Review paper

Reumatologia 2025; 63, 6: 405–415
DOI: https://doi.org/10.5114/reum/203750

Efficacy of biologic and targeted synthetic disease-modifying antirheumatic drugs in non-infectious uveitis in axial spondyloarthropathy and their ocular side effects

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Abstract

Axial spondyloarthropathy (axSpA) belongs to a group of chronic, progressive inflammatory diseases with a variety of clinical manifestations, including musculoskeletal and extra-articular symptoms. The most common extra-articular manifestation in patients with axSpA is uveitis, which usually involves the anterior segment, can be recurring, and is a vision-threatening complication. Ocular complications can result from the disease itself, as well as from the therapy used to treat it. Treatment for axSpA is based on both pharmacological and non-pharmacological management. Biologic and targeted synthetic disease-modifying antirheumatic drugs (DMARDs) are an effective and constantly evolving form of axSpA therapy; however, their application and side effects remain under study. The aim of this article is to summarize current knowledge about the efficacy of biologic and targeted synthetic DMARDs in non-infectious uveitis in axSpA and delineate their effect on the organ of vision.

Key words: adverse events, biological treatment, ocular complications, axial spondyloarthropathy.

Introduction

Axial spondyloarthropathy (axSpA) belongs to a group of chronic, progressive inflammatory diseases with a variety of clinical manifestations, including musculoskeletal and extra-articular symptoms [1]. It includes ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA). It is estimated that the incidence of spondyloarthropathies is in the order of 1% [2]. Ocular changes can result not only from the disease itself, but also from the therapy used to treat axSpA. The most frequent ocular complication is uveitis [2]. Treatment for axSpA is based on both pharmacological and non-pharmacological management [1]. The principles of therapy are defined by the Assessment of SpondyloArthritis international Society (ASAS) and European Alliance of Associations for Rheumatology (EULAR) recommendations [3]. Some patients are eligible for biologic and targeted synthetic disease-modifying antirheumatic drugs (DMARDs), which are an effective and constantly evolving form of axSpA therapy.

Biologics include:

- tumor necrosis factor inhibitors (TNFi): infliximab (INF), adalimumab (ADA), etanercept (ETC), certolizumab pegol (CZP), golimumab (GOL),
- interleukin-17 (IL-17) inhibitors: secukinumab (SCK), ixekizumab (IXE), bimekizumab (BKZ).

Targeted synthetic DMARDs are: Janus kinase inhibitors (JAKi): tofacitinib (TOFA), filgotinib (FIL), upadacitinib (UPA), and baricitinib (BARI) [4, 5].

Despite the many benefits and good therapeutic effects of biologicals and targeted synthetic DMARDs for the treatment of axSpA and other chronic inflammatory diseases, the long-term safety of their use, and the possible side effects, are not yet well understood [6].

The aim of this review is to summarize the current knowledge about the efficacy and safety of biologic and targeted synthetic DMARDs in non-infectious uveitis

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Submitted: 04.02.2025, **Accepted:** 06.04.2025

(NIU) in axSpA and delineate their effect on the organ of vision.

Material and methods

Using electronic databases – PubMed, Google Scholar, and Medscape – we reviewed publications on biological therapy, targeted synthetic DMARDs, and ocular changes and complications in patients with axSpA. The aim was to identify reports evaluating the efficiency of biologics and targeted synthetic DMARDs in NIU and to assess their side effects. Additionally, studies using optical coherence tomography (OCT) and OCT angiography (OCTA) were highlighted. The following key words were used: "axial spondyloarthropathy," "ocular changes," "biological treatment," "uveitis," "changes on OCT/OCTA," "anti-TNF alpha," "anti-IL17," "JAK inhibitors," in various combinations. Seventy-one publications from the period 2004–2024 were selected for the review.

Ocular changes in axial spondyloarthropathy

Uveitis is the most common extra-articular manifestation in patients with axSpA, most often involving the anterior segment. It occurs in about 40% of patients and is one of the diagnostic criteria for axSpA [7, 8]. The exact pathogenesis of spondyloarthropathy (SpA) and ocular complications remains unknown. Nevertheless, a strong link can be seen between the 2 diseases, which is due to the interaction of a specific, usually shared genetic inheritance, as well as external factors such as the microbiome, bacterial infections or mechanical stresses, and the activation of the immune system and inflammatory processes [8]. The prevalence of acute anterior uveitis depends on genetic and geographical factors. Human leukocyte antigen (HLA) B27 positivity is also an associated factor [8]. This condition appears primarily through eye redness, pain, photophobia and blurred vision and can lead to serious complications such as macular edema, retinal detachment, cataracts, or glaucoma. Other ocular diseases are occasionally observed, such as intermediate and posterior uveitis, scleritis, episcleritis and conjunctivitis, as well as keratitis and keratoconjunctivitis sicca.

