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BRIEF REPORT

JAK inhibitors in refractory juvenile idiopathic arthritis-associated uveitis

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Abstract

To present our preliminary experience with JAK inhibitors in treating patients affected by juvenile idiopathic arthritis (JIA) and associated uveitis. Case series. Four consecutive patients with long-term history of juvenile idiopathic arthritis and severe associated uveitis were included in the study. Indication for treatment with JAK inhibitors was uncontrolled arthritis and/or uveitis despite different treatments with conventional and biologic disease modifying antirheumatic drugs (DMARDs). While on treatment with JAK inhibitors, namely, baricitinib (three cases) and tofacitinib (one case), all our patients showed improvement of uveitis defined as a reduction of intraocular inflammation according to Standardized Uveitis Nomenclature criteria. However, we observed a different response to treatment between the uveitis and the articular disease, as the latter did not respond as favorably as the former. Overall, the treatment was well tolerated by all patients and no ocular discomfort, ocular side effects, or allergic reactions were registered. JAK inhibitors may provide a new valuable treatment option in the therapeutic armamentarium for patients affected with JIA-associated uveitis, particularly in those refractory cases that are not adequately responding to conventional or biologic DMARDs.

Key Points
- *A subset of patients with JIA uveitis either remain unresponsive or experience loss of efficacy*
- *JAK inhibitors may provide a new valuable treatment option in JIA patients with uveitis*
- *The safety profile was good with no occurrence of systemic side effects*

Keywords Baricitinib · JAK inhibitors · JIA-associated uveitis · Juvenile idiopathic arthritis · Pediatric uveitis · Tofacitinib

Introduction

Juvenile idiopathic arthritis (JIA) is the most common pediatric rheumatic disease with both articular and ocular involvement with a prevalence of about 80% of cases of uveitis related to this condition in the USA [1].

Despite advances in the diagnosis and treatment, uveitis in patients with JIA continues to be a critical health issue for the long-life duration of the disease and a relevant cause of visual loss. Severe ocular complications including cataract, glaucomatous optic neuropathy, and cystoid macular edema may occur in 50–70% of patients and are eventually responsible for permanent visual loss [2–4].

Local and systemic corticosteroids are effective in controlling intraocular inflammation of the anterior and the posterior segment, but the high risk of long-term ocular and systemic complications limits their use in the acute and early phase of the disease [5].

Second line systemic immunosuppressants are usually introduced rapidly as steroid-sparing agents to reduce and eliminate intraocular inflammation [6]. Methotrexate is the most commonly conventional disease modifying antirheumatic drug (DMARD) employed for treatment of JIA-associated uveitis, used as a monotherapy or combined in association with a biologic DMARD. TNF-alpha blockers are the most frequently used biologics in JIA-associated uveitis, and adalimumab is currently the only FDA-approved steroid-sparing agent for the treatment of uveitis [7, 8]. Other classes of

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biologics including rituximab, tocilizumab, and abatacept have been proven effective in the treatment of recalcitrant cases of JIA-associated uveitis [9–12].

However, despite the introduction of new and potent therapeutic agents, some patients fail to reach control and remission of intraocular inflammation or develop treatment intolerance. In this particular subset of patients, there is a desperate need for new treatments that are selecting novel target molecules in order to control severe uveitis.

JAK inhibitors (Jakinibs) are small molecules that inhibit the Janus kinase family of receptors. JAK-mediated pathways are involved in the pathogenesis of several autoimmune diseases including rheumatoid and psoriatic arthritis, inflammatory bowel disease, and other immune-mediated inflammatory diseases. There are four known JAKs (JAK 1,2,3, and TYK2) which are members of the tyrosine kinase family of protein kinases. Tofacitinib (Xeljanz, Pfizer, USA) and baricitinib (Olumiant, Eli Lilly/Incyte, USA) are first-generation JAK inhibitors. Tofacitinib inhibits JAK 1, JAK 3, and to a lesser extent JAK 2, and baricitinib inhibits JAK 1 and JAK 2.

Different clinical trials on rheumatoid and psoriatic arthritis have demonstrated efficacy of JAK inhibitors in the treatment of these conditions [13–16]. Conversely, very little evidence is currently present on the use of JAK inhibitors in the treatment of ocular inflammation and in JIA-associated uveitis [17–19].

The purpose of this study was to present our preliminary experience with JAK inhibitors in treating patients affected by JIA and uveitis. To the best of our knowledge, there is only one previously published case report of JAK inhibition for JIA-associated uveitis.

