Title: The management of adult and paediatric uveitis for rheumatologists

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Abstract

Uveitis encompasses multiple different conditions that are all characterised by intra-ocular inflammation. Uveitis occurs in the context of many different rheumatological conditions and carries a significant risk to vision. It can occur early in the course of rheumatic disease and may even precede other clinical features, or it may present much later. Uveitis can also occur both as a direct or indirect complication of therapies used for patients with rheumatic disease. Conversely, patients with uveitis of non-rheumatic aetiology may require immunosuppression that is not readily accessible to ophthalmologists. Thus, collaborative working between rheumatologists and ophthalmologists is critical for optimal management of patients with uveitis. This review is written with rheumatologists in mind, to assist in the care of patients with uveitis. We collate and summarise the latest evidence and best practice in the diagnosis, management and prognostication of uveitis, including future trends and research priorities.

Introduction

Uveitis is an umbrella diagnosis for a collection of more than 30 diseases, all of which are characterised by intra-ocular inflammation and, untreated, may lead to visual loss[1]. It has an estimated worldwide incidence and prevalence of 17-52/100,000 and 115-204/100,000 respectively[2]. Globally, uveitis accounts for about 5-10% of cases of visual impairment and is responsible for up to a quarter of cases leading to legal blindness in developing countries[3]. It is a significant clinical manifestation associated with multiple rheumatological conditions and associated treatments, impacting both adults and children. An estimated 30% of cases of uveitis are related to systemic immune-mediated diseases[2], with the majority of these diagnoses falling under rheumatology. Therefore, the assessment and management of patients with ocular inflammation, including uveitis, are integral to clinical practice for all rheumatologists.

The effective diagnosis and management of patients with uveitis requires close collaboration with ophthalmologists. This interdisciplinary effort is essential not only for detecting uveitis in "at risk" rheumatology patients, but also for determining a unifying systemic condition for patients who present with uveitis and managing immunosuppressive therapy. There has been substantial progress in developing therapies for uveitis guided by clinical trials, which has significantly improved outcomes for this patient population. However, there remains much work to be done to enable a more precise and personalised approach to patient care.

This article provides a comprehensive overview of the classification, natural history and management of uveitis for rheumatologists, with three major focus areas. Firstly, we highlight the relevant symptoms and signs that rheumatologists may encounter, which will aid in the diagnosis of uveitis and underlying aetiology. Secondly, we collate the latest clinical trial data to support patient management for adult and paediatric patients using a mechanistic approach. Finally, we emphasise the importance of working closely with ophthalmologists to create a unified treatment plan, selecting the most effective therapies to tackle both eye conditions and the underlying rheumatic disease for holistic patient care. This crucial collaboration also allows ophthalmologists access to uveitis treatments through rheumatology, which they might not be able to prescribe independently.

Definition and classification

Uveitis is a collective term encompassing many discrete conditions and is classified by the "Standardization of Uveitis Nomenclature (SUN)" classification system, based on anatomical location, onset, duration and clinical course of uveitis[4,5]. Any, or multiple, areas of the uveal tract can be inflamed in uveitis (Figure 1). Where the inflammation affects a single site, uveitis is classified as anterior (inflammation of the anterior chamber), intermediate (inflammation of the vitreous), or posterior uveitis (inflammation of the retina or choroid). If all three

anatomical structures of the uveal tract (anterior chamber, vitreous and retina or choroid) show evidence of inflammation, this is classified as panuveitis. Patients can have uveitis restricted to two compartments, such as anterior and intermediate uveitis or intermediate and posterior uveitis.

Uveitis is further classified based on onset (sudden or insidious), duration (limited or persistent, where symptoms last less or more than 3 months respectively) and clinical course (acute, chronic and recurrent)[4]. Acute uveitis represents sudden onset inflammation of limited duration, while chronic uveitis is characterized by persistent inflammation lasting less than 3 months without treatment. Recurrent uveitis refers to disease that relapses after a period of inactivity lasting 3 months or more following cessation of treatment.

It is important for rheumatologists to note that the classification of uveitis can help to narrow the differential diagnosis for the underlying aetiology, and thus guide patient management (Tables 1-2). Uveitis in both children and adults can have similar clinical presentations, such as anterior chamber inflammation in anterior uveitis; however, the particular constellation of ocular symptoms and signs can provide clues to the underlying cause when considering the patient's age. The systemic inflammatory causes of uveitis in children are also different from those in adults. For example, in children Juvenile Idiopathic Arthritis-associated uveitis (JIA-U) is the most common systemic cause accounting for up to 21-25% of cases [6]. JIA-U most commonly presents with anterior uveitis, which accounts for >95% of all cases [7,8]. Intermediate, posterior and panuveitis are rare in JIA (Table 2)[8]. In contrast, in adults, uveitis associated with HLA-B27, represents up to 50% of anterior uveitis cases, most common in young adults aged 20 to 40 years [9]. Other significant causes in adults include sarcoidosis, multiple sclerosis (associated with intermediate uveitis)[10], and region-specific conditions like Behçet's disease[11]. Meanwhile, panuveitis, though rare in both age groups, is characteristic of Blau syndrome, where a recent study reported its development in 100% of patients with ophthalmology follow-up for more than 10 years[12].

