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Therapeutic potential of JAK inhibitors in juvenile idiopathic arthritis-associated uveitis

Ilaria Maccora[1,2,3], **Preston Land**[3,4], **Virginia Miraldi Utz**[4,5], **Sheila T Angeles-Han**[3,4,5,*]

[1]NeuroFARBA Department, University of Florence, Florence, Italy;

[2]Rheumatology Unit, ERN ReCONNET center, Meyer Children's Hospital IRCCS, Florence, Italy;

[3]Division of Rheumatology, Cincinnati Children's Hospital Medical Center and Department of Pediatrics, University of Cincinnati, Cincinnati, OH;

[4]Abrahamson Pediatric Eye Institute, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, OH, USA;

[5]Department of Ophthalmology, University of Cincinnati, Cincinnati, OH, USA

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1. Introduction

Uveitis is an ocular inflammatory disease that can lead to visual complications and permanent vision loss, if not promptly detected and treated [1,2]. The etiology of uveitis includes infections, autoimmune conditions, and autoinflammatory disorders. Juvenile idiopathic arthritis (JIA) is the most common systemic disease associated with uveitis in childhood [3]. However, in many cases, investigations for a systemic association are unrevealing, rending a diagnosis of "idiopathic uveitis".

JIA is the most common pediatric rheumatic disease, and up to 20% of patients develop associated uveitis depending on the population studied [1]. Further, approximately 50% of patients still experience ocular complications despite the availability of effective medications [3]. Expert consensus guidelines generally recommend a step-ladder approach to treat JIA-associated uveitis (JIA-U) with corticosteroids as first-line agent followed by steroid-sparing systemic treatment with methotrexate. Methotrexate is combined with tumor necrosis factor alpha inhibitors (TNFi) (adalimumab or infliximab) if vision-threatening disease is present at initial presentation or sequentially if the patient has an inadequate response to methotrexate. [1,2] TNFi have dramatically changed the uveitis prognosis

[*]**Corresponding author:** Sheila Angeles-Han, Cincinnati Children's Hospital Medical Center, 3333 Burnett Avenue, Cincinnati, OH 45229; Department of Pediatrics, University of Cincinnati, Cincinnati, OH; Phone: 513-636-4676, Fax: 513-636-4116, sheila.angeles-han@cchmc.org; Twitter: STHanMD.

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in children[4,5]. However, 15–30% of patients still do not achieve inactive uveitis on anti-TNFi [4,5]. No consensus exists regarding the subsequent treatment of those who fail methotrexate and TNFi at above standard doses or increased frequency[1–3]. Based on limited evidence, biologics that target specific molecules of inflammation such as anti-interleukin (IL)-6 (tocilizumab), CTLA4 inhibitors (abatacept), and antiCD20 (rituximab) have been recommended, but there is still no preferred agent [1,2]. However, some cases of uveitis are recalcitrant to all of these biologics, thus there is a need for alternative therapy. As the etiology and pathogenesis of JIA-U remain poorly understood, new targeted therapy using Janus Kinase Inhibitors (JAK-I) has been trialed. JAK-I are small molecules administered orally, include baricitinib, tofacitinib or upadacitinib, and are potential alternatives for children with autoimmune disorders such as JIA-U[6–8].

2. Role of JAK Pathway or Rationale for Janus Kinase inhibition

In uveitis, dysregulated activation of the immune system leads to hyper-activation of T Cells (Th1 and Th17) and B cell subsets[7]. Studies in models of experimental autoimmune uveitis and in biospecimens such as aqueous humor and tears highlight the crucial role of Th1 and Th17 as in the development of uveitis, triggering the inflammatory cascade[7,9]. The secretion of inflammatory mediators such as cytokines (IL-6, TNF-α, interferon-gamma [IFN-γ], IL-2, and IL-17), and chemokines amplify the inflammatory cascade. Recruitment of additional inflammatory cells and increased cytokines and chemokines locally leads to a consequent breakdown of the blood retina barrier[7,8]. Cytokines and chemokines interact with their receptors resulting in receptor oligomerization with subsequent activation and phosphorylation of JAK. Subsequently, JAK phosphorylates the signal transducer and activator of transcription (STATs), a superfamily of DNA binding proteins (STAT1, 2, 3, 4, 5A, 5B, and 6)[7,8]. After phosphorylation, STAT will then dimerize and translocate to the nucleus where it regulates the expression of specific genes critical for enhancing inflammation [7]. Different ligand and receptors activate different subtypes of JAK, which then influence inflammatory cell proliferation, development, differentiation, migration and apoptosis [7]. In this context, Janus Kinase acts as a signaling pathway mediator for cytokines and chemokines by transducing the signals affecting and regulating the immune response[6].

Humans have multiple JAK enzymes, JAK1, JAK2, JAK3, and tyrosine kinase (TYK2); three of the four JAK enzymes are ubiquitously expressed, while JAK3 is restricted to immune cells [7,8]. Thus, inhibition of the JAK pathway may play a key role in regulating the inflammatory and autoimmune response pathway in uveitis.