Some ocular changes in axSpA can be detected using modern imaging techniques in ophthalmology. Studies using OCT confirmed differences in choroidal thickness (CT), retinal nerve fiber layer (RNFL) thickness and retinal ganglion cell complex (GCC) thickness in patients with AS, compared to controls, regardless of the history of uveitis incidents [9]. Studies evaluating the CT and choroidal vascularity index in patients with axSpA have shown that total choroidal area, luminal area, and stromal area were elevated in patients with axSpA compared to healthy subjects, but this difference was not associated with disease activity and functional level [10]. Choroidal thickness may be a marker of systemic inflammation in the course of AS and a biomarker of response to biologic therapy. During the 6-month follow-up of patients with AS undergoing biological treatment, a reduction in choroidal thickness and its 95% concordance with CRP levels was observed. Studies have confirmed that choroid that is thicker at the baseline is associated with a poorer prognosis of response to treatment [11]. Choroidal thickness and central retinal thickness may also be biomarkers for the treatment of acute anterior uveitis in patients with axial spondyloarthritis, including AS [12]. Studies using OCTA have confirmed that capillary plexus density, measured in the superficial and deep plexus, is reduced in patients with axSpA, and its decrease correlates with disease duration but not its activity. This demonstrates that small vascular structures can be affected in the axSpA, and OCTA can be used to detect subclinical vasculitis in these patients [13].

Efficacy of tumor necrosis inhibitors in the treatment of non-infectious uveitis

Non-infectious uveitis is a complex and heterogeneous group of inflammatory ocular disorders that, if untreated, can lead to severe visual impairment or blindness. It accounts for 10–15% of blindness cases in developed countries and remains a therapeutic challenge [14–16]. Pathogenesis of uveitis is driven by immune dysregulation and chronic inflammation, with TNF playing a pivotal role [17]. Tumor necrosis factor is a pleiotropic cytokine involved in amplifying intraocular inflammation, making it a critical target for therapeutic intervention. The introduction of TNFi has revolutionized the management of uveitis, providing significant benefits in controlling inflammation, reducing the need for glucocorticosteroids (GCs), and preventing relapses. Tumor necrosis factor inhibitors are a class of biologic therapies that have transformed the treatment landscape for inflammatory conditions and NIU. Their primary mode of action involves neutralizing TNF activity, either by directly binding to the cytokine or by blocking its interaction with TNF receptors on the surface of target cells. By preventing the activation of these receptors, TNFi effectively interrupt the inflammatory cascade driven by this pivotal cytokine. One of the key therapeutic effects of TNFi is their ability to reduce inflammation. By neutralizing TNF, these drugs lower the levels of pro-inflammatory cytokines that contribute to immune cell recruitment and activation. This results in decreased infiltration of leukocytes into ocular tissues, thereby reducing intraocular inflammation and alleviating

the clinical manifestations of uveitis, such as pain, redness, and vision disturbances [17]. Another critical benefit of TNFi lies in their role in preserving the integrity of the blood-ocular barriers. Tumor necrosis factor contributes to vascular permeability and endothelial activation, which can compromise the blood-retinal and blood-aqueous barriers in uveitis. By inhibiting these processes, TNFi reduce fluid leakage and restore barrier function, leading to improved ocular outcomes and a reduction in complications such as macular edema [18]. In addition to controlling active inflammation, TNFi play a significant role in preventing long-term tissue damage. Chronic inflammation mediated by TNF can lead to structural damage, fibrosis, and scarring within ocular tissues, ultimately resulting in complications such as glaucoma or permanent vision loss. Long-term use of TNFi mitigates these risks by curbing ongoing inflammatory activity and preserving ocular structures. Among TNFi, ADA has emerged as one of the most effective treatments for non-infectious uveitis. Its fully human monoclonal antibody structure minimizes immunogenicity and enhances tolerability. Studies have demonstrated the ability of ADA to reduce intraocular inflammation and the frequency of uveitis flares. Notably, the STOP trial and other investigations have established its efficacy in both treatment-naive patients and those with refractory disease, highlighting its role as a first-line biologic therapy. Additionally, its long-term safety and GC-sparing effects have been emphasized in clinical practice, supporting its broad use in managing challenging cases of uveitis [15, 16].

