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Janus Kinase Inhibitors – a New Effective Treatment Option for Refractory Isolated Non-infectious Ocular Inflammatory Disorders

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SUMMARY

The Janus kinase (JAK) pathway regulates inflammatory responses, with dysregulation implicated in various autoimmune disorders, including non-infectious orbital or ocular inflammation. While corticosteroids are commonly used, their long-term use is limited by side effects. Janus kinase inhibitors (JAK-i) present an emerging therapeutic option. This study systematically reviewed the effectiveness and safety of JAK-i in managing isolated non-infectious ocular inflammation. A comprehensive literature review utilizing MEDLINE/PubMed, Cochrane and Web of Science search identified studies reporting isolated non-infectious ocular inflammation cases treated with JAK-i up to May 2025. Search terms combined JAK-i keywords with ocular inflammation terms. Among 21 isolated non-infectious ocular inflammation cases treated with JAK-i, tofacitinib was predominant. Most patients received JAK-i after disease-modifying antirheumatic drug therapy, with additional corticosteroid usage. Ocular inflammation was successfully controlled in 21 out of 21 patients, with one case of herpetic keratitis necessitating additoinal systemic virostatics. JAK-i show promise as an effective option for refractory isolated non-infectious ocular inflammation. However, further research is warranted with longer follow-up periods. Safety concerns underline the importance of personalized risk-benefit assessments in JAK-i therapy. While limitations exist, this review supports the potential of JAK-i use in managing isolated non-infectious ocular inflammation.

KEYWORDS

Janus kinase inhibitors; Non-infectious ocular inflammation; Uveitis

Introduction

The Janus kinase (JAK) pathway plays a pivotal role in the regulation of inflammatory cells by transmitting signals from cytokines and growth factors. Dysregulation of the JAK pathway significantly contributes to the pathogenesis of diverse inflammatory and autoimmune disorders[1-3].

Non-infectious ocular inflammation can occur either isolated on a specific part of the eye or as part of a systemic autoimmune disease[4,5]. Our manuscript addresses isolated cases.

The initial therapeutic approach for addressing non-infectious ocular inflammation involves the use of corticosteroids. However, prolonged systemic corticosteroid administration is limited due to associated side effects. Patients who are corticosteroid-resistant or present with severe cases featuring vision-threatening complications may require treatment with disease-modifying antirheumatic drugs (DMARDs)[6-9].

JAK inhibitors (JAK-i), which block one or more molecules involved in this pathway, including interleukin (IL)-2, IL-4, IL-7, IL-9, IL-15 and IL-21, have been developed and evaluated to treat various systemic and ocular inflammatory diseases, such as rheumatic arthritis, psoriasis, and inflammatory bowel disease[2,10]. However, their use in the treatment of non-infectious ocular inflammation is relatively new, resulting in limited study data. Tofacitinib, baricitinib and upadacitinib have received approval from both the US Food and Drug Administration[11] and European Medicines Agency for the treatment of various diseases[12-14]. Despite this, they are rarely used off-label to treat non-infectious ocular inflammation, even more rarely in a specific subgroup which is isolated to the eye with no systemic involvement or disease[6,15-21]. Current ongoing research is assessing the safety and efficacy of baricitinib in patients with active juvenile idiopathic arthritis (JIA)-associated uveitis. One randomized, placebo-controlled trial demonstrated that 200 mg filgotinib decreased the risk of non-infectious uveitis flares compared to placebo[11,22].

Our study presents a systematic review of the existing literature to assess the effectiveness and safety of various JAK-i in managing isolated non-infectious ocular inflammation without systemic involvement.

Material and Methods

The MEDLINE, PubMed, Cochrane and Web of Science databases were searched for all studies reporting cases of isolated non-infectious ocular inflammation treated with JAK-i up to May 2025. The primary search concepts were non-infectious ocular and orbital inflammation and JAK-i. The search algorithm involved connecting the keywords “JAK inhibitor”, “Janus kinase inhibitor”, “tofacitinib”, “baricitinib”, “jakinib”, “ruxolitinib” and “filgotinib” with the Boolean operator OR. Then we connected the keywords “ocular inflammation”, “episcleritis”, “scleritis”, “keratitis”, “conjunctivitis”, “retinitis”, “uveitis”, “retinal vasculitis”, “retinitis”, “idiopathic orbital inflammation”, “nonspecific orbital inflammation” with the Boolean operator OR, and then we finally connected these search results using the Boolean operator AND.