3. Current evidence for the treatment of JIA associated uveitis with JAKi

Current evidence on the use of JAK-I in the treatment JIA-U remain scarce, with most focused on adult patients with a history of JIA-U (Table 1)[10–12]. As shown in Table 1, in two case reports and one case series of four patients, all six patients treated with JAK-I had uveitis that was recalcitrant to several non-biologic and biologic disease modifying anti-rheumatic drugs (DMARDs) including anti-TNF, anti-IL6 or antiCD20, with many developing ocular complications[10–12]. After JAK-I (3 baricitinib, 2 tofacitinib, and

1 upadacitinib) was initiated, all patients achieved ocular disease control. Moreover, a systematic review published in 2021 reported the effectiveness of JAK-I not only in adult patients with JIA-U, but also in other types of uveitis and ocular inflammatory conditions including autoimmune scleritis.[6,13]

Recently, the results of a randomized clinical trial (RCT) that evaluated the effectiveness of tofacitinib in the treatment of polyarticular JIA led to FDA approval for the treatment of JIA[14]. Although this RCT did not evaluate the effectiveness on uveitis, notably no patients experienced flares of or new onset uveitis during the observation period[14].

To date, there is an ongoing multicenter, phase 3 clinical trial evaluating the efficacy of Baricitinib for pediatric chronic anterior uveitis associated with JIA or ANA (+) idiopathic disease. This trial will include up to 40 patients ages 2 to < 18 years with an inadequate response or intolerance to methotrexate (NCT04088409)[15]. In this trial conducted by open-label Bayesian design, children will be randomly assigned (1:1) to either baricitinib or adalimumab, which is currently considered the reference drug for the treatment of pediatric uveitis. Moreover, 20 additional patients who are methotrexate or biologic resistant will be assigned to baricitinib. However, the results are still pending as of this publication.

4. Conclusion & Expert Opinion

Because of the sight-threatening nature of uveitis in children, specifically in JIA-U, the availability of effective therapeutic agents is critical to prevent permanent vision loss. As highlighted, targeting the JAK pathway, a key kinase in the transduction of signal of inflammatory cascade, may potentially lead to the control of inflammation in several inflammatory diseases, including JIA-U. JAK-I has already shown to be effective treatment for JIA, but data on JIA-U are lacking.

Studies in adult patients demonstrate that JAK-I is effective in patients with inflammatory ocular disease recalcitrant to standard treatment, specifically in JIA-U[6,10–12]. However, where JAK-I fits in pediatric uveitis treatment algorithms is unclear. Clarification is needed regarding the optimal time to start JAK-I, dosing strategies, and indications. Subsequent therapy in children with JIA-U who have an inadequate response to first-line treatment remains unclear. Although abatacept, tocilizumab, golimumab, and rituximab are recommended as next options, there is no preference for which agent to start. Further, there are no recommendations for when and whether to initiate JAKi. The multicenter phase 3 trial *Juve-Bright* (NCT04088409) comparing baricitinib to adalimumab may better elucidate the role of JAKi for JIA-associated chronic anterior uveitis (CAU) and ANA+, idiopathic CAU phenotypes.[15] If more children on baricitinib meet the primary and secondary endpoints compared to adalimumab, baricitinib may be indicated earlier, after methotrexate failure/ intolerance or failure of TNFi agents. (Figure 1). Further studies are needed to determine if there are specific populations that better respond to JAKi such as those with certain subtypes of uveitis based on biologic pathways or who have distinct complications such as cystoid macular edema, and whether combination therapy is more effective.

Results have been encouraging for adult patients with JIA-U[6,10–12]. When considering dosage of JAKi, we must be cognizant of the fact that many cases of uveitis require higher than standard JIA treatment doses. ACR and CARRA expert consensus groups recommend escalating infliximab and adalimumab to doses as high as 20 mg/kg/dose q4 weeks or weekly respectively[1]. The optimal dose of JAKi for pediatric uveitis is unknown. In our practice, we have successfully used tofacitinib at standard JIA dosing to treat uveitis (unpublished). However, the uveitis phenotype, presence of active ocular complications, systemic disease activity, and resistance to standard dosing will likely dictate and personalize future treatment strategies. The side effect profile of higher dosing, and long-term systemic effects of JAKi on children is also relatively unknown. Thus, the potential benefits must be weighed against systemic risks of infection, cardiovascular disease, and a patient's individual risk factors. A recent RCT by Ruperto *et al.* reported a favorable safety profile of tofacitinib in children with JIA wherein there were only a few cases of increased levels of liver enzymes, upper respiratory tract infections and reactivation of herpes zoster [14]. Moreover, targeting a more restricted pattern of JAK might be beneficial in order to prevent side effects as hepatotoxicity as recently demonstrated in children [16,17].