The benefits of TNFi extend beyond inflammation control. These agents have demonstrated improvements in visual acuity and reductions in central macular thickness, outcomes that are critical in chronic posterior uveitis and related conditions such as birdshot chorioretinopathy and sympathetic ophthalmia [19].

A Swiss multicenter retrospective cohort study evaluated the efficacy of systemic TNFi in the treatment of non-infectious uveitis. Of the patients with uveitis 71 were followed for 40.2 ±17.3 months after addition of TNFi. The study emphasized the importance of TNFi in routine clinical practice, particularly in patients who fail to respond to conventional immunosuppressive therapies. Under TNFi, visual acuity improved from 0.2 ±0.3 to 0.1 ±0.3 logMAR ($p < 0.001$). The proportion of patients under systemic GCs decreased from 81.7% to 25.4% ($p < 0.001$). Moreover, the study demonstrated the importance of systemic TNFi in real-world settings and supports their continued use as a cornerstone therapy in the management of severe and refractory uveitis. Adverse events under TNFi were encountered in 49.2% of eyes, including recurrence (5 eyes) and new onset of macular edema (14 eyes) [19].

Systematic reviews and clinical trials have highlighted the broad efficacy of TNFi across various subtypes of NIU, confirming their central role in treatment paradigms. For example, INF and ADA have consistently shown superiority in managing complex posterior segment inflammation, reducing the risk of vision loss [19–22].

Infliximab

The chimeric monoclonal antibody INF has also shown significant efficacy, particularly in cases of severe or refractory uveitis. Its effectiveness has been highlighted in Behçet's disease and other immune-mediated conditions associated with uveitis. Studies have demonstrated the ability of INF to rapidly control ocular inflammation, maintain remission, and reduce GCs dependency. While not always approved for uveitis, it is widely used off-label and is particularly effective in managing sight-threatening manifestations. However, its chimeric nature may lead to the development of anti-drug antibodies, potentially reducing its long-term efficacy [22–24].

Certolizumab pegol

Another well-proven TNFi is CZP, a pegylated, Fc-free biologic agent that has demonstrated efficacy in treating refractory uveitis associated with immune-mediated diseases. Its Fc-free design reduces placental transfer, making it particularly suitable for patients of childbearing potential. Multicenter studies have reported significant improvements in ocular parameters, including best-corrected visual acuity and anterior chamber cell counts, with CZP therapy. These findings suggest its utility in specific patient populations, especially those with chronic or refractory inflammation [25].

Golimumab

Golimumab, a fully human monoclonal antibody, has been explored as a therapeutic option for non-infectious uveitis, including panuveitis. Studies have shown that GOL effectively reduces the rate of relapses and exhibits GCs-sparing properties. Its potential as a second-line therapy, particularly for patients unresponsive to other TNFi, highlights its versatility in uveitis management. Clinical outcomes suggest that GOL may provide a viable alternative in cases where ADA or INF are not well tolerated or effective.

The multicenter experience highlighted that GOL, a TNFi, effectively reduced intraocular inflammation and achieved disease remission in cases unresponsive

to conventional treatments and other biologics, such as INF or ADA [26].

Tumor necrosis factor inhibitors – ocular side effects

Among biologic drugs, the literature most extensively describes the ocular complications of TNFi use. The role of TNFi in the pathogenesis of ocular adverse events when used to treat diseases with ocular involvement is not yet fully understood [27].

Tumor necrosis factor is a cytokine synthesized by cells of the immune system. This molecule plays an important role in pro-inflammatory and immunoregulatory processes. It influences the expression of other pro-inflammatory cytokines and chemokines, molecular adhesion, and angiogenesis, and can also directly induce cytotoxicity. Overexpression and impaired regulation of TNF underly many chronic inflammatory diseases [6]. In their report, Roche et al. [28] assert that in patients with axSpA, the incidence of anterior uveitis episodes is lower when using TNFi than when using IL-17 inhibitors and a placebo. During treatment with TNFi, systemic adverse effects may occur, including: serious infections, including opportunistic infections, e.g., tuberculosis, tumors (e.g., lymphomas), demyelinating diseases and exacerbation of heart failure [29]. Furthermore, reports describe cases of ocular complications, which we can divide into the following groups: development of tumors, severe infections of the eye and orbit, retinal vein thrombosis, inflammation, and demyelination.