Aetiology and mechanisms

The diagnosis and management of uveitis sits at the intersection of ophthalmology and rheumatology, requiring close collaboration between these two specialties. Ophthalmologists play a crucial role in the identification and classification of uveitis, while rheumatologists are essential in identifying the underlying aetiology and guiding immunosuppressive therapy when needed. Rheumatologists are skilled in multi-disciplinary care and in the case of uveitis, collaborative working between specialties is vital for optimising patient management.

Uveitis can be broadly categorised based on aetiology. Approximately 50% of cases of uveitis in children and adults have no clear underlying cause[11,13]. The terminology for cases without a clear underlying cause is debated among experts. In this manuscript, we will use the term

"undifferentiated," but it is important to note that terms such as "idiopathic," "incompletely classifiable," "not otherwise specified," and "primary" are also used interchangeably in the literature to describe these cases. The remaining cases occur due to underlying infection, trauma, ocular syndromes, systemic immune-mediated inflammatory diseases (IMIDs), medication reactions and masquerade syndromes (Table 1). Uveitis varies significantly according to population and individual risk factors, with developing countries generally having higher rates of infectious causes (such as tuberculosis), while developed countries more commonly see IMID causes[11]. Masquerade syndromes refer to conditions that mimic uveitis but are caused by non-inflammatory processes, such as intraocular lymphoma or retinal detachment. Among these categories, IMIDs and medication reactions are most frequently encountered in rheumatological practice.

More than a third of cases of uveitis are associated with systemic disease. A thorough history combined with systematic clinical evaluation looking for associated systemic features is key to discerning the underlying condition associated with uveitis (Table 1). The most common IMIDs associated with non-infectious uveitis globally are spondyloarthritis, sarcoidosis and Behçet's disease in adults and JIA in children (Table 1), although prevalence varies by ethnicity[13,14]. Uveitis has also been described for a number of monogenic auto-inflammatory syndromes such as Familial Mediterranean Fever, Blau syndrome and Cryopyrin-associated periodic syndrome[15]. Medication reactions resulting in uveitis have also been described for drugs regularly used in rheumatological practice, such as anti-tumour necrosis factor (TNF) agents[16,17], and bisphosphonates[14,18].

Anti-TNFs are a prominent therapy for patients with IMIDs but ocular complications, including uveitis, are well recognised. Evidence supporting the causative role of anti-TNF medications in uveitis includes cases of new-onset or recurrent uveitis in patients with ankylosing spondylitis who are taking these drugs, particularly etanercept[19]. Hypotheses for this include a cytokine imbalance between TNF and interferon levels, a dose-related phenomenon whereby higher doses are needed to control ocular versus rheumatic disease leading to "breakthrough" ocular inflammation and increased rates of infection with non-caseating granuloma-associated organisms[20].

Bisphosphonates are established first-line treatments for osteoporosis and other metabolic bone diseases. They also have a growing role in adult and paediatric inflammatory rheumatic diseases, including rheumatoid arthritis, Synovitis-Acne-Pustulosis-Hyperostosis-Osteitis syndrome, chronic recurrent multifocal osteomyelitis and juvenile dermatomyositis, due to their dual immunomodulatory and bone remodelling effects. However, a recent large retrospective study using the WHO international pharmacovigilance database found that bisphosphonates accounted for over a quarter of cases of drug-induced uveitis[21]. The proposed mechanism is the release of the inflammatory cytokines IL-1, IL-6 and TNF, which then target the uveal tract[22].

Rheumatologists must maintain a high index of suspicion for various causes of uveitis in their patients, particularly those on immunosuppressive therapies. Uveitis can manifest in several ways in these patients, and understanding these distinctions is crucial for appropriate management. Firstly, uveitis can occur as a primary infectious condition. In this scenario, pathogens such as herpes simplex virus, varicella zoster virus, cytomegalovirus, toxoplasma, tuberculosis, or syphilis directly cause ocular inflammation. Patients on immunosuppressive therapies are also at increased risk of opportunistic infections, which can lead to secondary infectious uveitis. Uveitis can be a manifestation of the underlying systemic IMID itself, such as ankylosing spondylitis, inflammatory bowel disease, and multiple sclerosis. Each of these conditions can have a propensity to develop uveitis in specific anatomical locations, as detailed in Table 2 of the manuscript. Lastly, uveitis can occasionally be a direct consequence of immunosuppressive therapy, namely drug-induced uveitis. Given these multiple potential etiologies, rheumatologists must approach uveitis with a broad differential diagnosis. A comprehensive workup with appropriate imaging and laboratory tests, coupled with close collaboration between rheumatologists and ophthalmologists, is strongly recommended to accurately diagnose and treat uveitis.

In healthy conditions, the eye is immune privileged, with active immune homeostatic mechanisms to maintain tissue health and function[23,24]. In the context of uveitis, immune privilege breaks down. Whilst the underlying mechanisms driving the development of uveitis vary by aetiology and are not fully elucidated, the collective end outcome in an aberrant inflammatory response within the eye, involves both innate and adaptive immune pathways (Figure 2). The anatomy of the eye provides a unique opportunity to both visualise and sample the immune response within the eye. This sampling involves collecting ocular fluids, such as aqueous humor from the anterior chamber or vitreous fluid, to analyze for various purposes, including identifying specific pathogens in infectious uveitis, characterizing immune cell populations and cytokine profiles in non-infectious uveitis, monitoring changes in inflammatory markers or drug levels to gauge treatment effectiveness, and furthering research to better understand the pathophysiology of different uveitic conditions. These procedures, while invasive, are feasible in both adult and pediatric patients when clinically indicated, though rarely performed in children who will require a general anaesthetic. This characterisation contributes not only to diagnosis uveitis and the underlying aetiology, but also provides opportunities to develop and target new therapies.