We collated a range of demographic , clinical, and therapeutic data, including authors, patient gender and age, diagnoses, disease laterality and duration, best corrected visual acuity (BCVA) before and after JAK-i therapy, prior therapy history, type, dose and duration of JAK-i treatment, treatment outcomes, and potential surgical interventions and adverse events.

This review included only cases of isolated non-infectious ocular inflammation without a systemic diagnosis, treated with JAK-i.

Results

Demographic and clinical characteristics of patients with isolated non-infectious ocular inflammation treated with JAK-I are presented in Table 1.

The first case of JAK-i therapy for ocular disease was published in 2014 by Meadow *et al.* describing the use of tofacitinib citrate in a patient with rheumatoid arthritis (RA) and associated peripheral ulcerative keratitis[23]. Our literature search specifically focused on isolated non-infectious ocular inflammation. A total of 162 articles were identified across MEDLINE, PubMed, Cochrane, and Web of Science, with only eight reporting on therapeutic use of JAK-i in this context. These comprised one retrospective cohort study[6], five case series[16,17, 19-21] and two case reports[15,18] reporting on the use of JAK-i in 21 patients who presented with isolated non-infectious ocular inflammation[6,15-21]. Out of these, one was diagnosed with nonspecific orbital inflammation (NSOI)[20], 6 patients with bilateral uveitis[6,15,16,19], and 14 with scleritis[16-18,20,21], of whom four had bilateral presentation[16,17,20]. The mean time from diagnosis to initiation of JAK-i treatment was 2 years. JAK-i were administrated as a first line corticosteroid-sparing treatment in three patients with scleritis[17] and a patient with NSOI[20]. Other patients were treated with at least one DMARD before starting JAK-i. Seventeen patients with isolated non-infectious ocular inflammation received treatment with tofacitinib, administered at either a daily dose of 11 mg or 5 mg twice daily[6,15-18,20,21]. Among them, 15 patients received additional therapy, i.e., 11 patients received corticosteroids (including one with uveitis[15], one with NSOI[20] and 8 with scleritis[16-18,21]), five were treated with methotrexate (two with uveitis[15,16] and three with scleritis[16,21]), one patient with scleritis was prescribed leflunomide[17], and another with scleritis received mycophenolate mofetil[17]. Four patients were treated with baricitinib 4 mg daily[19,20]. One patient was later switched to upadacitinib 15 mg daily[19]. Among them, three received additional corticosteroids, which were tapered and discontinued in two cases, while the third continued on a low dose, 4 mg methylprednisolone every other day[19]. Ocular inflammation was successfully controlled with JAK-i in 21 out of 21 patients[6,15-21]. Tofacitinib treatment was discontinued in one patient with scleritis due to the onset of herpetic keratitis[17]. Additionally, a recurrence of herpes labialis was documented in a patient with scleritis treated with tofacitinib, necessitating supplemental virostatic therapy while maintaining JAK-i treatment. Both patients with herpes reactivation received corticosteroid treatment alongside JAK-i[17]. A transient rise in liver aminotransferases was observed in two patients, one with scleritis and one with uveitis, both treated with baricitinib[19,20]. No other adverse events have been reported in the literature included in our literature review.

Discussion

Managing non-infectious ocular disease continues to present challenges. Unanswered questions, such as the optimal duration of non-infectious ocular disease treatment and the most effective way of managing a persistent or relapsing disease, continue to pose challenges in daily practice.

Although the precise etiology of ocular inflammation remains incompletely understood, studies on experimental autoimmune

TABLE 1. Demographic and clinical characteristics of patients with isolated non-infectious ocular/orbital inflammation