As demonstrated, these complications can have a variety of clinical manifestations and a complex etiology, and can affect any ocular and orbital structure except the lacrimal organ and lens [6].

Ocular adnexa and oculomotor system

The orbit – along with its fascicles, eyelids, and lacrimal organ – form the ocular adnexa, while the oculomotor muscles and associated structures comprise the oculomotor system. Complications affecting the above-mentioned structures after ADA and ETC have been reported: orbital necrotizing fasciitis [30], orbital granuloma (also associated with sarcoidosis) [31], and ocular myositis [27].

Anterior segment of the eyeball

Inflammation: The mechanisms whereby TNFi cause paradoxical inflammatory effects are unclear [27]. Reports show that ETC and INF are associated with the occurrence of scleritis – an inflammation of the sclera which is the outer layer protecting internal structures of the eyeball. This autoimmune condition is characterized by pain and tenderness of the eye, blurred vision, redness, and swelling of the sclera. According to research, it is more frequent with ETC [32]. Gaujoux-Viala et al. [33] described 3 cases of severe scleritis associated with ETC when used for rheumatoid arthritis (RA). TNFi (most commonly ADA and INF) have been successfully used and are registered for the treatment of NIU. However, it was observed that, paradoxically, they can cause *de novo* or recurrent NIU. Reports state that uveitis is the second most common paradoxical adverse autoimmune condition, with a rate of 19.85 cases per 1,000 patients exposed [34]. In the case of TNFi, it is more frequent with ETC and less frequent with ADA and INF [32, 35, 36].

Infections: Study reviews suggest that TNFi may lead to reactivation of herpes zoster keratitis [35, 36]. This corneal disease can lead to persistent vision loss, and therefore early diagnosis and treatment are crucial. Additionally, in patients on biological therapy, vaccines containing live viruses should not be used [37].

A case of NIU caused by tuberculosis was also reported [38]. Officially, TNFi therapy is associated with an increased risk of developing tuberculosis, so we should rule it out before treatment is initiated [35].

Tumors: A case of squamous cell carcinoma of the conjunctiva was reported in a patient receiving ETC [39]. It is a malignant tumor that can infiltrate adjacent ocular and orbital structures and produce distant metastases.

Posterior segment of the eyeball

Inflammation: Complications of blocker therapy can manifest as inflammation of the intermediate, posterior, or entire uvea and also of the vitreous body [6].

Tumor formation: Tumor formation may also occur in the posterior segment. The authors point out the possibility of the development of choroidal melanoma as a dangerous complication. Three cases of this tumor have been reported after the use of TNFi. In 1 of these cases, melanoma developed as a result of a transformation of a previously present choroidal nevus. Therefore it is important to examine patients ophthalmologically before starting TNFi to detect suspicious lesions on the fundus of the eye and to check them regularly during treatment [40].

Hemorrhagic complications: Anti-tumor necrosis factor drugs have been shown to be associated with hemorrhagic complications, such as vitreous hemorrhage [41, 42]. Although TNFi therapy theoretically reduces cardiovascular risk, thromboembolic incidents leading to retinal venous thrombosis (RVO) have been observed in approximately 4.5% of patients [43–46]. However, further studies in this regard, involving larger

groups of patients, are required to definitively confirm the increased risk of thromboembolic incidents associated with TNFi therapy.

Retinal detachment: Retinal detachment is another important and sight-threatening complication associated with the use of ETC. In a study evaluating the efficacy of TNFi treatment in juvenile idiopathic arthritis (JIA) – associated uveitis, 24 patients taking ETC and 21 taking INF were studied. Retinal detachment was identified as an adverse effect in 1 patient taking ETC [47]. This condition manifests as blurred vision, flashes of light, moving shadows or floaters, and changes in peripheral vision, and often requires surgical treatment.

Disorders of neural structures

The literature describes the occurrence of side effects related to neural structures, as well as the association of TNFi with demyelinating processes. Pérez-De-Lis et al. [34] reported that central nervous system demyelination was found in 0.33 cases per 1,000 patients exposed, mostly associated with the use of ETC and INF. Moreover, 1 case of chiasmopathy related to INF and 2 cases of oculomotor nerve demyelination related to CZP and INF have been reported [48]. Therefore, TNFi are contraindicated in patients with a diagnosed demyelinating disease. In the event of such complications, discontinuation of the drug, intravenous GC injections and regular observation until symptoms resolve are recommended. Non-demyelinating optic nerve pathologies and anterior ischemic optic neuropathy may also occur as complications of TNFi therapy [49].

