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Review

Uveitis in Psoriatic Arthritis: A Comprehensive Review

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Abstract

Psoriatic arthritis (PsA) belongs to the spectrum of spondyloarthritides, primarily affecting skin and joints. Apart from skin involvement, other extra-articular manifestations can coexist. Uveitis, although not very frequently encountered, is one of the most serious of them, necessitating prompt diagnosis and proper treatment to prevent irreversible sight-threatening complications. Psoriatic arthritis-related uveitis is usually unilateral, characterized by anterior segment inflammation, with the absence of redness or pain making it possible to miss the diagnosis. This review gives a comprehensive insight into the pathophysiology and clinical manifestations of PsA-related uveitis, along with an exposition of various epidemiologic features, as derived from relevant observational studies. Therapeutic approaches and available treatments are also reviewed. Although definitive recommendations on treatment seem rather challenging for PsA-related uveitis, tumor necrosis factor inhibitors appear to have the lead over other biologic therapies. A multi-disciplinary approach, tight screening, and disease activity control, as well as proper targeted therapy, remain pivotal.

Keywords: Biologic DMARDs, psoriatic arthritis, uveitis

Introduction

Uveitis is an inflammatory process affecting the middle intraocular level, the uvea. It can affect the anterior part of the uvea, which includes the iris and the ciliary body, and is subsequently called iritis or iridocyclitis (anterior uveitis), or the posterior part, affecting the retina and the choroid, in which case it is called chorioretinitis or posterior uveitis.[1] Primary infiltration of vitreous humor by neutrophils and other immune cells, with limited involvement of other sites, is addressed as intermediate uveitis.[1] The extensive inflammation of the anterior chamber, vitreous humor, and retina is referred to as panuveitis.[1] The incidence is 17-52/100 000 person-years, while the prevalence is 38-714/100 000 individuals.[2-4] Etiology of uveitis can be classified as infectious, immune-mediated, which is associated with multiple systemic or rheumatic inflammatory conditions, intraocular, which is confined primarily to the eye and excludes infectious or systemic involvement, or masquerade syndromes, which can mimic uveitis, such as malignancies and drug-induced uveitis. Causes of infectious origin include viral, bacterial, fungal, or protozoan infections. Systemic autoimmune disorders that cause uveitis include systemic lupus erythematosus and vasculitides, while some autoinflammatory conditions that complicate with uveitis are psoriatic arthritis (PsA), ankylosing spondylitis, juvenile idiopathic arthritis, inflammatory bowel diseases, Adamantiades-Behcet disease, and sarcoidosis.[5,6]

Pathophysiology

Uveitis can occur as an extra-articular manifestation of PsA and is a relatively frequent entity, belonging to the whole spectrum of SpA. Ocular inflammation in various degrees (anterior, posterior segment, or panuveitis) can manifest either acutely or insidiously.[7] There is a widely known association of human leukocyte antigen (HLA) B-27 with PsA and ocular involvement, which is considered multifactorial.[8,9] Human leukocyte antigen-B27 (HLA-B27) testing was not available in all studies retrieved, and the prevalence among those studies reporting HLA-B27 positivity differed (range 21%-100%). The Assessment of SpondyloArthritis International Society (ASAS) peripheral SpA (perSpA) study proved that HLA-B27 positive PsA patients presented a significantly higher frequency of uveitis at diagnosis as compared to negative ones (11.6% vs. 1.8%, $P < .001$).[10,11] A well-established hypothesis is that the lens or the ciliary body is affected by inflammation in a way similar to that of the enthesitis in an incomplete form, a prominent characteristic of PsA. Uveitis in itself is considered a risk factor for inflammatory arthritis or psoriasis (PsO).[6,9]

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Intestinal tissue is also under investigation as a site where alterations in microbiota can be partly responsible for inflammatory processes affecting the uvea. Human leukocyte antigen-B27 also instigates changes in microbiota. The disruption of the immune homeostasis controlled by the microbiota can lead to the inflammatory activation of T helper 17 cells against microbial-associated molecular patterns or danger-associated molecular patterns.[8,12] Molecular mimicry of arthritogenic bacterial peptides is another proposed pathogenetic mechanism of PsA-associated uveitis, which has been identified in the past but lacks objective proving points, further weakened by the limited-to-insignificant role of autoreactive T-cells and autoantibodies.[8,13] Alterations in mucosal intestinal permeability and the subsequent bacterial product translocation are processes heavily involved in developing arthritis and can also contribute to ocular manifestations via an inflammatory cascade, although there is no documented presence of such products in any segment of the eye, in part due to the difficulty of accessing it, in contrast with their known presence in various joint sites.[9] Direct inflammatory action of immune cells, migrating from the intestine to various ocular sites, is also incriminated in uveitis related to PsA.[14,15]