Materials and methods

Patients included in this series were seen at the Pediatric Rheumatology Unit at the tertiary referral center "G. Pini," Milan, Italy, between August 2018 and September 2019. Complete ophthalmological evaluations have been always performed by the same uveitis expert (EM). Anterior segment inflammation was graded clinically by means of slit-lamp cells and flare quantification according to the SUN criteria [20] and semi-automated flare measurement with the Kowa FC500 Laser Flare Meter (LFM). In addition, a macular scan by means of optical coherence tomography (OCT) (Spectralis, Spectral domain-OCT; Heidelberg Engineering, Germany) was performed in all the patients.

Rheumatologic assessment was performed on the same day of each ophthalmologic visit [21].

Uveitis response to JAK inhibitors was defined as a reduction of anterior chamber cells (two step decrease) according to SUN criteria [20], a reduction of flare by means of LFM (under 50 ph/ms), and resolution of macular edema on OCT (under 300 μm). The mean number of flare-up recurrence (2+ flare in anterior chamber) before starting Jakinibs was 4.2 episodes/year and was reduced to 1.4 episodes/year after the beginning of the treatment.

Informed consent was obtained, as required by the Italian bioethical legislation, in agreement with the Declaration of Helsinki for research involving human subjects and was approved by the IRB of G. Pini hospital.

Results

Case series.

Case 1

A 43-year-old female was diagnosed with oligoarticular ANA-negative JIA at the age of 9. One year later the patient showed a severe and aggressive anterior uveitis in both eyes complicated by cataract, band keratopathy, and posterior pole involvement, with development of macular edema and retinal vasculitis. The patient underwent cataract extraction and was left aphakic. Different non-biologic and biologic DMARDs were used during her childhood to control the disease including TNF-alpha blockers (infliximab 5 mg/Kg every 4 weeks for 9 months, adalimumab 40 mg every 2 weeks for 3 years), leflunomide, abatacept, rituximab, and tocilizumab that led only to partial control of the arthritis and uveitis. During the course of the disease, intraocular inflammation of the left eye caused severe retinal complications leading to retinal detachment and phthisis bulbi. The patient's visual acuity decreased to 20/40 in the right eye and no light perception in the left eye. In March 2019, although the uveitis was inactive, the arthritis activity was not well controlled despite tocilizumab therapy. Thus, the patient was started on oral tofacitinib 5 mg twice daily. During the 6 months of monotherapy treatment with tofacitinib, the arthritis reached control, and her uveitis remained inactive with no additional ocular complications and complete resolution of her long-standing macular edema.

Case 2

An 18-year-old girl was diagnosed with polyarticular ANA-positive JIA and anterior bilateral uveitis at 1 year of age. During follow-up, the uveitis became chronic with persistent flare in the anterior chamber and development of bilateral synechiae. Despite good control of joint flares, the anterior uveitis was poorly responsive to methotrexate, and long-term courses of topical corticosteroids were needed, which eventually caused cataract formation. Conventional DMARDs were not effective in controlling either the arthritis or the uveitis, requiring also chronic systemic prednisone. The patient was subsequently started on different biologic DMARDs. TNF-alpha blockers (adalimumab 40 mg every

2 weeks for 4 years, infliximab 5 mg/Kg every 4 weeks for 2 years), although initially effective, were discontinued due to infusion reactions and drug-induced side effects, i.e., gastrointestinal intolerance and skin rash. Other biologics were employed, including rituximab and abatacept with poor control of both articular and ocular disease. Baricitinib was then started on March 2019 at the dose of 5 mg/day in association with weekly methotrexate (15 mg). The uveitis reached inactivity with no cells in the anterior chamber and a final visual acuity of 20/40 in the right eye and 20/200 in the left eye. Topical corticosteroids were also able to be discontinued 2 months after initiation of treatment. However, the polyarthritis remained active and did not reach quiescence while on baricitinib; therefore several intraarticular corticosteroid injections and daily doses of systemic prednisone (12.5 mg/day) were needed.

Case 3

A 37-year-old female was diagnosed with oligo-extended JIA, ANA-positive, at the age of 2, and with bilateral anterior uveitis 1 year later. The arthritis was well controlled with gold salts and occasional intraarticular corticosteroid injections for 15 years, but at the age of 20, the patient required conventional DMARDs (methotrexate and azathioprine) and subsequently biologics. TNF-alpha blockers (infliximab 5 mg/Kg every 4 weeks for 3 years, adalimumab 40 mg every 2 weeks for 4 years, golimumab 50 mg every 4 weeks for 9 months) were effective in controlling both arthritis and uveitis, but the patient developed severe gastrointestinal intolerance. The patient was then switched to subcutaneous tocilizumab 162 mg/week, which effectively controlled both joint and ocular flares, but was discontinued after 6 months for severe skin lesions. In August 2018, baricitinib monotherapy was started (4 mg/day). During the 13 months of follow-up, both arthritis and uveitis remained inactive. The visual acuity at last visit was 20/60 in both eyes.