Other possible side effects described in the literature include Guillain-Barré's syndrome, Miller-Fisher's syndrome, homonymous hemianopia, nystagmus, diplopia, visual field loss, and floaters [50].

The potential impact of anti-TNF drugs on the eye can also be assessed during OCT and OCTA examinations: short-term (6-month) use of TNFi (ETC, or ADA, or INF) has been shown to not affect parameters such as peripapillary RNFL thickness, ganglion cell-inner plexiform layer (GCIPL) thickness, and macular retinal thickness [51]. In contrast, a 1-year follow-up of patients taking ADA demonstrated that a longer duration of therapy can cause structural changes, as confirmed by optical coherence tomography. In a group of patients treated with ADA, the peripapillary retinal nerve fiber layer thickness, GCC thickness, and macular retinal thickness were lower than in the control group. In addition, the c/d ratio (the ratio of the size of the optic cup to the optic disc) and mean optic disc depression area were higher in the group taking ADA. Moreover, the cited study showed no effect of ADA on parameters such as visual acuity, spherical equivalent, and intraocular pressure [52].

Safety profile and adverse effects

The safety profile of TNFi has been extensively studied, demonstrating overall effectiveness but also specific risks that require careful monitoring. One of the most significant concerns is an increased susceptibility to infections, particularly opportunistic infections such as tuberculosis and fungal infections.

Reactivation of latent tuberculosis is a well-documented risk, necessitating screening before initiating therapy. According to the reports, the reporting odds ratio (ROR), a disproportionality measure used to identify drug-associated adverse events, for tuberculosis is: ADA – 12.63 (6.00–26.57), GOL – 46.43 (26.28–82.01), CZP – 12.39 (5.15–29.82), ETC – 7.53 (4.82–11.73), INF – 16.33 (9.26–28.81) [53].

Tumor necrosis factor inhibitors have also been associated with an increased risk of malignancies, though the evidence remains controversial and varies among patient populations. Injection site reactions and infusion-related hypersensitivity reactions are commonly reported but are generally mild and manageable. Autoimmune phenomena, such as lupus-like syndromes and demyelinating disorders, have been observed in some patients receiving these therapies. Cardiovascular risks, including potential exacerbation of heart failure, have been noted, particularly in individuals with preexisting cardiac conditions. The development of anti-drug antibodies may reduce drug efficacy over time, leading to a loss of response. Long-term safety data suggest that while TNFi are generally well tolerated, ongoing pharmacovigilance is essential [53].

Summary

Tumor necrosis factor inhibitors have significantly advanced the management of non-infectious uveitis, providing robust and targeted treatment options for this potentially blinding condition. Adalimumab and INF remain the most extensively studied and widely used agents, while CZP and GOL offer additional options for refractory cases. The choice of therapy should be individualized based on disease severity, underlying systemic conditions, and patient-specific factors.

While TNFi are generally well tolerated, they are not without risks. Paradoxical induction of uveitis has been reported with some agents, particularly etanercept, underscoring the importance of agent selection based on the clinical profile of the patient. Long-term safety data have emphasized the need for vigilant monitoring to mitigate risks such as infections and immunogenicity.

These considerations are particularly relevant in chronic uveitis, where prolonged therapy is often required to maintain disease control [22, 54].

Interleukin-17 inhibitors in uveitis management: current insights and challenges

While the introduction of biologics targeting TNF has revolutionized treatment for certain types of uveitis, there remains a subset of patients who do not respond adequately to these therapies. Interleukin-17 inhibitors, including SCK, IXE, and BKZ, have emerged as potential alternatives due to their central role in modulating inflammatory pathways.

Interleukin-17, a pro-inflammatory cytokine primarily produced by Th17 cells, plays a pivotal role in the pathogenesis of immune-mediated diseases such as axSpA and psoriatic arthritis (PsA). Its involvement in recruiting and activating inflammatory cells suggests a plausible role in the development and progression of uveitis. Interleukin-17 inhibitors have been shown to modulate these pathways effectively in systemic inflammatory diseases, leading to interest in their application for ocular inflammation [55].