Clinical Manifestations

Ocular inflammation in PsA can be unilateral or bilateral, with the patient complaining about pain and exhibiting redness during the clinical examination. Chronic pain is the hallmark of uveal inflammation. Sensitivity to light is another symptom that, while not being specific to uveitis, is described commonly in reports. Loss of visual acuity can also be a presenting feature of uveitis, usually found in cases with a more insidious onset.[6] Non-specific visual phenomena, such as "floaters" or visual loss, are described in uveitis.[16] Anterior involvement is usually accompanied by pain, in contrast to posterior uveitis. Pupils can be constricted in iritis, while redness is detected at the junction between the cornea and the sclera. The posterior segment is more frequently affected, with simultaneous bilateral inflammation also being frequent in patients with psoriatic arthritis.[17] Posterior uveitis is more likely to be painless, when there is no anterior involvement, and can even be the first presenting symptom of the disease, preceding skin or articular manifestations.[7] Slit-lamp examination can detect inflammation of the retina and the presence of leukocytes in the vitreous humor.

Ophthalmologic examination may also reveal possible complications from remitting disease or even a single self-limiting episode of uveitis. The first studies of uveitis in the early 2000s in PsA provide a perplexing account of sequelae. Two studies report 0 complications,[11,18] while another report 25% developing cataract, 19% glaucoma, 19% with cystoid macular edema, and 31% with posterior synechiae from a total of 16 patients.[6] Discrepancies continue with a retrospective study reporting that none of the patients had permanent eye complications,[17] versus a series of 3 other studies acknowledging a wide variety of visional sequelae. Abbouda et al[7] report 25 PsA patients with 33 eyes afflicted with uveitis and experiencing complications as follows: blepharitis (3/33), dry eye (8/33), episcleritis (3/33), cataract (12/33), glaucoma (5/33), vitritis (20/33), posterior vitreous detachment (9/33), chorioretinal atrophy (3/33), epiretinal membrane (2/33), macular oedema (2/33), and retinal vasculitis (2/33). Complete resolution of eye inflammation was not possible for 30% of PsA patients (3/10) patients in the Greek study, all of whom had recurrent disease.[19] Similarly, 5 out of 13 patients (38.46%) suffered long-term sequelae, namely cataract, glaucoma, or macular edema.[20]

Notwithstanding the topical eye complications, a recent study from rheumatologists in Spain emphasizes the overall health-related ramifications of uveitis in PsA. Indeed, when their group of 406 PsA patients was studied, those with uveitis had worse functionality and quality of life (QoL) despite treatment with biologics (40% of patients).[17]

Main Points

- Uveitis is a well-established extra-musculoskeletal manifestation in psoriatic arthritis.
- A significant proportion of patients may exhibit permanent eye complications.
- Biologic disease-modifying anti-rheumatic drugs constitute an effective treatment choice in the majority of cases.
- Increased awareness and early immunosuppression are required.

Epidemiology

The prevalence of PsA-related uveitis has been investigated by various studies (Table 1) and was estimated to be about 3.2% (95% CI 1.9%, 5.3%), as derived from a meta-analysis of 21 studies, including 145 262 PsA patients.[21] A Greek multicenter cohort revealed that PsA-related uveitis was correlated with a family history of SpA, longer disease duration, axial disease at diagnosis, as well as with ever-occurrence of enthesitis, dactylitis, or bowel involvement.[19]