	First author	Gender	Age (y)	Diagnosis	Laterality	Duration of ocular involvement before JAK-i	Previous systemic therapy	BCVA before JAK-i	BCVA after JAK-i	JAK-i (dose)	Duration of JAK-i therapy/follow up	Additional systemic therapy (duration)	Surgical interventions	Time to improvement	Ocular symptoms	Adverse events
1	Liu *et al.*	F	18	Anterior uveitis	Bilateral	5 y	CS, ADA, MM, CsA	RE: 0.06 / LE: CF/ 20 cm	RE: 0.075 / LE: CF/ 1m	TFC (5 mg / BD)	9 m	CS, MTX	LE: cataract surgery	4 w	Inactive	None
2	Sharma *et al.*	M	58	Intermediate uveitis	Bilateral	NA	CS, MTX, sulfasalazine	NA	NA	TFC (5 mg / BD)	4 m	None	None	NA	Inactive	None
3	Paley *et al.*	F	45	Anterior uveitis	Bilateral	NA	CS, MTX, AZA, LFN, MMF, ADA, IFX, CZP	NA	NA	TFC (11 mg/ day)	3 m	MTX (stopped in 1 m)	None	4 w	Inactive	None
4	Paley *et al.*	F	40	Anterior scleritis	Bilateral	NA	CS, MTX, MMF, AZA, CP	NA	NA	TFC (11 mg / day)	9 m	MTX	None	3 w	Inactive	None
5	Pyare *et al.*	M	65	Scleritis	Unilateral	2 y	CS, NSAID, MMF	LE: 0.17	LE: 0.25	TFC (5 mg / BD to 5 mg / 2 days)	1 m	MMF (500 mg / BD), CS (2.5 mg / 2 days)	None	4 w	Inactive	None
6	Pyare *et al.*	F	51	Necrotising anterior scleritis	Unilateral	1 y 11 m	CS, MMF	NA	NA	TFC (5 mg / BD)	5 m	CS (10 mg / day)	None	NA	Inactive	None
7	Pyare *et al.*	M	41	Diffuse anterior scleritis	Unilateral	4 m	CS, AZA	NA	NA	TFC (5 mg / BD)	3 m	/	None	NA	Inactive	None
8	Pyare *et al.*	F	41	Diffuse anterior scleritis	Bilateral	5 y	CS	NA	NA	TFC (5 mg / BD), for 1 month	Discontinued after 1 m / follow up: 7 m	CS (10 mg / day)	None	NA	Inactive	Reactivation of herpetic keratitis

TABLE 1. [Continued]

	First author	Gender	Age (y)	Diagnosis	Laterality	Duration of ocular involvement before JAK-i	Previous systemic therapy	BCVA before JAK-i	BCVA after JAK-i	JAK-i (dose)	Duration of JAK-i therapy/follow up	Additional systemic therapy (duration)	Surgical interventions	Time to improvement	Ocular symptoms	Adverse events
9	Pyare *et al.*	F	58	Diffuse non-necrotising scleritis	Bilateral	1.5 m	CS	NA	NA	TFC (5 mg / BD)	7 m	None	None	NA	Inactive	None
10	Pyare *et al.*	F	39	Nodular anterior scleritis	Unilateral	4.5 m	CS, MTX	NA	NA	TFC (5 mg / BD)	7 m	LFN (10 mg / day)	None	4 w	Inactive	None
11	Pyare *et al.*	M	51	Nodular anterior scleritis	Unilateral	1 y 7.5 m	CS, MMF, MTX	NA	NA	TFC (5 mg / BD)	7 m	CS (tapered and stopped in 1 m)	None	4 w	Inactive	None
12	Pyare *et al.*	F	22	Nodular anterior scleritis	Unilateral	2 y 2 m	CS, MTX, MMF, AZA	NA	NA	TFC (5 mg / BD)	11 m	Valacyclovir. CS (2.5 mg) / day	2 scleral biopsies, filtration surgery + MMC	NA	Inactive	Herpes labialis
13	Pyare *et al.*	M	41	Anterior and posterior scleritis	Unilateral	1.5 m	CS	NA	NA	TFC (5 mg / BD)	6 m	None	None	NA	Inactive	None
14	Vidic Krhlikar *et al.*	F	28	Anterior and intermediate uveitis	Bilateral	1 y 4 m	CS, MMF, ADA, TCR	RE: 0.02 / LE: 0.2	RE: 0.8 / LE: 0.1	BRC (4 mg / day)	1 y 11 m	CS (tapered to 4 mg / 2 days)	RE: cataract surgery	4 m	Inactive	ALT: 0,65 µkat/L (NR: 0-0.56 µkat/L)
15	Vidic Krhlikar *et al.*	M	41	Anterior and intermediate uveitis	Bilateral	6 y 5 m	CS, MTX, MMF, CsA, ADA	RE: 0.6 / LE: 1.0	RE: 1.0 / LE: 1.0	BRC (4 mg daily), UPDC (15 mg / day)	4 y 7 m	CS (tapered and stopped)	RE, LE: cataract surgery, LE: TREC + MMC	6 m	Inactive	None
16	Vidic Krhlikar *et al.*	M	59	Posterior uveitis	Bilateral	3 y 1 m	CS, MMF, ADA,	RE: 0.4 / LE: 0.6	RE: 0.4 / LE: 0.5	BRC (4 mg / day)	1 y 5 m	CS (tapered and stopped)	None	9 m	Inactive	None