Diagnosis

Diagnosis of rheumatological conditions requires the integration of a thorough clinical evaluation with laboratory testing (haematological, biochemical, immunological and serological) and/or histological assessment(s) and/or imaging finding(s). Internationally agreed classification criteria exist for many of the systemic diseases associated with uveitis.

This includes adult Behçet's disease (International Criteria for Behçet's Disease[25]), spondyloarthritis (Assessment of Spondyloarthritis International Society classification criteria[26,27]), adult sarcoidosis (World Association of Sarcoidosis and Other Granulomatous Disorders assessment instrument[28]) and JIA (international League Against Rheumatism classification[29]). Given the prevalence of uveitis in these conditions, eye manifestations are listed within the classification or assessment criteria. However, uveitis can precede the onset of other systemic symptoms, with up to 41% of patients diagnosed with axial spondyloarthropathies experiencing uveitis as the first manifestation that leads to diagnostic evaluation[30].

In uveitis, the cornerstone of diagnosis is a slit lamp examination of the eye to detect, localize and quantify ocular inflammation, alongside dedicated ocular imaging. The SUN Working Group comprises international experts to standardise clinical research in uveitis have developed detailed criteria for classifying uveitis. Their first consensus statement was the anatomical classification of uveitis[4] as described earlier. In 2021, the SUN Nomenclature Working Group published their approach to developing classification criteria for the most common uveitides using a machine learning approach in a database of 5,766 retrospectively collected cases of 25 uveitic diseases. The same year the group published disease-specific criteria for those 25 causes of uveitis, predominantly for research use. These included the most common rheumatology associations - Behçet's[31], JIA[32], spondyloarthritis/HLA-B27-associated[33], and sarcoid[34]. Subsequently a study of 522 cases of uveitis from a large uveitis practice showed high concordance (94.3%) between clinical diagnoses and SUN diagnoses, where SUN diseases-specific criteria were available[35]. Concordance further increased to 97% with the inclusion of cases of undifferentiated uveitis, suggesting clinical utility of these classification criteria. For other systemic diseases, uveitis is a recognised manifestation but doesn't form part of the diagnostic or classification criteria, for example cryopyrin-associated periodic syndrome[36], therefore it is important that clinicians maintain a high degree of suspicion with regards uveitis in all patients with systemic rheumatic diseases.

The existence of reciprocal classification criteria for many uveitis-associated rheumatological diseases – as viewed through the lenses of rheumatologists and ophthalmologists – highlights the close interplay between uveitis and systemic diseases. However, the uveitis classification criteria will need to be dynamic; the rheumatology-associated SUN uveitis classification criteria may need updating as classification systems for rheumatological disorders continue to be refined and revised. Furthermore, whilst the majority of uveitis occurring in the context of rheumatology patients is a manifestation of the underlying systemic disease, it is important to rule out infectious causes of uveitis especially for patients who are on systemic immunosuppressive therapies. In some cases, assessment of patients with uveitis will include microbiological and virological investigations such as serological testing and aqueous or vitreous sampling. It is crucial to consider masquerade syndromes, such as intraocular lymphoma, which can mimic immune-mediated uveitis. Misdiagnosis of these conditions and

subsequent immunosuppressive treatment can lead to delayed diagnosis and potentially harmful outcomes. Therefore, a high index of suspicion and appropriate diagnostic workup are essential, especially in cases that are atypical or unresponsive to standard therapy.

Treatment

Deciding on the appropriate treatment strategy for a patient with uveitis is a complex process that requires an individualised and multidisciplinary approach. Providing evidence-based decision-making for uveitis is challenging due to its heterogeneous nature, comparatively low prevalence, and limited randomised controlled trial (RCT) data. The most significant factor in determining the appropriate first-line treatment for uveitis is its anatomical location[37]. For anterior uveitis, the typical first choice is topical corticosteroid drops, except in patients with high-risk disease and poor prognostic features, such as those with JIA-U, where systemic immunosuppression is recommended[38]. For intermediate, posterior, or pan-uveitis, the typical first choice, after excluding infectious causes, includes temporising oral corticosteroids and systemic immunosuppression. Peri-ocular corticosteroid injections and slow-release intravitreal steroid implants are particularly useful for unilateral disease or as adjuncts in uveitic macular oedema. They may also be used for bilateral disease.