As for uveitis characteristics, several studies reported the type of uveitis (acute, recurrent), the site of eye involvement (anterior, posterior), and whether there was a unilateral or bilateral insult. Uveitis was acute in most cases, while the majority of studies reported a relapsing type of uveitis. Anterior rather than posterior uveitis was most often diagnosed, and unilateral insult was observed in most cases (Table 2). Concerning recurrence and flares, a Korean study reported that the incidence rate ratio (IRR) for uveitis recurrence in PsA was 1.49 (95% CI: 1.31, 1.7),[22] while a Swedish nationwide study reports sex differences in incidence rate for anterior uveitis flare [5.1 (95% CI: 4.2, 6.3) vs. 4.1 (95% CI: 3.4, 5.0) for men and women respectively].[23]

The risk of developing PsA in uveitis patients, and vice versa, was also calculated in some studies. A meta-analysis revealed a significant association between PsA and uveitis risk ratio (RR: 3.16, 95% CI: 2.16-4.63), as well as an elevated risk of PsA in patients with pre-existing uveitis (RR: 4.44, 95% CI: 3.52-5.60).[24] Furthermore, as revealed by a Danish nationwide cohort study, the uveitis IRR for PsA was 3.77 (95% CI: 2.66-5.34), after adjustments for age, sex, comorbidities, and socioeconomic status.[25] Additionally, a cohort from a primary care-based registry in the United Kingdom revealed an increased risk ratio for uveitis in PsA patients (RR: 3.55, 95% CI: 2.21-5.7) as compared to the general population (RR: 2.13, 95% CI: 1.40-3.24).[26]

Diagnostic delay of PsA was not found to be significant for uveitis development, as illustrated in a study of 1456 PsA patients, while 33% of PsA patients exhibited an episode of uveitis before PsA diagnosis.[27] Finally, a meta-analysis demonstrated that there is no statistical difference in uveitis frequency between adult and juvenile onset PsA.[28]

Treatment

Steroids

The initial method for treating uveitis often involves using topical corticosteroids.[29] Although these medications are usually effective, their ability to go beyond the lens is limited. Additionally, there are risks linked to the use of corticosteroids, such as causing cataracts

Table 1. PsA-Related Uveitis Prevalence

Study	Study Type	Date	Study Date	Country	Prevalence
Hijazi et al[65]	Retrospective cohort (from a healthcare provider)	2005-2020	2024	Israel	107/6147 (1.7%)
Kougkas et al[19]	Multicenter retrospective cohort	2018-2023	2023	Greece	10/369 (2.7%)
Michelena et al[27]	Multicentre retrospective cohort	NA	2023	Latin America (RESPONDIA)	18/392 (4.7%)
				Spain (Barcelona)	11/442 (2.5%)
				UK (Leeds)	26/622 (4.2%)
Delmás et al[17]	Single-center retrospective cohort	1990-2020	2022	Türkiye	20/406 (4.9%)
Michelena et al[66]	Multicenter cross-sectional study (from national registry REGISPONSER)	2004-2007	2022	Spain	3/109 (2.8%)
Salaet et al[10]	Observational cross-sectional worldwide registry (ASAS perSpA)	2018-2020	2022	Multinational	17/474 (3.6%)
Casanova et al[20]	Single-center retrospective cohort	2017-2019	2023	Spain (Madrid)	13/494 (2.6%)
Kim et al[22]	Multicenter observational study (KOBIO registry)	2012-2022	2022	Korea	0/109 (0%)
Bilge et al[67]	Multicenter retrospective cohort	2017-2020	2021	Türkiye	17/536 (3.6%)
Bengtsson et al[23]	Observational, prospective cohort (National Patient Regisity)	2001-2015	2020	Sweden	356/22,667 (1.6%)
Gonzalez-Mazon et al[68]	Single-center retrospective cohort	NA	2020	Spain	10/320 (3.13%)
Charlton et al[26]	Observational cohort from registry (Clinical Practice Research Datalink)	1998-2014	2018	UK	100/6,783 (1.47%)
Abbouda et al[7]	Single-center retrospective cohort	2003-2013	2016	Italy	25*
Egeberg et al[25]	Multicenter retrospective cohort (National Patient Registry)	1997-2011	2015	Denmark	16/6,735 (0.23%)
Tanaka et al[69]	Single-center retrospective cohort	1995-2014	2015	Japan	4*
Niccoli et al[70]	Single-center prospective cohort	2000-2009	2012	Italy	22/242 (9%)
Sampaio-Barros et al[18]	Single-center retrospective cohort	NA	2006	Brazil	5/63 (8%)
Queiro et al[11]	Single-center retrospective cohort	1991-2000	2002	Spain	13/71 (18%)
Paiva et al[6]	Single-center retrospective cohort	1985-1997	1999	USA	16*