Case 4

A 21-year-old boy was diagnosed with polyarticular JIA, ANA-positive, and RF-negative, at the age of 10 years. The articular disease was well controlled on conventional treatment including biologics (etanercept). However, at the age of 15, due to the development of anterior uveitis in the right eye, the patient was switched to other c-DMARDs (methotrexate, cyclosporin) and b-DMARDs (infliximab 5 mg/Kg every 4 weeks for 1 year, adalimumab 40 mg every 2 weeks for 1 year, abatacept, tocilizumab, and rituximab) sequentially, without complete remission. The uveitis remained unilateral but ocular complications, i.e., synechiae, band keratopathy, and cataract developed during the course of the disease requiring cataract extraction with intraocular lens implantation. The arthritis remained active despite different biologics including infliximab 5 mg/Kg every 4 weeks, adalimumab 40 mg every

Table 1 Demographics and ophthalmologic and articular features of patients in the study cohort

Patient	Gender	Age at JIA onset (years)	JIA category	Age at uveitis onset (years)	Uveitis type	Uveitis complications at Jakinibs onset	AC cells		AC flare (ph/ms)		OCT CRT (μm)	
							Before Jakinibs	After Jakinibs	Before Jakinibs	After Jakinibs	Before Jakinibs	After Jakinibs
1	F	9	Oligo-extended; ANA -	10	Bilateral, chronic panuveitis	Cataract, band keratopathy, macular edema	2+	0	200	33	350	270
2	F	1	Poliarticular; ANA +	1	Bilateral, chronic panuveitis	Cataract, band keratopathy, glaucoma	3+	0.5+	150	25	320	264
3	F	2	Oligo-extended; ANA +	3	Bilateral, chronic anterior	Cataract, band keratopathy	2+	0	130	15	450	276
4	M	10	Poliarticular; ANA +	15	Unilateral RE, chronic panuveitis	Cataract, band keratopathy, macular edema	3+	0.5+	300	36	400	280

F, female; M, male; ANA, antinuclear antibodies; RE, right eye; AC, anterior chamber; OCT, optical coherence tomography; CRT, central retinal thickness

AC cells, AC flare, and OCT CRT values represent a mean between the two eyes

2 weeks, tocilizumab, and rituximab, with the need of continuous systemic corticosteroid treatment and multiple intraarticular injections of affected joints. Unfortunately, the patient developed corticosteroid-induced side effects, and the different biologics used for controlling arthritis were also poorly effective on uveitis. Visual acuity worsened during follow-up due to macular edema, and baricitinib (4 mg/day) was therefore introduced, in association with methotrexate (15 mg/week) and prednisone (7,5 mg/day). After 6 months of baricitinib treatment, the patient was able to taper corticosteroid drops until complete discontinuation after 3 months. Uveitis was under control with no cells or flare in the anterior chamber of the right eye and restoration of visual acuity to 20/20 in both of the eyes. Also the macular edema completely resolved. However, response of arthritis was incomplete with relapsing episodes of active joint inflammation that led to change of therapy.

Demographic data of patients, classification and type of JIA, uveitis characteristics, and ocular complications are listed in Table 1. All four patients included in the study (three females, one male) had a long-term history of arthritis and associated uveitis. The mean duration of articular disease was 23 years, whereas the mean duration of uveitis was 21 years. The mean age of our patients at the time of treatment with JAK inhibitors was 30 years.

Table 2 lists the different type of treatment received before the institution of JAK inhibitors, type and dosage of JAK inhibitors, follow-up time, and occurrence of side effects.

All patients showed improvement of uveitis and control of ocular disease while on treatment with baricitinib (three cases) and tofacitinib (one case).

Discussion

In the present manuscript, we report our preliminary data about JAK inhibitors treatment in the most severe and recalcitrant cases of JIA uveitis. Three patients received baricitinib, while another patient was treated with tofacitinib. In all patients the uveitis was chronic, associated with severe complications such as cataract, macular edema, and glaucoma, requiring different surgical interventions during follow-up and eventually leading to severe loss of vision. Indication for treatment with JAK inhibitors was active arthritis and/or active uveitis, despite different treatments with conventional and biologic DMARDs [20, 21].