Corticosteroid eyedrops

In ophthalmology practice, anterior uveitis is the most common type of uveitis seen in both adult and pediatric patients, accounting for up to 90% of cases in primary care and 50 to 60% of cases in tertiary care[39]. Since the 1950s, the first-line treatment has been topical corticosteroids and mydriatics. Despite the low quality of evidence, which stems from the long-standing acceptance of topical corticosteroids as a standard treatment, frequent initial administration of these agents is generally advised, followed by gradual tapering, with prednisolone acetate 1% being one of the most used formulations. Corticosteroid drops carry an increased risk of cataract formation and glaucoma, which is particularly significant in children due to the added risk of developing amblyopia secondary to cataracts. Uveitis in childhood is further complicated by its typically "silent" nature, with no external signs, and potential issues with medication compliance. In JIA-U, there is growing evidence that instilling topical corticosteroids more frequently than twice a day significantly increases the risk of intraocular pressure elevation, potentially leading to glaucoma and subsequent visual field loss[40,41]. Moreover, administration exceeding three times daily significantly elevates the risk of cataract formation. While in adults, 1-2 drops of topical steroids per day are well-tolerated and generally accepted in clinical practice to maintain remission, in children with JIA-U, the American College of Rheumatology/Arthritis Foundation guidelines recommend initiating systemic immunosuppression[38]. The overarching goal in managing JIA-U is to completely discontinue topical steroids, recognizing their associated risks even at lower frequencies. A low frequency of topical steroids may be tolerated in JIA-U if there are no complications, no

difficulties with instillation or compliance, and regular close follow-up with an ophthalmologist is maintained.

Corticosteroid injections/implants

In adult patients, localized corticosteroid injections have shown efficacy for unilateral, non-vision-threatening uveitis. The SITE study in adults demonstrated that periocular corticosteroid injections led to complete response in 72.7% of patients at 6 months, albeit with risks of cataract (13.8%) and glaucoma (2.4%) surgeries[42]. Sustained-release intravitreal implants have been developed to provide extended steroid release, ranging from 6 to 36 months[43-45]. The POINT RCT in adults showed that intravitreal dexamethasone implants and triamcinolone were more effective than periocular triamcinolone in resolving uveitic macular oedema, with improved vision outcomes[46]. However, these treatments were associated with a higher risk of elevated intraocular pressure. The surgically implanted fluocinolone acetonide device demonstrated efficacy in controlling uveitis in adults but led to high rates of cataract surgery (93%) in implanted eyes. The MUST trial in adults compared this implant to systemic therapy, finding initial superior control with the implant but better long-term visual outcomes with systemic treatment[47]. Recently, the PEACHTREE trial in adults explored suprachoroidal triamcinolone injections, showing promising efficacy in resolving macular oedema without significantly increased risks of elevated intraocular pressure or cataracts compared to placebo[48]. These various approaches to localized corticosteroid administration offer effective options for managing uveitis in adults, particularly for targeting macular oedema and reducing reliance on systemic corticosteroids, but require careful consideration of their respective risk profiles. However, corticosteroid injections are not routinely used in children and young people. A retrospective study of orbital floor corticosteroids in children found that while 74% had a reduction in inflammation, this led to 21% developing cataracts just 5 months after injection, highlighting the potential risks of this approach in paediatric populations[49].

Systemic Corticosteroids

A systemic approach to treatment is often required for posterior segment inflammation and chronic or recurrent anterior uveitis in both children and adults. This approach involves the use of oral corticosteroids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), and biologic disease-modifying drugs (bDMARDs). Systemic corticosteroids are recommended to control acute inflammation in adults when there is a significant risk of vision loss, in cases of bilateral involvement, and increasingly as a bridge to systemic immunosuppression. Treatment typically begins with 1 mg/kg/day of oral prednisolone, up to a maximum of 60mg daily[50]. A systematic review of RCTs in RA demonstrated fewer side effects at a prednisolone dose of 7.5 mg/day over months to years[51]. However, while this dose is considered safer than higher doses, it is still associated with some toxicities. This has influenced consensus guidance in uveitis clinical practice to

recommend tapering oral prednisolone to doses below 7.5 mg or 5 mg once daily, when possible[50]. Systemic corticosteroids are generally avoided in children with uveitis due to significant side effects[38,52], and it should be noted that most dosing recommendations are based on studies primarily in adults. In children, weight-based dosing is a more appropriate approach to minimize these risks. Instead, csDMARDs are preferred as initial therapy, with biologics considered if csDMARDs are insufficient to control inflammation. For severe inflammatory conditions, such as Vogt-Koyanagi-Harada syndrome, or Behçet's disease, a regimen of high-dose intravenous methylprednisolone, may be instituted. Rheumatologists are well-aware of the risks of prolonged high-dose corticosteroid therapy, including decreased bone density, peptic ulceration, mood changes and Cushing syndrome, with associated blood sugar and blood pressure deregulation, and weight gain. Many specialist ophthalmologists are comfortable prescribing oral corticosteroids at high doses, but historically they have been slow to adopt steroid-sparing medications[53]. More recent data suggests an earlier adoption of DMARDs and biologics in line with published guidance[54].