Interleukin-17 inhibitors, including SCK, IXE, and BKZ, hold promise for addressing inflammatory pathways in systemic diseases. However, their efficacy in non-infectious uveitis remains uncertain. While disappointing SCK trial outcomes have tempered enthusiasm, BKZ dual IL-17A and IL-17F blockade offers a potential avenue for future research. Ixekizumab, though less studied in uveitis, may also warrant further investigation. Ongoing efforts to unravel the complexities of ocular inflammation and identify responsive patient populations will be critical to optimize the use of IL-17 inhibitors in uveitis management.

Continued research into the IL-17/IL-23 axis, as well as exploration of combination therapies, will likely play a pivotal role in advancing the field. For now, IL-17 inhibitors remain a promising yet challenging option for uveitis treatment, emphasizing the need for personalized and evidence-based therapeutic strategies.

Secukinumab

Secukinumab, a monoclonal antibody that selectively targets IL-17A, has undergone rigorous evaluation in 3 large-scale phase III trials – SHIELD, INSURE, and ENDURE – for its potential in non-infectious uveitis. These trials aimed to reduce uveitis recurrence and manage intraocular inflammation. Unfortunately, SCK failed to meet primary efficacy endpoints, leading to the discontinuation of its development for this indication [56, 57]. Despite robust evidence of IL-17's role in uveitis pathogenesis, the lack of clinical efficacy highlights the complexity of immune mechanisms involved in ocular inflammation and suggests that IL-17A blockade alone may be insufficient.

However, case studies and smaller reports have hinted at possible benefits of SCK in specific patient subgroups, such as those with refractory uveitis secondary to axSpA. Efficacy differences between the SCK and the placebo groups were highest in the CRP+, MRI+, HLA-B27+, and male subgroups. This suggests a potential niche application, warranting further exploration [58].

Ixekizumab

Ixekizumab, another IL-17A inhibitor, has been evaluated for its potential in managing uveitis. While it has shown efficacy in treating systemic inflammatory diseases such as psoriasis and axSpA, there is limited published evidence supporting its use in uveitis. Early investigations indicate that it may have some benefit in reducing inflammation in associated ocular conditions, but comprehensive clinical trials are necessary to establish its therapeutic role [59].

Bimekizumab

Bimekizumab, a monoclonal antibody targeting both IL-17A and IL-17F, represents an evolution in IL-17 inhibition. Phase 2b/3 trials in axSpA have reported a low incidence of uveitis among treated patients, suggesting a potential protective effect against ocular inflammation. Unlike SCK, the dual mechanism of BKZ may provide broader modulation of inflammatory pathways, which could be beneficial for uveitis. However, these findings are indirect and require validation through dedicated studies focusing on uveitis outcomes [55]. So far, data on BKZ vs. placebo are available, so we are waiting for an active comparison with TNFi to establish the appropriate position of this molecule in uveitis.

Reported adverse ocular effects

The safety of IL-17 inhibitors in chronic inflammatory disease (ulcerative colitis, Crohn's disease, psoriasis), where IL-17i are effective, is well documented, but their use in uveitis has been associated with some ocular side effects. Reports of eyelid dermatitis, scleritis (linked to *Histoplasma capsulatum*), and endogenous endophthalmitis during IL-17 inhibitor therapy highlight the need for cautious monitoring in uveitis patients [50, 60]. Additionally, the risk of paradoxical reactions, as observed with certain TNF-α inhibitors, underscores the importance of individualized therapy and vigilant follow-up.

Eyelid dermatitis, characterized by redness, swelling, and discomfort of the eyelids, has been documented as an inflammatory reaction potentially linked to IL-17 inhibition. This condition may represent a localized hypersensitivity response, highlighting the need for careful evaluation of new or worsening periocular symptoms during therapy [50, 60].

Scleritis, an inflammation of the sclera, is a potentially sight-threatening condition that presents with severe eye pain, redness, and tenderness. While the pathogenesis of scleritis in the context of IL-17 inhibitor use is not fully understood, it has been associated with immune dysregulation that may be exacerbated by these agents. Infections, such as those caused by *Histoplasma capsulatum*, have also been implicated, necessitating careful differentiation between immune-mediated and infectious causes [61].

Endogenous endophthalmitis, a severe intraocular infection, is another rare but serious adverse event reported in association with IL-17 inhibitors. This condition, which can result in vision loss, requires immediate medical intervention. It underscores the importance of recognizing systemic infections that may disseminate to the eye, especially in immunocompromised patients or those with underlying infections [62].

