2.17 (0.5) and 4.54 (1.1), respectively; p=0.010, Mann-Whitney U=4; Fig. 2). A pre-treatment DAS28-CRP <3.76 predicted remission with JAKi with 100% sensitivity and 84.6% specificity (AUC 0.88, p=0.023, 95% CI 0.71–1.05). Starting JAKi treatment in case of DAS28-CRP below 3.76 conferred an OR for remission at 3 months of 22 (95% CI 1.5–314.5, p=0.009).

Patients with oligoarticular JIA, those with DAS28-CRP <3.76 at JAKi start and those who had tried less than 2 bDMARDs displayed a similar retention in treatment compared to the remaining included subjects (p=0.386, p=0.235 and p=0.866, respectively).

Sequential treatment with JAKi

Two patients with a hardly treatable articular disease, refractory to cDMARDs and several bDMARDs, were sequentially treated with both JAKi. A female patient with ERA, who experienced primary failure with etanercept, infliximab, golimumab, certolizumab, rituximab and abatacept, received first baricitinib in association with prednisone 12.5 mg daily; after 90 days, she was switched to tofacitinib and methotrexate 10 mg weekly combo. Disease activity increased with both agents (DAS28-CRP from 5.11 at baseline to 5.48 after 3 months of treatment with baricitinib and from 3.32 at baseline to 5.64 after 3 months of treatment with tofacitinib). A male patient with oligoarticular JIA, who later on developed also Crohn's disease, had been unsuccessfully treated with etanercept, infliximab, golimumab, certolizumab and adalimumab. He received as first JAKi tofacitinib, which was replaced by baricitinib after 335 days of treatment. Disease activity remained stable with both JAKi, with a DAS28-CRP of 4.98. He also had uveitis, which was clinically inactive before and throughout treatment with the 2 JAKi.

Both patients discontinued even the second line JAKi, another pharmacological tool (sarilumab) was introduced without achieving disease control.

Beyond the joints

Five patients also presented JIA-uveitis, as detailed in Table IV. At JAKi start, uveitis was active in 3 cases (60%); all patients with active uveitis achieved complete treatment response after 3 months of JAKi treatment. One subject (Patient 5) required systemic steroids during the follow-up, but all patients (3/3, 100%) discontinued topical corticosteroid therapy at the 3-month visit. No uveitis relapses were observed during follow-up and no ocular side effects or new-onset complications were observed during the treatment period. One female patient with ERA had skin psoriasis, which was under good control at the time of tofacitinib initiation, preventing any conclusion.

Comorbidities underpinned by an autoimmune aetiology were registered in 2 subjects (11.8%). These 2 patients, all with disease resistance to at least 3 bDMARDs, received JAKi (tofacitinib in 1 case, tofacitinib and baricitinib sequential treatment in another case) without any clinical benefit on joint involvement. The optimal disease control of hidradenitis suppurativa at JAKi start in one female patient, with oligoarticular JIA persisted throughout treatment course with tofacitinib. Similarly, Crohn's disease remained under remission during treatment first with tofacitinib and then baricitinib in a male patient with oligoarticular JIA.

Response to JAKi beyond 3 months of treatment

Ten patients discontinued JAKi at 3 months due to primary failure while 7 subjects (41.2%) persisted on treatment with JAKi beyond 3 months: 3 subjects

were on tofacitinib and 4 received baricitinib. At survival analysis, there was no difference in the retention in treatment between the 2 agents (p=0.926). DAS28-CRP were evaluated quarterly in all 7 patients, with a median follow-up of 1088 days (IQR 1195). To note, DAS28-CRP fluctuated significantly over follow-up (p=0.0009, Friedman statistics 18.79), and a significant decrease in disease activity was registered even after 12 months of treatment (median DAS28-CRP [IQR] at baseline 3.13 [1.35], 1 at 3 months 1.00 [2.00], at 6 months 1.00 [1.00], at 12 months 1.00 [0], at last visit 1.00 [1.00]).