csDMARDs

Effective csDMARDs for the treatment of non-infectious uveitis include the antimetabolites azathioprine (AZT), methotrexate (MTX), and mycophenolate mofetil (MMF), as well as the calcineurin inhibitors cyclosporine and tacrolimus[55]. There are few small placebo-controlled RCTs demonstrating the efficacy of DMARDs in the treatment of adult non-infectious uveitis, partly due to the clinical heterogeneity of uveitides and their early adoption in clinical practice[56,57]. In adults, MMF has been shown to reduce relapses by 40% in non-infectious uveitis[56], while AZT significantly decreased the frequency of uveitis episodes in Behçet's disease[57]. In a comparative RCT of oral MTX vs. MMF, similar rates of treatment success were observed: 64 (66.7%) patients in the methotrexate group vs. 56 (57.1%) in the mycophenolate group[58]. In a small comparative RCT of cyclosporine and tacrolimus, there were similar rates of treatment success: 13 (68.4%) patients in the tacrolimus group vs. 12 (66.7%) patients in the cyclosporine group[59]. The SITE study is the largest retrospective study conducted to date, reviewing medical records of all eligible patients seen at five tertiary uveitis referral clinics in the United States from 1979 to 2005[60]. One year after initiating therapy, sustained control of inflammation was achieved in 62.2% of patients on AZT, 66.0% on MTX, 73.1% on MMF, and 51.9% on cyclosporine[61-64]. While a significant portion of these patients were able to taper oral prednisolone to ≤5 mg daily, treatment failure was observed once prednisolone was discontinued, regardless of the immunosuppressive agent used. Specifically for patients with ankylosing spondylitis who experience recurrent episodes of anterior uveitis, the use of sulfasalazine has been associated with a reduced frequency of episodes[65,66], and international guidelines recommend either sulfasalazine or MTX as first-line csDMARDs[67]. While in adults there is low-quality evidence of comparable efficacy between the csDMARDs discussed[68], in rheumatological conditions with uveitis (Table 1), MTX is considered a reasonable first-line therapy.

In children with JIA-U, consensus guidelines based on several studies examining safety and safety and efficacy[69-72] have recommended that MTX is the first line csDMARD[38,52], with a preference of subcutaneous over oral formulations[38]. Systemic immunosuppression is recommended for active uveitis if poor prognostic factors are present at the first visit, such as male gender, uveitis predating arthritis, poor initial vision, or ocular complications including band keratopathy, glaucoma, hypotony, cataract, intermediate involvement, and macular oedema[38,52]. Additionally, systemic immunosuppression should be considered if there is a poor response to topical treatment after 3 months of follow-up.

bDMARDs

Biologic DMARDs (bDMARDs) have revolutionised the fields of rheumatology and ophthalmology, with their use being essential for optimal patient outcomes. Close cooperation between these specialties is paramount, as it often enables ophthalmologists to access treatments, they might not be able to prescribe otherwise. Many studies in uveitis have focused on anti-TNFs, with the strongest evidence supporting adalimumab[73-75]. Adalimumab and golimumab are fully human monoclonal anti-TNFs, consisting entirely of human protein sequences. Infliximab is a chimeric monoclonal anti-TNF, combining human constant regions with murine variable regions. Etanercept is a fusion protein composed of the extracellular ligand-binding portion of the human TNF receptor linked to the Fc portion of human IgG1. Certolizumab pegol is a unique pegylated Fab fragment of a humanized anti-TNF-α monoclonal antibody. It lacks the Fc portion found in full antibodies and has a polyethylene glycol chain attached. These structural differences influence each biologic's pharmacokinetics, immunogenicity, and mechanisms of action in treating uveitis.

We will first discuss the evidence of bDMARDs in adults, where, unless otherwise stated, the participants had non-infectious posterior segment uveitis (NIPU), which includes intermediate, posterior, and panuveitis. These studies have encompassed a diverse range of uveitis patients, including those with undifferentiated uveitis, Behçet’s disease, and sarcoidosis. The VISUAL studies were international, double-blind, placebo-controlled RCTs that demonstrated the efficacy of adalimumab in treating adults with NIPU[74-76]. In both the VISUAL-I trial for patients with active uveitis and the VISUAL-II trial for patients with inactive uveitis, the risk of treatment failure was reduced by half, and the time until treatment failure was nearly doubled[74,75]. While the VISUAL studies included rheumatological populations such as Behçet’s disease and sarcoidosis, additional lower-quality studies in specific populations have shown supporting evidence for other conditions, such as ankylosing spondylitis and Blau syndrome[15,77]. For a more comprehensive review of biologic therapy in uveitis associated with other monogenic autoinflammatory syndromes, our previous work provides a more extensive overview[15]. In summary, while treatment options for monogenic autoinflammatory syndromes typically begin with conventional therapies like colchicine, NSAIDs, and

corticosteroids, they often progress to more targeted biologic therapies. Biologic treatments, particularly IL-1 inhibitors (such as anakinra, canakinumab, and rilonacept) and anti-TNFs (like adalimumab and infliximab), have shown efficacy in managing both systemic and ocular manifestations of these disorders, with the choice of agent depending on the specific syndrome and its underlying molecular pathway[15]. Biosimilars are being rapidly developed as patent rights for original biologics expire. A comprehensive review of studies comparing adalimumab to its biosimilars in rheumatoid arthritis, psoriasis, and inflammatory bowel disease revealed comparable efficacy, safety, and immunogenicity profiles[78]. Additionally, smaller studies focusing on uveitis patients demonstrated that transitioning from adalimumab to biosimilars was both safe and effective[79].

Infliximab has similarly shown promising results in reducing inflammation, improving visual acuity and reducing the steroid burden in open-label and retrospective studies of NIPU, anterior and Behçet's uveitis[80-83]. There is moderate non-randomised prospective and retrospective evidence to suggest that golimumab, in patients with AS reduced the occurrence of anterior uveitis episodes, leading to remission and improving visual acuity[84-86]. Similarly, certolizumab pegol has demonstrated a reduced rate of anterior uveitis episodes in patients with axial spondyloarthritis[87,88]. Importantly for rheumatologists, several studies, including RCT evidence, have shown that while the incidence of uveitis decreases after starting anti-TNFs like infliximab and adalimumab, it actually increases with etanercept[89,90]. Therefore, expert guidance strongly recommends against using etanercept in patients with ocular inflammatory disease, instead advocating for infliximab or adalimumab as the preferred treatment options[37,91].