Uveitis: Although IL-17 inhibitors have been explored for their therapeutic potential in uveitis, paradoxical cases of new-onset or recurrent uveitis have been reported in some patients [56]. This phenomenon, observed in biologic DMARDs including IL-17 inhibitors, may reflect a complex interplay between immune modulation and inflammatory pathways. These cases highlight the need for personalized treatment approaches and close collaboration between rheumatologists and ophthalmologists.

Safety profile and adverse effects

In addition to specific ocular events, IL-17 inhibitors have been linked to an increased risk of systemic infections, particularly respiratory tract infections and candidiasis. While these infections are generally mild, they may predispose patients to secondary complications, including ocular involvement. Reviews focusing on SCK have noted a higher incidence of these infections, although direct causal relationships with ocular conditions remain unclear [57, 58]. This raises the importance of monitoring for signs of infection, both systemic and ocular, during treatment.

Challenges and unresolved questions

The mixed results of IL-17 inhibitors in uveitis trials highlight several challenges. First, the immune mechanisms driving uveitis are complex and may involve multiple pathways beyond IL-17, such as IL-23 and interferon-gamma. This raises the question of whether combination therapies targeting multiple cytokines could yield better outcomes. Additionally, the lack of efficacy observed in SCK trials suggests that the relationship between systemic inflammation and intraocular disease is not straightforward and may require a more nuanced therapeutic approach [56, 57].

Another unresolved question pertains to patient selection. Identifying biomarkers to predict response to IL-17 inhibitors could enhance treatment outcomes and prevent unnecessary exposure to ineffective therapies. Furthermore, understanding the differences between IL-17A and IL-17F in disease modulation may guide the development of more targeted interventions [55].

Summary

Interleukin-17 inhibitors have revolutionized the management of several immune-mediated inflammatory diseases, offering significant therapeutic benefits. However, rare ocular adverse effects, including eyelid dermatitis, scleritis, and endogenous endophthalmitis, necessitate awareness and vigilance among healthcare providers. Although causal relationships between IL-17 inhibitors and these adverse effects are not fully established, the emerging evidence highlights the importance of multidisciplinary care in managing patients on these therapies. Further research is needed to clarify the mechanisms underlying these events and to identify strategies for mitigating risks while maintaining the benefits of IL-17 inhibition.

Janus kinase inhibitors in the management of uveitis

Janus kinase inhibitors, including TOFA, UPA, BARI, and FIL, have emerged as promising therapeutic options for autoimmune and inflammatory diseases. These agents target the JAK-STAT signaling pathway, a critical mediator in cytokine-driven inflammatory processes, and have demonstrated efficacy in conditions such as axSpA, RA, and PsA. Recent investigations have explored their potential utility in treating non-infectious uveitis, a significant cause of visual impairment often associated with chronic inflammatory diseases.

The JAK-STAT pathway regulates cytokine activity, immune cell function, and the transduction of pro-inflammatory signals. Dysregulation of this pathway contributes to the pathogenesis of various inflammatory conditions, including uveitis. By inhibiting JAK isoforms, these agents modulate inflammatory cytokine

production and immune cell recruitment, offering a targeted approach to managing uveitis [63, 64].

Filgotinib

Filgotinib, a JAK1-preferential inhibitor, has demonstrated promise in the management of non-infectious uveitis. However, more reliable studies are needed on the use of this drug.

Tofacitinib and upadacitinib

A retrospective case series evaluated the use of TOFA and UPA in the management of non-infectious uveitis, specifically in patients who were unresponsive to conventional immunosuppressive therapies. While both agents appeared to reduce ocular inflammation and improve clinical outcomes, the study involved a limited sample size of only 8 patients, making it insufficient to draw definitive conclusions about their efficacy or safety. The findings highlight the need for larger, controlled studies to better understand the potential role of these JAKi in treating refractory immune-mediated ocular conditions [65].

Baricitinib in juvenile idiopathic arthritis-associated uveitis

Baricitinib has shown efficacy in managing juvenile idiopathic arthritis (JIA)-associated uveitis (the form of axSpA in children), particularly in cases refractory to multiple lines of immunosuppressive therapy. Studies suggest that JAKi such as BARI may offer a valuable addition to the therapeutic arsenal for this challenging condition, especially given their favorable safety and tolerability profiles [66].