*Only PsA uveitis patients included.

or increasing pressure. An alternative option, difluprednate, has shown results in treating inflammation behind the lens. However, its usage is connected with a chance of developing cataracts or glaucoma.[29,30]

When topical corticosteroids do not work effectively, injected corticosteroidslike triamcinolone can be considered. This approach has its difficulties, including discomfort from the injection and potential risks like cataracts, glaucoma, drooping eyelids (lid ptosis), and in rare cases, retinal detachment. Injecting triamcinolone directly into the humor may offer advantages but also comes with a higher risk of intraocular infection or bleeding.

Oral corticosteroids provide another choice for managing uveitis. However, their extended use is linked with known effects that rheumatologists are familiar with and requires attentive monitoring.[31]

Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs

Methotrexate (MTX) surveys conducted showed that it effectively treats acute anterior uveitis (AAU).[32,33] One prospective study on 9 AAU patients exemplified a significant reduction in uveitic flares from an average of 3.4 before starting the drug to only 0.9.[32] Another study stressed the ability of MTX to reduce cortisone usage with a consequent decrease in recurrence rate. The surprising finding of this research was that all 19 AAU patients enrolled in the study could stop taking corticosteroids completely.[33] Patients with AAU were also included in the largest retrospective analysis done on non-infectious uveitis, which is the Systemic Immunosuppressive Therapy for Eye Diseases cohort study.[34] The study compared different forms of immunomodulatory therapy like cyclosporine A, mycophenolate mofetil (MMF), azathioprine, and MTX with special emphasis on their steroid-sparing effects. Mycophenolate mofetil and MTX had the most efficacy among these agents in terms of decreasing reliance on corticosteroids.[35] Moreover, although no PsA patients were recruited, a randomized controlled trial (RCT) assessing the QoL among uveitis patients treated with MTX or MMF yielded some intriguing results.[36] Although both interventions led to an improvement in vision-related symptoms, no significant increase was observed in overall physical health scores. In addition, the mental health-related QoL scores worsened, which suggests how treatment outcomes can sometimes be conflicting compared to self-reported findings among uveitic patients.

Table 2. PsA-Related Uveitis Characteristics

		Disease Duration	Uveitis Type, n (%)		Uveitis Site, n (%)		Uveitis Side, n (%)	
Study	HLA-B27, n (%)	Years (SD)	Acute	Reccurent	Anterior	Posterior	Unilateral	Bilateral
Hijazi et al[65]		5.28 (4.69)			44/107 (41)	0	69/107 (64)	10/107 (9)
Kougkas et al[19]	3/7 (43)	14.8 (9.2)	2 (20)	8 (80)				
Delmás et al[17]	9/20 (45)	12.7(9.2)	20 (100)	0 (0)	16/20 (80)	4 (20)	16/20 (80)	4/20 (20)
Michelena et al[66]	2/3 (67)	7.0 (2.5-13.0)*			3/3 (100)			
Salaet et al[10]	10/17 (59)	12.7						
Casanova et al[20]	3/13 (23)		2 (15)	9 (69)	12/13 (92)	1/13 (8)	9/13 (69)	4/13 (31)
Kim et al[22]		4.4 (5.4)						
Bengtsson et al[23]			348/356 (97)	250/356 (70)	356/356 (100)			
Gonzalez-Mazon et al[68]	6/10 (60)	10 (7.9)	10/10 (100)	4/10 (40)	10/10 (100)		9/10 (90)	1/10 (10)
Abbouda et al[7]	4/19 (21)				23/25 (92)	1/25 (4)	8/25 (32)	17/25 (68)
Tanaka et al[68]			4/4 (100)	4/4 (100)	4/4 (100)		1/4 (25)	1/4 (25)
Niccoli et al[70]	5/22 (23)	8.0 (7.9)		2/22 (9)			20/22 (91)	
Sampaio-Barros et al[18]	5/5 (100)		5/5 (100)		5/5 (100)			
Queiro et al[11]	8/13 (61)	13.0 (7.0)	9/13 (69)		10/13 (77)	1/13 (8)		5/13 (39)
Paiva et al[6]	6/9 (67)		13/16 (81)		9/16 (56)	7/16 (44)	4/16 (25)	6/16 (38)