After JAKi failure, 8 patients were switched to a bDMARD, and primary failure was registered in 5 patients. Patients were mainly started on anti-IL-6 agents (tocilizumab in 4 cases and sarilumab in 2 cases), with a single patient responding to tocilizumab. One subject was started on etanercept and one on secukinumab, in both cases a primary response was observed but the patient started on IL-17A inhibitor lost response at 10 months.

Safety profile of JAKi

Over a median treatment with JAKi of 297 days (IQR 655.5), none of the patients experienced side effects as hypercholesterolaemia and thromboembolic events during JAKi treatment. An overweight female patient with oligoarticular JIA developed, at the age of 27 years, severe arterial hypertension while receiving tofacitinib and leflunomide combo treatment; both pharmacological agents were promptly discontinued and a progressive normalisation of blood pressure was observed.

Discussion

To our knowledge, the present cohort study is the first report in literature describing the efficacy of first-generation JAKi in a neglected population as adult patients with JIA. Noteworthy, the introduction of JAKi allowed obtaining remission in approximately a quarter of patients at 3 months. Such remission rate is not negligible, given that the present cohort was composed of patients with longstanding refractory disease, with previous failure of 2 bDMARDs in median. Even though modern rheumatology aims at obtaining full control of articular and systemic inflammation leading to remission of disease activity, inadequate response is still an issue in JIA, as confirmed by available epidemiological data: approximately half of JIA patients have active disease despite 2 or more sequential bDMARDs (15). To note, the remission rate in our JIA cohort was similar to the figures emerged after 3 months of treatment with tofacitinib in rheumatoid arthritis (RA) across 5 clinical trials, where 18–22% of patients achieved remission according to DAS28-CRP (16).

JIA subsets, although unified by the onset of chronic arthritis, are underpinned by diverging pathophysiologic mechanisms that account for the differential treatment algorithms (17). In our cohort, JAKi exerted the highest therapeutic effect in JIA patients with persistent oligoarticular subset followed by polyarticular JIA. Such finding is in partial agreement with the only available withdrawal phase 3 trial conducted on 184 patients, which showed that tofacitinib represents an effective option for patients with polyarticular course JIA (extended oligoarthritis, polyarticular JIA and systemic JIA without active systemic features) aged between 2 and 18 years (18); unfortunately, no further subanalysis upon disease categories was performed. In our cohort, none of the patients with systemic JIA achieved disease remission with JAKi; some data can be extrapolated from a French national survey that included 2 paediatric patients with systemic JIA who achieved clinical and biological disease remission at the latest follow-up (19). We observed JAKi treatment failure even in both patients with ERA, in partial agreement with an exploratory efficacy analysis in the PRINTO trial: among 16 enrolled patients with ERA, the flare rate at 44 weeks was 44% in the tofacitinib-treated arm *versus* 57% in those receiving placebo (18). Conversely, in patients with adult-onset spondyloarthritis, clinical trials have demonstrated the superior efficacy of JAKi over placebo in case of failure of first line treatments (20). Importantly, our data confirm the rapid and sustained effect of JAKi even in JIA: if changes in DAS28-CRP levels were registered as early as 3 months, a significant decrease in the same score was reported even at one year.

Although the homology within the JAK family challenges the selectivity of JAKi, *in vitro* studies have shown that baricitinib is more selective for JAK1 and JAK2 (21, 22), whereas tofacitinib is considered as a pan-JAKi that preferentially targets JAK1 and JAK3 with minor activity on JAK2 and TYK2 (21, 23). To date, there is no evidence that such diverging behaviour might translate into a differential therapeutic effect: comparative studies between JAKi are lacking, even though a propensity score-based analysis suggested a higher efficacy for baricitinib than tofacitinib in RA (24). Conversely, our data do not support a differential effect for baricitinib *versus* tofacitinib in adult patients with JAKi, both in the short and the long terms. In our JIA cohort, the concomitant treatment with cDMARDs, either methotrexate or leflunomide, did not affect the response to JAKi, consistently with registrational trials that led to the licensing of these drugs in monotherapy as well as in association with cDMARDs (6).