On Jakinibs, we observed a good response of the uveitis. However, the articular disease did not respond as successfully as the ocular condition. The reason for this different behavior is still far from being elucidated. JAK inhibitors have a broad spectrum of activity over different organs and systems, but many of their actions are still a matter of study.

The safety profile in our patients was good with no occurrence of systemic side effects, laboratory abnormalities, or infections during the mean follow-up time on treatment of 7 months (range 4–13).

Literature data on the use of these small molecules in ocular inflammation is lacking, and to date, this is the only published series reporting the use of JAK inhibitors in JIA-associated uveitis. A case report of an adult patient with severe JIA-associated uveitis and macular edema that was successfully treated with tofacitinib and showed resolution of retinal edema after 1 year of treatment has been published [17]. Another study showed good results in treating two adult patients with noninfectious uveitis and scleritis with tofacitinib [19].

Our small case series is representative of the most severe and complicated cases of long-standing arthritis and uveitis that required several different drugs, without achieving long-term remission or developing unacceptable adverse events, especially when increasing the dose [22]. Hence, in this particular subset of subjects, there is a continuous need to find new target molecules to control inflammation.

Table 2 Treatment characteristics for each patient before and after the beginning of JAK inhibitors therapy

Patient	DMARDs before Jakinibs	Age at onset of Jakinibs (years)	Type of treatment and follow-up	Associated DMARDs while on Jakinibs	Response of arthritis	Response of uveitis	Side effects
1	TNF-alpha blockers, leflunomide, abatacept, rituximab, tocilizumab	43	Tofacitinib 10 mg/day; 7 months	None	No	Yes	None
2	MTX, TNF-alpha blockers, rituximab, abatacept	18	Baricitinib 4 mg/day; 5 months	MTX 15 mg/wk	No	Yes	None
3	MTX, azathioprine, TNF-alpha blockers, tocilizumab	36	Baricitinib 4 mg/day; 13 months	None	Yes	Yes	None
4	TNF-alpha blockers, MTX, CsA, abatacept, tocilizumab, rituximab	20	Baricitinib 4 mg/day; 4 months	MTX 15 mg/wk	No	Yes	None

(b-)DMARDs, (biologic-) disease modifying antirheumatic drugs; TNF, tumor necrosis factor; MTX, methotrexate; CsA: cyclosporin A

JAK inhibitors have been approved for rheumatoid and psoriatic arthritis [14–16], and phase 3 studies are ongoing in JIA.

We acknowledge the limitations of the retrospective nature of this report, the small number of patients, and the lack of predefined standardized outcome measures. However, we believe that JAK inhibitors may provide a new valuable treatment option in the therapeutic armamentarium for JIA patients with uveitis. This is particularly important for the most severe and refractory cases that are not adequately responding to conventional or biologic DMARDs. An open label clinical trial on baricitinib use for pediatric uveitis is ongoing (ClinicalTrialsGov NCT04088409) [23].

Compliance with ethical standards

Disclosures None.