Despite the encouraging results from initial studies, further research is needed to establish the long-term efficacy and safety of JAKi in uveitis. Large-scale randomized controlled trials, such as the HUMBOLDT study, provide critical insights but must be complemented by real-world data to refine patient selection criteria and optimize treatment protocols. Additionally, exploring combination therapies that include JAKi alongside other immunomodulatory agents may enhance treatment outcomes for refractory cases [67].

Ocular adverse effects

Janus kinase inhibitors have also been linked to the following ocular complications.

Scleritis: Characterized by significant pain and redness, it is one of the more notable ocular complications associated with these agents.

Peripheral ulcerative keratitis: Although rare, it is a serious condition involving corneal inflammation and ulceration that can lead to vision loss if not promptly treated.

Uveitis: Paradoxical onset or recurrence of uveitis has also been observed, particularly in patients with pre-existing autoimmune conditions.

While these events are rare, they highlight the need for multidisciplinary care involving rheumatologists and ophthalmologists to promptly identify and manage adverse outcomes [68, 69]. Patients should be educated to recognize symptoms such as eye pain, redness, and vision changes, and to seek immediate medical attention if these arise.

Safety profile and adverse effects

While JAKi are generally well tolerated, they are associated with specific risks that warrant careful consideration. The most commonly reported systemic adverse effects include an increased susceptibility to infections, cardiovascular events, and venous thromboembolism. These risks, though infrequent, emphasize the need for vigilant monitoring, especially in patients with predisposing conditions. Additionally, concerns have been raised regarding a potential increased risk of malignancies with JAKi, highlighting the importance of long-term safety evaluation [66, 70].

Among the most notable risks associated with JAKi is an increased susceptibility to infections. Upper respiratory tract infections are the most frequently reported, with herpes zoster also emerging as a significant concern. The elevated risk of herpes zoster in patients treated with JAKi has been linked to the suppression of antiviral immune defenses. Studies underscore the need for preventive measures, such as herpes zoster vaccination, prior to initiating treatment in appropriate patients. These findings highlight the importance of proactive monitoring to mitigate the risk of infection during therapy [70].

Cardiovascular events, including myocardial infarction and stroke, represent another potential complication associated with JAK inhibitors. In a study assessing the association between JAKi and the risk of venous (VTE) and arterial thromboembolic events (ATE), among 5870 patients receiving JAKi, 92 experienced an incident VTE or ATE within the study period [70]. While these events are infrequent, they occur more often in patients with pre-existing cardiovascular risk factors. These warnings underscore the need for individualized care plans tailored to each patient's specific risk profile [70].

Summary

Janus kinase inhibitors, such as TOFA, UPA, BARI, and FIL, have significantly improved the therapeutic land-

scape for autoimmune and inflammatory diseases, including RA, axSpA, and PsA. These medications work by disrupting the JAK-STAT signaling pathway, a critical driver of cytokine-mediated inflammation. Their ability to modulate immune responses has made them effective treatments for conditions that do not respond to conventional therapies. Despite their efficacy, however, the safety profiles of JAKi warrant careful scrutiny due to their potential to cause systemic and localized adverse effects.

Agents such as FIL, TOFA, and UPA have demonstrated potential in both clinical trials and real-world settings. While safety considerations and the risk of ocular and systemic adverse effects necessitate careful patient monitoring, the benefits of JAKi in managing complex autoimmune conditions are substantial. Ongoing research will further elucidate their role in uveitis management, paving the way for improved patient outcomes and expanded therapeutic options.

Conclusions

In patients with axSpA, ocular complications occur not only due to the course of the disease itself, but also as a side effect of the treatment used, mainly TNFi. Biologicals and targeted synthetic DMARDs are very effective in the treatment of rheumatic diseases and are being used increasingly. However, they are not free of serious side effects. The choice of therapy should be individualized based on disease severity, systemic conditions, and patient-specific factors. Careful observation of the side effects of individual drugs and their impact on the human body will enable the best possible therapeutic management. Modern imaging technologies in ophthalmology, such as OCT and OCTA, provide, among other things, the ability to predict the course of the disease and to assess the effectiveness of the treatment applied. In addition, regular ophthalmological check-ups can help prevent serious ocular complications.

Disclosures

Conflict of interest: *The authors declare no conflict of interest.*
Funding: *No external funding.*
Ethics approval: *Not applicable.*
Data availability: *Not applicable.*

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