In the clinical approach to a heterogeneous disease as JIA, it is pivotal to profile the clinical features of patients with the highest chance of responding to a given therapeutic tool. Importantly, this study offers several insights into the decision process for JAKi prescription to adult patients with JIA. First, JAKi were more effective in JIA patients with moderate disease activity, in particular in case of a DAS28-CRP below 3.76 according to ROC curve analysis. In addition, patients with previous failure to 2 or more bDMARDs (in particular if anti-TNF-α agents) had a lower beneficial effect with JAKi. These findings are in conflict with literature on RA, which supports the efficacy of JAKi even in severe RA, to an extent that was comparable – or even superior – to bDMARDs (6). Secondly, the therapeutic tailoring upon patient's features should take into account that JAKi exert a notable therapeutic effect on uveitis. This is highly relevant,

as uveitis provides the most common and potentially serious extra-articular manifestation of JIA and still poses therapeutic challenges due to its recalcitrant behaviour with potential visual complications. Novel agents allowing to control both sites of inflammation are highly warranted, as adalimumab is currently the only approved steroid-sparing agent for the treatment of non-infectious uveitis (25). Since the trial of tofacitinib in JIA excluded patients with active uveitis within 3 months from enrolment and recruited only one participant with a history of inactive uveitis, particular attention should be devoted to the data about JAKi in uveitis presented in this study, which add on the case reports already published by our group (18, 26). Together with some other case reports, this bulk of evidence prompted an open-label adalimumab active controlled phase 3 trial of baricitinib in JIA-uveitis or ANA-positive uveitis, which is currently recruiting (NCT04088409) (27-30).

Thirdly, comorbidities provide an additional key driver for therapeutic strategy: two recent phase 2 studies support a clinical utility for JAKi in individuals with hidradenitis suppurativa (31) whereas clinical trials of tofacitinib in Crohn's disease have been disappointing, with no differences in response or remission compared with placebo (6). We cannot comment on our experience since all comorbid diseases were under remission when our patients were started on JAKi, as well as psoriatic skin disease where available evidence suggests JAKi efficacy (32).

The safety of JAKi has been matter of vibrant debate in RA, with particular focus on the risk of thromboembolic events, herpes zoster and malignancies following the warning by regulatory agencies (33-38). Consistently with the reassuring data from the PRINTO trial (18), in our cohort JAKi emerged as a safe therapeutic tool: the only registered adverse event was the onset of severe arterial hypertension, possibly ascribed to the concomitant leflunomide treatment.

Limitations of this study include the retrospective design and limited sample size, which hampers the drawing of robust conclusions. The recruitment of subjects in a single third-level clinic might unveil a selection bias as patients with active recalcitrant disease are followed up in this setting. The rate of withdrawal from JAKi was rather elevated at 3 months, and this precludes a complete analysis of the benefits. However, we believe our data add relevant insights into the efficacy and safety of JAKi in a clinical scenario that is seldom a focus of research in adult rheumatology. Furthermore, disease activity was evaluated by the means of DAS28-CRP, which has been recently identified as the most reliable clinimetric score among adults with JIA (39). DAS28-CRP holds clinical significance even in the setting of longstanding systemic JIA, given that systemic manifestations tend to remit with time while the articular involvement remains active (4). Half of the patients with oligoarticular JIA had extended disease, and the activity of uveitis was captured by means of inflammation score according to SUN criteria (12).