The development of anti-adalimumab and anti-infliximab antibodies is an additional consideration in the treatment of uveitis. In the VISUAL studies, all patients who developed antibodies against adalimumab experienced treatment failure[74]. While there is no unifying guideline regarding the significance of these antibodies, evidence suggests that in uveitis, anti-adalimumab antibodies are associated with a reduced treatment response[92,93]. Concomitant immunomodulatory therapy, commonly with MTX or MMF, reduces the likelihood of antibody development. In patients with Crohn's disease treated with infliximab, concomitant immunomodulatory therapy also decreases the formation of anti-infliximab antibodies and prolongs the effectiveness of infusions[94], although this effect has been disputed in patients with uveitis[95,96]. When patients develop anti-drug antibodies and experience reduced treatment efficacy, switching to another anti-TNF agent may be beneficial[97]. This strategy allows continued targeting of TNF while potentially overcoming the limitations imposed by anti-drug antibodies. While the evidence supporting anti-TNFs in uveitis treatment is robust, particularly for adalimumab and infliximab, the data for other classes of biologic agents is generally less extensive, with most studies being smaller in scale or of lower quality.

Another medication in the rheumatology arsenal, secukinumab, a monoclonal antibody targeting interleukin-17A, has not yielded positive results in uveitis trials, despite being licensed for the treatment of psoriatic arthritis and ankylosing spondylitis. Secukinumab did not demonstrate efficacy for Behçet's uveitis and non-Behçet's uveitis in three phase III multi-centre, double-blind, placebo-controlled RCTs of subcutaneous administration, leading to premature halting[98]. A smaller RCT similarly showed a low response following subcutaneous secukinumab, although higher responder rates were observed with intravenous administration[99]. The efficacy of secukinumab in these conditions remains inconclusive, with some guidelines advising against its use[100]. Bimekizumab, a monoclonal antibody that selectively inhibits both IL-17A and IL-17F, was studied in adult patients with axial spondyloarthritis to assess its effect on uveitis[101]. These findings suggest that bimekizumab may offer protective benefits against uveitis, lowering incidence of uveitis (0.6%) compared to placebo (4.6%).

Another approach for treating NIPU in adults has been targeting IL-6. Tocilizumab has the largest body of evidence for efficacy, showing significant reductions in uveitis and improvements in visual acuity in a phase 2 trial[102,103]. This trial randomised patients to receive either 4mg or 8mg of IV tocilizumab, including adults with undifferentiated uveitis, sarcoidosis, and Behçet's disease. However, the route of administration may impact efficacy. While IV tocilizumab has shown promise, the APTITUDE trial, which used subcutaneous (SC) tocilizumab in children with JIA-U, showed a lower response rate of only 33.3% by month 3[104]. Sarilumab, which also inhibits IL-6 receptor signaling, has demonstrated efficacy in a placebo-controlled RCT for adults with NIPU, resulting in reduced inflammation, lower steroid dependence, and enhanced visual acuity[105]. Abatacept is a fusion protein that modulates T-cell activation by binding to CD80 and CD86, preventing their interaction with CD28 on T cells. Abatacept has shown some promise in treating adults with NIPU, as a prospective study in birdshot uveitis demonstrated that it was well-tolerated and reduced most of the clinical inflammatory parameters[106]. However, this did not translate to an improvement in visual acuity. Rituximab is a monoclonal antibody that targets CD20, leading to the depletion of B cells and has been used as a third-line bDMARD in treating NIPU and appears to be effective and well-tolerated, particularly in patients with Behçet's uveitis[107]. JAK inhibitors have been more recently used for the treatment of NIPU that does not respond to other bDMARDs[108]. The strongest current evidence supports the use of filgotinib, as demonstrated by a placebo-controlled RCT showing a reduction in adults with NIPU flares with good tolerability[109]. Filgotinib has been approved for the treatment of adults with rheumatoid arthritis and inflammatory bowel disease in the European Union, Great Britain, and Japan, but it has not yet been approved in the United States.

In children with JIA-U, several RCTs have been conducted on bDMARDs, with the strongest evidence supporting the use of adalimumab[110,111]. Adalimumab has been shown to prevent treatment failure in patients with JIA-U who were already stable on MTX[110], and to improve