TABLE 1. [Continued]

	First author	Gender	Age (y)	Diagnosis	Laterality	Duration of ocular involvement before JAK-i	Previous systemic therapy	BCVA before JAK-i	BCVA after JAK-i	JAK-i (dose)	Duration of JAK-i therapy/follow up	Additional systemic therapy (duration)	Surgical interventions	Time to improvement	Ocular symptoms	Adverse events
17	Vidic Krhlikar *et al*.	M	46	Scleritis	Bilateral	5 y 1 m	CS, NSAID, MTX, MMF, TCR, RTX	RE: 1.0 / LE: 1.0	RE: 1.0 / LE: 1.0	BRC (4 mg / day)	1 y 6 m	none	RE, LE: cataract surgery	3 w	Inactive	ALT: 1,51 µkat/L (NR: 0-0.56 µkat/L) AST: 1.06 µkat/L (NR: 0-0.58 µkat/L)
18	Vidic Krhlikar *et al*.	F	28	Nonspecific orbital inflammation	Unilateral	6 m	CS	RE: 1.0 / LE: 0.4	RE: 1.0 / LE: 1.0	TFC (5 mg / BD)	1 y 2 m	CS (64 mg / day tapered and stopped in 3 m)	Two orbital biopsies	2 m	Inactive	None
19	Suvankar *et al*.	F	53	Necrotising anterior nodular scleritis with keratitis	Unilateral	1 y	CS, NSAID, MMF, ADA	RE: 0.25 / LE: 1.0	RE: 1.0 / LE: 1.0	TFC (5 mg / BD)	6 m	CS (tapered and stopped)	None	1 m	Inactive	None
20	Suvankar *et al*.	M	18	Anterior nodular scleritis	Unilateral	NA	CS, MMF, MTX	RE: 1.0 / LE: 1.0	RE: 1.0 / LE: 1.0	TFC (5 mg / BD)	3 m	MTX (15 mg / w), CS (5 mg / day)	None	2 w	Inactive	None
21	Suvankar *et al*.	F	47	Diffuse anterior scleritis	Unilateral	14 m	CS, MTX, ADA	RE: 1.0 / LE: 1.0	RE: 1.0 / LE: 1.0	TFC (5 mg / BD)	6 m	MTX (15 mg / w), CS (0.5 mg / kg / day tapered to 2.5 mg / day)	None	1 m	Inactive	None

BCVA = best corrected visual acuity; F = female; M = male; LE = left eye; RE = right eye; m = months; w = weeks; y = years; NR = normal range; CS = corticosteroids; ADA = adalimumab; BRC = baricitinib; CsA = cyclosporine; JAK-i = Janus kinase inhibitor; LEF = leflunomide; MMF = mofetil mycophenolate; MTX = methotrexate; NSAID = nonsteroidal anti-inflammatory drugs; RTX = rituximab; TCR = tacrolimus; TFC = tofacitinib; UPDC = upadacitinib; ALT = alanine transferase; AST = aspartate transferase; TREC = trabeculectomy; MMC = mitomycin C

uveoretinitis suggest that all major T cell subsets (Th1, Th2, Th17, Tr1 and Treg) infiltrate the eye during uveitis. Therefore, the Janus kinase inhibitor/signal transducer and activator of the transcription (JAK/STAT) pathway may play a role in regulating differentiation of these pathogenic T cell subsets[24-26]. Studies conducted in experimental uveitic models have demonstrated that tofacitinib modulates pro-inflammatory T cells and decreases inflammatory cytokine gene expression in the iridociliary body and retina, leading to reduced levels of inflammatory cytokines in the vitreous[27-30]. Similarly, experimental uveitic models have revealed that upadacitinib can regulate the composition of inflammatory cells in uveitis[31]. Despite these promising findings, reports from the literature on the use of JAK-i remain limited, especially in the treatment of isolated non-infectious ocular inflammatory conditions.

A range of JAK-i have been introduced into clinical practice, including baricitinib, which inhibits JAK1 and JAK2, tofacitinib additionally inhibits JAK3, and upadacitinib, which selectively inhibits JAK1[2,32]. JAK-i exhibit lower selectivity compared to other biologics, allowing them to simultaneously block multiple cytokine signaling pathways. This characteristic opens new potential therapeutic strategies[33].

The present review demonstrates that treatment with JAK-i may be an effective option for patients with refractory and severe isolated non-infectious uveitis, scleritis, and even for cases of NSOI.