Timely vaccination for varicella zoster in patients without previous immunization or who are not up to date with their vaccination might be considered prior to JAK-I initiation as recommended in adulthood [18].Vaccine recommendations have been published by the ACR for JIA which may be applicable to children with uveitis on similar treatment [19].

In conclusion, JAK-I has shown to be effective for children with JIA and as potentially promising treatment of ocular inflammatory disease. The oral route of administration may also be of benefit in the pediatric population, as likely to be better tolerated than injectable routes of administration. In addition, it is less burdensome to families than a hospital infusion. However, this must be weighed against adherence to daily administration as lapses in treatment in combination with short half-life may pose challenges to long-term disease control. Overall, in the absence of long-term efficacy and safety data, we remain cautious, but optimistic. We will engage in shared decision making with patient and families, sharing the available evidence for or against JAKi, taking into account individual patient factors when selecting JAK-I treatment..

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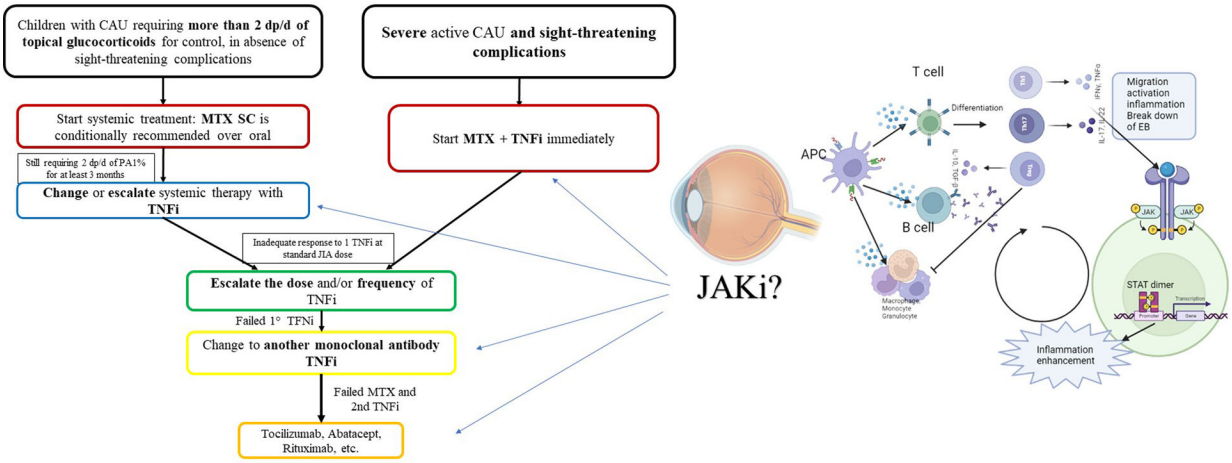

Figure 1:

Proposed therapeutic approach based on the 2019 American College of Rheumatology recommendations for the treatment of JIA associated uveitis.

List of abbreviations: APC antigen presenting cell, CAU chronic anterior uveitis, d daily, dp drops, EB endothelial barrier, os oral, JAKi Janus Kinase inhibitor, JIA Juvenile Idiopathic Arthritis, MTX Methotrexate, PA prednisone acetate, sc subcutaneous, TNFi Tumor Necrosis factor alpha inhibitor.

Table 1:

Current evidence about the efficacy of Jak-inhibitors in uveitis.

Reference and number	# of patients and disease	JAK-I treatment	Previous treatment	Effect on uveitis	Effect on systemic disease
Miserocchi *et al*., Clinical Rheumatology, 2020 (12)	4 adults with JIA-U	3 baricitinib (1 pt: 5mg/ daily 2 pts: 4 mg/daily) 1 pt: tofacitinib 5mg × 2 / daily	INF, ADA, Leflu, MTX, TCZ, AZA, ABA, RTX	Inactive JIA-U	3 pts: arthritis controlled (1 tofacitinib, 2 baricitinib) 1 pt arthritis not controlled (baricitinib)
Bauermann *et al*., Ocul Immunol Inflamm 2019 (11)	1 adult JIA-U	1 tofacitinib (5 mg × 2/ daily	MTX, ADA, RTX, GOL, INF, cyclosporine, TCZ, MMF	Control of JIA-U	Not reported
Baquet-Walscheid *et al*., Ocul immunol Inflamm 2022 (10)	1 JIA-U	1 upadacitinib (15 mg/ daily)	MTX, cyclosporine, ADA, IFN, TCZ, tofacitinib	Inactive JIA-U	Arthritis inactive

JIA-U Juvenile idiopathic arthritis-associated uveitis, Leflu leflunomide, MTX methotrexate, TCZ tocilizumab, AZA Azathioprine, ABA abatacept, RTX rituximab, MMF mycophenolate mofetil, GOL golimumab, INF infliximab, ADA adalimumab