References

1. Smith JA, Mackensen F, Sen HN et al (2009) Epidemiology and course of disease in childhood uveitis. Ophthalmology 116:1544–1551
2. Constantin T, Foeldvari I, Anton J, de Boer J, Czitrom-Guillaume S, Edelsten C, Gepstein R, Heiligenhaus A, Pilkington CA, Simonini G, Uziel Y, Vastert SJ, Wulffraat NM, Haasnoot AM, Walscheid K, Pálinkás A, Pattani R, Györgyi Z, Kozma R, Boom V, Ponyi A, Ravelli A, Ramanan AV (2018) Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis: the SHARE initiative. Ann Rheum Dis 77:1107–1117
3. Sood AB, Angeles-Han ST (2017) An update on treatment of pediatric chronic non-infectious uveitis. Curr Treatm Opt Rheumatol 3:1–16
4. Gueudry J, Touhami S, Quartier P, Bodaghi B (2019) Therapeutic advances in juvenile idiopathic arthritis - associated uveitis. Curr Opin Ophthalmol 30:179–186
5. Skrabl-Baumgartner A, Seidel G, Langner-Wegscheider B, Schlagenhauf A, Jahnel J (2019) Drug monitoring in long-term treatment with adalimumab for juvenile idiopathic arthritis-associated uveitis. Arch Dis Child 104:246–250
6. Wentworth BA, Freitas-Neto CA, Foster CS (2014) Management of pediatric uveitis. F1000Prime Rep 6:41
7. Horton S, Jones AP, Guly CM et al (2019) Adalimumab in juvenile-idiopathic arthritis-associated uveitis (JIA-U): 5-year follow-up of the Bristol participants of the SYCAMORE trial. Am J Ophthalmol S0002-9394(19):30274–30270. https://doi.org/10.1016/j.ajo.2019.06.007
8. Hughes DA, Culeddu G, Plumpton CO, Wood E, Dick AD, Jones AP, McKay A, Williamson PR, Compeyrot Lacassagne S, Hardwick B, Hickey H, Woo P, Beresford MW, Ramanan AV (2019) Cost-effectiveness analysis of adalimumab for the treatment of uveitis associated with juvenile idiopathic arthritis. Ophthalmology 126:415–424
9. Miserocchi E, Modorati G, Berchicci L, Pontikaki I, Meroni P, Gerloni V (2016) Long-term treatment with rituximab in severe juvenile idiopathic arthritis-associated uveitis. Br J Ophthalmol 100:782–786
10. Dipasquale V, Atteritano M, Fresta J (2019) Tocilizumab for refractory uveitis associated with juvenile idiopathic arthritis: a report of two cases. J Clin Pharm Ther 44:482–485
11. Tappeiner C, Mesquida M, Adán A, Anton J, Ramanan AV, Carreno E, Mackensen F, Kotaniemi K, de Boer JH, Bou R, de Vicuña CG, Heiligenhaus A (2016) Evidence for tocilizumab as a treatment option in refractory uveitis associated with juvenile idiopathic arthritis. J Rheumatol 43:2183–2188
12. Tappeiner C, Miserocchi E, Bodaghi B, Kotaniemi K, Mackensen F, Gerloni V, Quartier P, Lutz T, Heiligenhaus A (2015) Abatacept in the treatment of severe, longstanding, and refractory uveitis associated with juvenile idiopathic arthritis. J Rheumatol 42:706–711
13. Kerrigan SA, McInnes IB (2018) JAK inhibitors in rheumatology: implication for paediatric syndromes? Curr Rheumatol Rep 20:83
14. Gladman D, Rigbt W, Azevedo VF et al (2017) Tofacitinib for psoriatic arthritis in patients with an inadequate response to TNF inhibitors. N Engl J Med 377:1525–1536
15. Jegatheeswaran J, Turk M, Pope JE et al (2019) Comparison of Janus kinase inhibitors in the treatment of rheumatoid arthritis: a systemic literature review. Immunotherapy 11:737–754
16. Harigai M (2019) Growing evidence of the safety of JAK inhibitors in patients with rheumatoid arthritis. Rheumatology (Oxford) 58(supplement 1):i34–i42
17. Bauermann P, Heiligenhaus A, Heinz C (2019) Effect of Janus kinase inhibitor treatment on anterior uveitis and associated macular edema in an adult patient with juvenile idiopathic arthritis. Ocul Immunol Inflamm 3:1–3. https://doi.org/10.1080/09273948.2019.1605453
18. Stevenson W, Sadrai Z, Hua J, Kodati S, Huang JF, Chauhan SK, Dana R (2014) Effects of topical Janus kinase inhibition on ocular surface inflammation and immunity. Cornea 33:177–183
19. Paley MA, Karacal H, Rao PK et al (2018) Tofacitinib for refractory uveitis and scleritis. Am J Ophthalmol Case Rep 13:53–55
20. Jabs DA, Nussenblatt RB, Rosenbaum JT (2015) Standardization of uveitis nomenclature (SUN) working group. Standardization of uveitis nomenclature for reporting clinical data. Results of the first international workshop. Am J Ophthalmol 140:509–516
21. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, He X, Maldonado-Cocco J, Orozco-Alcala J, Prieur AM, Suarez-Almazor ME, Woo P, International League of Associations for Rheumatology (2004) International league of associations for rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 31:390–392
22. Correll CK, Bullock DR, Cafferty RM et al (2018) Safety of weekly adalimumab in the treatment of juvenile idiopathic arthritis and pediatric chronic uveitis. Clin Rheumatol 37:549–553
23. Eli Lilly and Company.A study of baricitinib (LY3009104) in participants from 2 years to less than 18 years old with active JIA-associated uveitis or chronic anterior antinuclear antibody-positive uveitis. https://clinicaltrials.gov/ct2/show/NCT04088409. ClinicaltrialsGovIdentifier:NCT04088409