As a whole, this study supports JAKi as additional pharmacological options in a unique population of adult patients with JIA. While awaiting results from ongoing clinical trials in paediatric populations (NCT04088396, NCT03773978 and NCT03000439), JAKi might allow enabling a full control of JIA underlying inflammation with a favourable risk-benefit balance even once the adult age is reached. Our data suggest that JAKi might be regarded as a suitable option in JIA patients with oligoarticular subset and moderate disease activity, even though further studies are warranted to profile the patients with the highest chance of response to JAKi.

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References

1. RAVELLI A, MARTINI A: Juvenile idiopathic arthritis. *Lancet* 2007; 369: 767-78. https://doi:10.1016/S0140-6736(07)60363-8
2. CIMAZ R, MARINO A, MARTINI A: How I treat juvenile idiopathic arthritis: A state of the art review. *Autoimmun Rev* 2017; 16: 1008-15. https://doi:10.1016/j.autrev.2017.07.014
3. VIDQVIST K-L, MALIN M, VARJOLAHTI-LEHTINEN T, KORPELA MM: Disease activity of idiopathic juvenile arthritis continues through adolescence despite the use of biologic therapies. *Rheumatology* (Oxford) 2013; 52: 1999-2003. https://doi:10.1093/rheumatology/ket256
4. MINDEN K: Adult outcomes of patients with juvenile idiopathic arthritis. *Horm Res* 2009; 72(S1): 20-25. https://doi:10.1159/000229759
5. COULSON EJ, HANSON HJM, FOSTER HE: What does an adult rheumatologist need to know about juvenile idiopathic arthritis? *Rheumatology* (Oxford) 2014; 53: 2155-66. https://doi:10.1093/rheumatology/keu257
6. TANAKA Y, LUO Y, O'SHEA JJ, NAKAYAMADA S: Janus kinase-targeting therapies in rheumatology: a mechanisms-based approach. *Nat Rev Rheumatol* 2022; 18: 133-45. https://doi:10.1038/s41584-021-00726-8
7. NASH P, KERSCHBAUMER A, DÖRNER T *et al*.: Points to consider for the treatment of immune-mediated inflammatory diseases with Janus kinase inhibitors: a consensus statement. *Ann Rheum Dis* 2021; 80: 71-87. https://doi:10.1136/annrheumdis-2020-218398
8. WELZEL T, WINSKILL C, ZHANG N, WOERNER A, PFISTER M: Biologic disease modifying antirheumatic drugs and Janus kinase inhibitors in paediatric rheumatology - what we know and what we do not know from randomized controlled trials. *Pediatr Rheumatol Online J* 2021; 19: 46. https://doi:10.1186/s12969-021-00514-4
9. PETTY RE, SOUTHWOOD TR, MANNERS P *et al*.: International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004; 31: 390-2.
10. PREVOO ML, VAN 'T HOF MA, KUPER HH, VAN LEEUWEN MA, VAN DE PUTTE LB, VAN RIEL PL: Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 44-8. https://doi:10.1002/art.1780380107
11. ANDERSON J, CAPLAN L, YAZDANY J *et al*.: Rheumatoid arthritis disease activity measures: American College of Rheumatology recommendations for use in clinical practice. *Arthritis Care Res* 2012; 64: 640-47. https://doi:10.1002/acr.21649
12. JABS DA, NUSSENBLATT RB, ROSENBAUM JT; STANDARDIZATION OF UVEITIS NOMENCLATURE (SUN) WORKING GROUP: Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. *Am J Ophthalmol* 2005; 140: 509-16. https://doi:10.1016/j.ajo.2005.03.057
13. FINGERHUTOVÁ Š, SRP R, HURŇÁKOVÁ J *et al*.: Can ultrasound help to overcome uncertainty in clinical joint assessment in juvenile idiopathic arthritis? *Clin Exp Rheumatol* 2023; 41: 177-85. https://doi:10.55563/clinexprheumatol/5lk4x2
14. CHHABRA A, ROBINSON C, HOUGHTON K *et al*.: Long-term outcomes and disease course of children with juvenile idiopathic arthritis in the ReACCh-Out cohort: a two-centre experience. *Rheumatology* (Oxford) 2020; 59: 3727-30.