*Median, (IQR)

Biologic Disease-Modifying Anti-Rheumatic Drugs

Tumor Necrosis Factor Inhibitors

Infliximab (IFX), Adalimumab (ADA), Golimumab (GOL), and Certolizumab Pegol (CZP) are monoclonal antibodies targeting TNFi that have been proven effective in the treatment of AAU by helping manage acute flares and reduce the recurrence rate.[37] Etanercept (ETN), an anti-receptor antibody, has also been used in the treatment of uveitis.[38] Efficacy of ADA in treating uveitic flares and improving visual acuity scores has been evaluated by a few RCTs.[39-41] It is worth that ADA demonstrated steroid-sparing effects, delaying uveitic flares compared to placebo-controlled groups.[39,40] Another study, which was a small RCT on unresponsive non-infectious uveitis, revealed a significant decrease in ocular inflammation among patients treated with ADA.[41] Pooling together data from RCTs that examined TNFi in AS, like IFX and ETN, identified a pronounced reduction in AAU flare frequency among TNFi-treated subjects compared to placebo-treated patients.[38] With regards to this, only 1 TNFi agent—ADA—has been licensed for use as an adult treatment for non-infectious uveitis after successful phase III RCTs.

In a parallel manner, CZP has been shown to be effective in reducing rates of uveitis flares, as illustrated by the RAPID-axial spondyloarthritis (axSpA) trial and small case series.[42-44] Reports from trials, such as the C-VIEW trial, show that AAU flare rates reduce significantly during CZP treatment.[45] Infliximab administered intravenously demonstrated its efficiency in reducing uveitis flares among AS patients when compared with placebo.[38,46] Golimumab also showed effectiveness in reducing uveitis flares, particularly in AS patients with a history of uveitis.[47,48] However, the use of ETN in managing uveitis has declined due to its weaker ability to prevent flares compared to other TNFi options.[49]

Table 3. Choosing Biologic for Uveitis in Psoriatic Arthritis

Steroids	++
MTX	++
TNFi	+++
IL-17i	++(iv)
IL12/23i (p40)	+
JAKi	+

i, inhibitors; iv, intravenous infusion; IL, interleukin; JAKi, Janus kinase inhibitors; MTX, methotrexate; TNF, tumor necrosis factors.
+ Strength of clinical efficacy.

Interleukin-17 Inhibitor

A small trial for acute-on-chronic noninfectious uveitis has shown that secukinumab (SEC), an interleukin-17 inhibitor (IL-17i), is efficacious.[50] The subcutaneous SEC group was less responsive compared to the intravenous SEC group and was given higher doses than the clinical practice standard ones, but exhibited faster responses and higher remission rates.[50] Therefore, it can be suggested that subcutaneous SEC could not have obtained sufficient concentration for effective treatment of uveitis in this context. In addition, SEC is the first licensed biologic disease modifying antirheumatic drug (bDMARD) targeting axSpA which is not a TNFi.[51] Comparisons between TNFis and SEC using ASAS response rate indicate similar findings with approximately 60% at week 16 for ASAS20 response rate.[52,53] Besides, though slightly lower response rates were observed within this particular subgroup than in other patients lacking appropriate TNFi therapy, SEC remained active in TNFi inadequate responses.[53] Therefore, these results strongly suggest that SEC could be an alternative treatment option for axSpA with comparable efficacy to TNFis and promising results for unresponsive TNFi therapy patients. However, results from 3 randomized, control clinical trials (SHIELD, INSURE, ENDURE) using SEC in the treatment of noninfectious uveitis did not demonstrate significant efficacy in the recurrence of uveitis compared to placebo. The studies emphasized the complex role of immune system factors in uveitis and the need for further research to determine which patient groups might benefit from SEC.[54] Similarly,

additional studies are required to investigate its use in treating uveitis, especially on optimal dosing strategies necessary for attaining maximal benefits from this drug.