In the literature review, we identified 6 patients with bilateral uveitis[6,15,16,19], 14 with scleritis[16-18,20,21], and one patient with NSOI[20]. The majority of these patients (81%) were treated with tofacitinib, and successful control of inflammation was achieved in all 21 patients with no relapses during a mean follow up of 11 months (range: 1-55 months)[6,15-21]. In one patient, treatment was discontinued after one month due to herpetic keratitis, but no relapse occurred thereafter in the follow up period[17].

The safety profile of JAK-i has undergone extensive investigation in terms of treatment-related side effects, primarily focusing on data derived from RA development programs[34,35]. The pivotal source of safety information, particularly concerning cardiovascular events, serious infections, and malignancy associated with JAK-i, stems from the phase IIIb-IV ORALSURV study, specifically pertaining to tofacitinib[36]. In this study, infections as the most frequently reported adverse events exhibited a similar incidence to that observed with other biologics, as demonstrated in both the RA development programs and ORALSURV study. In terms of major adverse cardiovascular events, data from both RA development programs and ORALSURV study indicate that the safety profile of JAK-i appears comparable to other biologics. However, the ORALSURV study revealed a dose-dependent association with venous thromboembolism, emphasizing the need of caution in patients with venous thromboembolism risk factors and recommending the use of only standard tofacitinib doses. In addition, in contrast to findings from the RA development programs, the ORALSURV study suggests a heightened risk of malignancy associated with JAK-i treatment compared to other DMARDs. This disparity emphasizes the importance of considering the specific risk-benefit profile when choosing JAK-i therapy, especially in patients with predisposition to venous thromboembolism or malignancy[34-36].

Other reported side effects of JAK-i include leukopenia, anemia, alterations in lipid profile, and elevated liver transaminases, all these well-tolerated or transient[2,32]. In our literature review, we encountered 2 instances of herpes reactivation during tofacitinib treatment. Treatment cessation was required in one case due to herpetic keratitis[17]. Additionally, we documented two instances of elevated liver transaminases,

both transient. No other serious side effects were reported.

In conclusion, our review suggests that JAK inhibitors, beyond tofacitinib, may represent a promising treatment option for refractory and severe cases of isolated non-infectious uveitis, scleritis, and even NSOI. However, current evidence remains limited, and further controlled studies are needed to confirm their efficacy and safety in this context.

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SAŽETAK

Inhibitori Janus kinaze – nova učinkovita mogućnost liječenja refraktivnih izoliranih nezaraznih očnih upalnih poremećaja

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Putanja Janus kinase (JAK) regulira upalne odgovore, uz deregulaciju uključenu u raznim autoimunim poremećajima uključujući nezaraznu upalu orbite ili oka. Iako se kortikosteroidi redovito primjenjuju u takvim slučajevima, njihova dugotrajna uporaba ograničena je nuspojavama, a tu se pojavljuju inhibitori Janus kinaze (JAK-i) kao mogućnost liječenja. U ovom istraživanju sustavno je obrađena učinkovitost i sigurnost JAK-i u liječenju izolirane nezarazne očne upale. U sveobuhvatnom pregledu literature pretragom izvora MEDLINE/PubMed, Cochrane i Web of Science identificirane su studije koje izvještavaju o slučajevima izolirane nezarazne očne upale liječene pomoću JAK-i do svibnja 2025. godine. Pretražni pojmovi kombinirali su ključne riječi JAK-i s terminima očne upale. Taofacitinib je prevladavao među 21 slučajem izolirane nezarazne očne upale. Većina bolesnika primala je JAK-i nakon terapije antireumatskim lijekovima koji mijenjaju tijek bolesti, uz dodatnu primjenu kortikosteroida. Očna upala je uspješno kontrolirana u 21 od 21 bolesnika, pričem je jedan slučaj herpetskog keratitisa zahtijevao dodatne sistemske virostatike. JAK-i obećava kao učinkovita opcija za refraktornu izoliranu nezaraznu upalu oka. Međutim, potrebna su daljnja istraživanja s dužim vremenom praćenja. Pitanja sigurnosti naglašavaju važnost personalizirane procjene rizika i koristi liječenja pomoću JAK-i. Iako postoje ograničenja, ovaj pregled podupire potencijal primjene JAK-i u liječenju izolirane nezarazne očne upale.

KLJUČNE RIJEČI

Inhibitori Janus kinaze; Nezarazna očna upala; Uveitis