https://doi:10.1093/rheumatology/keaa118
15. BRUNNER HI, SCHANBERG LE, KIMURA Y *et al*.; PRCSG ADVISORY COUNCIL AND THE CARRA REGISTRY INVESTIGATORS: New medications are needed for children with juvenile idiopathic arthritis. *Arthritis Rheumatol* 2020; 72: 1945-51. https://doi:10.1002/art.41390
16. SMOLEN JS, ALETAHA D, GRUBEN D, ZWILLICH SH, KRISHNASWAMI S, MEBUS C: Remission rates with tofacitinib treatment in rheumatoid arthritis: A comparison of various remission criteria. *Arthritis Rheumatol* 2017; 69: 728-34. https://doi:10.1002/art.39996
17. DE NARDI L, PASTORE S, RISPOLI F *et al*.: Type I interferon signature as a possible new marker for stratification of patients with juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2023; 41: 1548-52. https://doi:10.55563/clinexprheumatol/b37xbd
18. RUPERTO N, BRUNNER HI, SYNOVERSKA O *et al*.: Tofacitinib in juvenile idiopathic arthritis: a double-blind, placebo-controlled, withdrawal phase 3 randomised trial. *Lancet* 2021; 398(10315): 1984-96. https://doi:10.1016/S0140-6736(21)01255-1
19. GILLARD L, POUCHOT J, COHEN-AUBART F *et al*.; CRI (CLUB RHUMATISMES ET INFLAMMATION): JAK inhibitors in difficult-to-treat adult-onset Still's disease and systemic-onset juvenile idiopathic arthritis. *Rheumatology* (Oxford) 2023; 62(4): 1594-604. https://doi:10.1093/rheumatology/keac440
20. KEELING S, MAKSYMOWYCH WP: JAK inhibitors, psoriatic arthritis, and axial spondyloarthritis: a critical review of clinical trials. *Expert Rev Clin Immunol* 2021; 17: 701. https://doi:10.1080/1744666X.2021.1925541
21. CLARK JD, FLANAGAN ME, TELLIEZ JB: Discovery and development of Janus kinase (JAK) inhibitors for inflammatory diseases. *J Med Chem* 2014; 57: 5023-38. https://doi:10.1021/jm401490p
22. KERRIGAN SA, MCINNES IB: JAK inhibitors in rheumatology: implications for paediatric syndromes? *Curr Rheumatol Rep* 2018; 20: 83-9. https://doi:10.1007/s11926-018-0792-7
23. GADINA M, LE MT, SCHWARTZ DM *et al*.: Janus kinases to jakinibs: from basic insights to clinical practice. *Rheumatology* (Oxford) 2019; 58(S1): i4-16. https://doi:10.1093/rheumatology/key432
24. MIYAZAKI Y, NAKANO K, NAKAYAMADA S *et al*.: Efficacy and safety of tofacitinib versus baricitinib in patients with rheumatoid arthritis in real clinical practice: analyses with propensity score-based inverse probability of treatment weighting. *Ann Rheum Dis* 2021; 80: 1130-6. https://doi:10.1136/annrheumdis-2020-219699
25. JAFFE GJ, DICK AD, BRÉZIN AP *et al*.: Adalimumab in patients with active noninfectious uveitis. *N Engl J Med* 2016; 375(10): 932-43. https://doi:10.1056/nejmoa1509852
26. MISEROCCHI E, GIUFFRÈ C, CORNALBA M, PONTIKAKI I, CIMAZ R: JAK inhibitors in refractory juvenile idiopathic arthritis-associated uveitis. *Clin Rheumatol* 2020; 39: 847-51. https://doi:10.1007/s10067-019-04875-w
27. RAMANAN AV, GULY CM, KELLER SY *et al*.: Clinical effectiveness and safety of baricitinib for the treatment of juvenile idiopathic arthritis-associated uveitis or chronic anterior antinuclear antibody-positive uveitis: study protocol for an open-label, adalimumab active-controlled phase 3 clinical trial (JUVEBRIGHT). *Trials* 2021; 22: 689. https://doi:10.1186/s13063-021-05651-5.