uveitis in patients who had shown an inadequate response to topical steroids and MTX[111] in placebo-controlled RCTs. The timing of discontinuing adalimumab in stable patients is currently under investigation in RCTs[112], as previous long-term follow-up data revealed a high rate of relapse and the need to restart adalimumab after stopping the treatment[113]. Early non-randomised studies have demonstrated the efficacy and tolerability of infliximab at higher doses (6-10 mg/kg every 4-6 weeks)[114,115], with no efficacy observed at lower doses (3-5 mg/kg every 6-8 weeks). Our recent findings suggest that infliximab can be effective in patients who did not respond to adalimumab, indicating that 'in-class switching' among anti-TNFs may have a role in management[97]. The ACR guidelines recommend increasing the dose/frequency of a anti-TNF over switching for children with JIA who do not respond to the standard dose, and switching to another anti-TNF over trying a different biologic if the higher dose also fails[38]. Non-randomised studies have shown efficacy of tocilizumab in JIA-U with intravenous administration[116]. However, in a phase 2 non-randomised trial, our examination of subcutaneous administration of tocilizumab did not meet the primary end point[117]. This study does suggest a role for tocilizumab in a third of those refractory to adalimumab and MTX. It is possible that intravenous administration of tocilizumab and a biomarker driven approach might maximise the success of tocilizumab for JIA-U. We are currently conducting adaptive design clinical trials in JIA-U of secukinumab[118] and baricitinib[119]. The ACR guidelines suggest that for patients who have failed MTX and two anti-TNF at above-standard dose and frequency, abatacept or tocilizumab are recommended as alternatives[38]. Other biologic agents have fewer data, typically consisting of small retrospective case series, and they have therefore been excluded from the scope of this review. Table 3 summarises the evidence levels for various bDMARDs used in the treatment of uveitis in both adults and children, including specific considerations for dosage and administration, and indicating whether the medications are licensed by NICE or FDA.

Prognosis

Visual prognosis in uveitis depends on the anatomical location and duration and severity of inflammation[120]. In adults with uveitis, posterior segment inflammation is typically associated with reduced vision at presentation, and a poorer visual outcome compared with anterior uveitis[121]. Systemic diseases with poorer prognosis in the longer term include Behçet's disease and Blau syndrome. A retrospective study involving 175 pediatric and adult patients with Behçet's disease reported a mean visual acuity of 0.39 logMAR (approximately 20/50 Snellen) at presentation and 0.34 logMAR (approximately 20/40 Snellen) at 60 months[122]. Blau-associated uveitis also carries a poor visual prognosis with 80% of eyes having a visual acuity of >0.3 (worse than 6/12) at 20 years in one retrospective study[12]. Conversely, HLA-B27 associated acute anterior uveitis tends to have a good visual prognosis with a 10-year median visual acuity of 0.1 LogMAR (6/7.5 Snellen), although ocular complications, including posterior synechiae and cataract, are common[123]. Similarly, patients with sarcoid-associated

uveitis also have good visual outcomes with a median visual acuity at 10 years of 0.0 (6/6), but high rates of cataract and macular oedema[124].

Maintenance of visual acuity in the medium term has been demonstrated in clinical trials of biologic treatment and intravitreal steroid therapy. The Visual III study, looking at 78 weeks of follow up data of adalimumab in non-infectious adult uveitis, showed an overall improvement in visual acuity in patients entering the study with active disease, and stable visual acuity in those with inactive disease at baseline[76]. Five year follow up of a cohort of participants in the SYCAMORE trial of adalimumab for JIA-U similarly showed stable visual acuity[113]. Intravitreal fluocinolone implants are effective at improving visual acuity over 36 months in adults, but the majority of patients require cataract surgery by 3 years[125].

Due to the high risk of asymptomatic uveitis and potential visual loss in children, targeted screening programs, particularly for JIA-U, are implemented to ensure early detection and effective management of uveitis[38,126]. Visual outcomes in children with JIA-U have improved over the last 10 years, with a median 5-year visual acuity of -0.1 (6/5) at 5 years and a reduction in cataract and glaucoma surgery[127]. This is likely to be due to earlier use of systemic therapies, biologic treatments and better screening for uveitis[128]. However, sight loss and ocular surgery are still common in adults with JIA-U[129]. A recent retrospective study of 166 pediatric uveitis patients, including JIA-associated cases, showed 72.9% received conventional immunosuppressants and 34.9% biologics[130]. Within this cohort, 7.3% developed cataracts, 8.1% had elevated intraocular pressure, and 0.9% required intraocular surgery. Visual acuity deterioration to worse than 20/200 occurred at 0.01 per eye-year.

Future directions

There remain several key priorities in relation to uveitis care (Table 4) – from early detection, diagnostic accuracy and prognostication, to identifying novel drug targets and precision therapies. With the growing availability of multi-omic datasets and disease registries, combined with the increased awareness of the need for large scale research collaborations, progress is being made in many areas.

Risk stratification, diagnosis and prognostication

Early detection and diagnostic accuracy are paramount, given the poor prognosis and risk to vision posed by uveitis. In the paediatric setting, JIA-U screening aids early detection but poses a significant burden on patients, families and health resources. The UK-based “ChiLdhood arthritis and its associated Uveitis: Stratification Through Endotypes and mechanism to delivER benefit (CLUSTER)” consortium is a unique example of a national alliance between clinicians, academics and industry partners aiming to define disease endotypes, and integrate these with prognostic biomarkers and treatment responses to develop a stratified medicine

approach for children with JIA and JIA-U[131]. The consortium and collaborators have recently presented data on the use of genetic biomarkers[132] for JIA-U risk stratification. Anterior segment OCT is emerging as an imaging modality for diagnosing and monitoring anterior uveitis in adults[133] and children[134], and could be further augmented using artificial intelligence[135]. However, there is a demonstrable need for ethnically diverse normative datasets using this approach[136].