As for bimekizumab (BZK), a humanized monoclonal IgG1 antibody that selectively and potentially inhibits both IL-17A and IL-17F,[12] results from 2 phase 3 studies (BE OPTIMAL, BE COMPLETE) demonstrated clinical efficacy in patients with psoriatic arthritis, but no cases of active uveitis were reported.[55,56] Moreover, results pooled from phase 2b/3 trials concerning BZK showed that the dual IL-17A/F inhibitor has protective effects for uveitis in patients with axSpA, which further needs to be investigated in PsA uveitis.[57]

IL12/23i

Studies regarding Ustekinumab, a human monoclonal antibody against the common subunit p40 of IL-23 and IL-12, have reported successful control of uveitis associated with PsA and plaque PsO.[58]

Moreover, a study, in moderate to severe psoriasis, compared the incidence of uveitis in patients being treated with ustekinumab and TNFi.[59] The ustekinumab group demonstrated a significantly lower risk of uveitis compared to the TNFi group.

On the other hand, Guselkumab, an interleukin-23 inhibitor, has demonstrated promising outcomes regarding uveitis in psoriatic arthritis. Post hoc analyses of the DISCOVER-2 trial (n=741), with a 112-week follow-up, reported a single case of uveitis that resolved without treatment modification. No recurrence of uveitis was observed among the 4 participants with a prior history of the condition.[60]

Janus Kinase Inhibitor

A case report of a patient with anterior and intermediate uveitis described a favorable outcome under tofacitinib, a Janus kinase inhibitor (JAKi).[61] While a phase II trial of tofacitinib in non-infectious uveitis is yet to report its outcomes [ClinicalTrials.gov identifier: NCT03580343], a prospective observational study of patients with refractory anterior uveitis reported remission and steroid tapering achievement in 3 PsA patients.[62] Another phase II trial investigated the effect of filgotinib, a selective JAK-1 inhibitor, in uveitis[63] The results demonstrated that 200 mg filgotinib decreased the risk of uveitis flares compared to placebo and was well tolerated. Last but not least, Vitale et al[64] published a prospective cohort study involving a patient with anterior uveitis associated with psoriatic arthritis treated with upadacitinib plus sulfasalazine, showing potential benefit in the management of both ocular and extraocular activity.

Refractory Uveitis

Uveitis's pathophysiology and epidemiology in PsA is gradually unraveling. Adding to it, there is the above summarized small selection of immunomodulating molecules (biological or not) to try alleviating its symptoms (Table 3). However, poor overall control of uveitis is still evident from remitting disease. Starting with a study before the use of biologics, Sampaio-Barros et al[18] report 5 HLA-B27 positive PsA patients suffering 13 episodes of AAU or 2.6 episodes per patient. More recently, 2 retrospective studies mention that 50% (10 out of 20) and 69.2% (9 out of 13) of PsA patients experienced recurrent uveitis episodes,[17,20] calculating a rate of 0.92 flare-ups per patient/year.[20] Another multi-center study from Greece reports that 20% of patients had a single uveitis incident, while 80% of patients (8 out of 10) exhibited more incidents and the median uveitis episodes were 0.285 episodes/year.[19] Importantly, biologics, and especially TNFi monoclonal antibodies, are minimizing the rate of recurrences with an exposure adjusted incidence rate of uveitis before and after treatment of 56.3 and 9.4 episodes/100 patients-year respectively. Etanercept and SEC did not perform as efficiently as TNFi monoclonal antibodies, and in fact, the rate of recurrence seemed to increase.[17]

Conclusion

The prevalence of PsA-related uveitis is estimated to be about 3.2%, while in the majority of cases, it is presented in an acute, unilateral, and anterior pattern. Psoriatic arthritis patients with uveitis have worse QoL, with more than half of them experiencing recurrent disease, and approximately 30% having permanent eye complications (e.g., glaucoma, cataract, edema). Uveitis presents a challenge in making definitive recommendations for treatment. Based on RCTs of ADA's beneficial use in uveitis, a strong recommendation exists for TNFi (except for ETN, which is contraindicated). There is also a weak recommendation for MTX based on improved QoL indicators. Secukinumab could be an alternative treatment option for patients unresponsive TNFi therapy. Ustekinumab showed successful control of uveitis, while BZK's protective role in axSpA-related uveitis still needs to be proven in PsA uveitis. Guselkumab has hitherto revealed a safe profile for uveitis. Finally, although evidence on JAKi is currently scarce, their efficacy and safety appear to be satisfactory.

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