28. BAUERMANN P, HEILIGENHAUS A, HEINZ C: Effect of Janus Kinase inhibitor treatment on anterior uveitis and associated macular edema in an adult patient with juvenile idiopathic arthritis. *Ocul Immunol Inflamm* 2019; 27: 1232-4. https://doi:10.1080/09273948.2019.1605453
29. STEVENSON W, SADRAI Z, HUA J *et al*.: Effects of topical Janus kinase inhibition on ocular surface inflammation and immunity. *Cornea* 2014; 33: 177-83. https://doi:10.1097/ico.0000000000000019
30. PALEY MA, KARACAL H, RAO PK, MARGOLIS TP, MINER JJ: Tofacitinib for refractory uveitis and scleritis. *Am J Ophthalmol Case Rep* 2018; 13: 53-5. https://doi:10.1016/j.ajoc.2018.12.001
31. ALAVI A, HAMZAVI I, BROWN K *et al*.: Janus kinase 1 inhibitor INCB054707 for patients with moderate-to-severe hidradenitis suppurativa: results from two phase II studies. *Br J Dermatol* 2022; 186: 803-13. https://doi:10.1111/bjd.20969
32. SADEGHI S, GOODARZI A: Various application of tofacitinib and ruxolitinib (Janus Kinase Inhibitors) in dermatology and rheumatology: A review of current evidence and future perspective. *Dermatol Pract Concept* 2022; 12: e2022178. https://doi:10.5826/dpc.1204a178
33. WINTHROP KL, COHEN SB: Oral surveillance and JAK inhibitor safety: the theory of relativity. *Nat Rev Rheumatol* 2022; 18: 301-4. https://doi:10.1038/s41584-022-00767-7
34. SMOLEN JS, GENOVESE MC, TAKEUCHI T *et al*.: Safety profile of baricitinib in patients with active rheumatoid arthritis with over 2 years median time in treatment. *J Rheumatol* 2019; 46: 7-18. https://doi:10.3899/jrheum.171361
35. KREMER JM, BINGHAM CO, CAPPELLI LC *et al*.: Postapproval comparative safety study of tofacitinib and biological disease-modifying antirheumatic drugs: 5-year results from a United States-based rheumatoid arthritis registry. *ACR open Rheumatol* 2021; 3: 173-84. https://doi:10.1002/acr2.11232
36. KHOSROW-KHAVAR F, KIM SC, LEE H, LEE SB, DESAI RJ: Tofacitinib and risk of cardiovascular outcomes: results from the safety of tofacitinib in routine care patients with rheumatoid arthritis (STAR-RA) study. *Ann Rheum Dis* 2022; 8: 798-804. https://doi:10.1136/annrheumdis-2021-221915
37. COHEN SB, VAN VOLLENHOVEN RF, WINTHROP KL *et al*.: Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT phase III clinical programme. *Ann Rheum Dis* 2021; 80(3): 304-11. https://doi:10.1136/annrheumdis-2020-218510
38. YTTERBERG SR, BHATT DL, MIKULS TR *et al*.: Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. *N Engl J Med* 2022; 386(4): 316-26. https://doi:10.1056/nejmoa2109927
39. MIYAMAE T, INOUE E, TANAKA E, KAWABE T, IKARI K, HARIGAI M: Association of disease activity using SDAI and DAS-28, but not JADAS-27, with subsequent changes in physical function in adult patients with juvenile idiopathic arthritis. *Mod Rheumatol* 2023; 33(3): 588-93. https://doi:10.1093/mr/roac063