Monitoring disease activity

Robust disease activity monitoring and biomarkers of treatment response will be critical to informing treatment withdrawal study design. Monitoring disease activity and treatment responses using tear samples in children and adults has had limited success[137,138]. The recently validated UVEDAI uveitis disease activity index in adults includes key indicators such as anterior chamber cell grade, vitreous haze, central macular edema, inflammatory vessel sheathing, papillitis, and choroidal/retinal lesions[139,140]. Patient evaluations are also incorporated. However, there is currently no validated tool for children. A recent open-label study in children with idiopathic, JIA or Behçet's associated uveitis assessed the ability to taper and withdraw adalimumab after a period of remission. However, the study reported a high uveitis recurrence rate, with only 4 out of 7 patients with Behçet's maintaining remission six months after stopping adalimumab[141], highlighting the need for tools not only to monitor disease activity but also to assess the likelihood of maintaining inactivity and guide therapeutic decisions. The ADJUST RCT, examining withdrawal of adalimumab for patients with JIA-U and 12 months of well controlled ocular inflammation[112], will imminently be reporting their findings.

Novel therapies

A proportion of patients remain intolerant of, or resistant to, current agents for treating uveitis. In addition to established treatments, several promising clinical trials are currently in progress. Researchers are investigating systemic therapies such as brepocitinib (TYK2/JAK1 inhibitor)[142], izokibep (IL-17A inhibitor)[143], and ustekinumab (IL-12/23 inhibitor)[144], as well as the intravitreal vamikibart (IL-6 inhibitor)[145]. The recent availability of large-scale genome wide association data for non-infectious uveitis in adults[146], means that genetic epidemiology methods for drug discovery[147] are now on the horizon. Research is also ongoing into advanced drug delivery systems, such as nano-based technologies, to improve drug availability of existing therapies whilst minimising systemic side effects[148]. While these have shown promise in animal models of experimental autoimmune uveitis[149], they have yet to be assessed in humans.

Conclusions

Uveitis is a wide-reaching condition affecting many adults and children with rheumatological diagnoses. Relevant to rheumatology, uveitis can occur as a direct result of systemic IMID or

associated therapies, or from ocular infections in the context of systemic immunosuppression. In this review we have underscored the need for effective collaborative working between rheumatologists and ophthalmologists to discern the underlying uveitis aetiology and guide patient care. With a growing number of therapies available to treat uveitis, prognosis for patients with uveitis in improving. Advancing our understanding of disease mechanism is helping to guide new therapies and treatment escalation strategies. However, there remains considerable unmet need for precision medicine approaches and novel therapies for this patient population, particularly those with refractory uveitis. Addressing these unmet needs will require large-scale multi-disciplinary partnerships to address.

Key points

- Uveitis accounts for up to 10% of visual impairment globally, highlighting the need for prompt recognition and management.
- TNF inhibitors have significantly improved outcomes in both adult and paediatric uveitis, with the strongest evidence for adalimumab. An exception is etanercept, which worsens uveitis.
- The second-line biologic option for uveitis are IL-6 inhibitors, with IV tocilizumab having the most substantial supporting evidence.
- Collaborative work between rheumatologists and ophthalmologists is critical for optimal management of uveitis.
- More trials are needed in uveitis, as there is a wide array of novel molecules available for systemic rheumatic diseases that need to be explored for therapeutic use in uveitis.

Figure Legends

Figure 1 Clinical Presentation in Uveitis

The figure illustrates the presenting symptoms and signs associated with different types of uveitis. Rheumatological conditions can manifest as various uveitis subtypes, making it crucial to consider these potential presentations during rheumatology clinic evaluations. If there is any evidence of ocular involvement, a referral to ophthalmology is recommended for further assessment and management. An important exception is Juvenile Idiopathic Arthritis-Associated Uveitis, which typically causes symptomatically silent chronic anterior uveitis. The figure will be professionally redrawn by the NRR graphics team.

Figure 2 Pathogenesis of uveitis and therapeutic targets

This figure illustrates the immunopathogenesis of uveitis. Within the thymus and bone marrow, the process of central tolerance eliminates lymphocytes with receptors specific for self-antigens through positive and negative selection. However, some cells with low affinity for self-antigens escape the thymus and, alongside deficient peripheral tolerance, circulate in the bloodstream. APCs present ocular antigens or PAMPs mimicking self-antigens to naive T-cells, leading to their activation and differentiation into TH1 or TH17 phenotypes. These activated T-cells migrate and infiltrate the eye, where they secrete pro-inflammatory cytokines, causing a breakdown of the blood-retina barrier and recruitment of macrophages and neutrophils. This cellular activity can be observed in the anterior chamber as AAU and in the vitreous humour as IU. The pro-inflammatory cytokines can induce thrombotic vasculitis, focal inflammation in the choroid or retina, and leakage of fluid from retinal vessels, leading to optic disc swelling and uveitic macular oedema. The specific cells and predominant antigens involved in each patient with uveitis depend on the underlying disease process, resulting in different ocular phenotypes. Medications targeting the various cytokine and signalling pathways are indicated in green lettering. All cytokines within a green box depend on JAK signalling and are therefore susceptible to treatment with JAK inhibitors. The figure

will be professionally redrawn by the NRR graphics team; AAU: Acute Anterior Uveitis, APCs: Antigen-Presenting Cells, IU: Intermediate Uveitis, PAMPs: Pathogen-Associated Molecular Patterns, TH1: T Helper 1, TH17: T Helper 17.

Competing interests

The authors declare no competing interests.

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