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Acute Anterior Uveitis and Spondyloarthritis: More Than Meets the Eye

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Abstract Ankylosing spondylitis (AS) and related forms of spondyloarthritis (SpA) are associated with some extra-articular features, and the most common symptomatic association is with acute anterior uveitis (AAU). Thus, approximately 40 % of patients with AS will experience a sudden onset of a unilateral anterior uveitis sometime during the course of their disease. Patients with AAU, especially those who are HLA-B27 positive, should be questioned about inflammatory low back pain and also evaluated for other clinical features of SpA. Since a prolonged delay in diagnosis is common among SpA patients and occurrence of AAU may be the reason for their first interaction with medical care, occurrence of AAU presents a unique opportunity for identifying such undiagnosed SpA patients. Therefore, a novel evidence-based algorithm called Dublin Uveitis Evaluation Tool (DUET) has been proposed to guide ophthalmologists and primary care physicians to refer appropriate AAU patients to rheumatologists. In a large two-phase study, approximately 40 % of patients presenting with idiopathic AAU were noted to have undiagnosed SpA, and DUET algorithm was noted to have excellent sensitivity (96 %) and specificity (97 %). It has a positive likelihood ratio (LR) 41.5 and negative LR 0.03. In most instances, the eye inflammation responds well to corticosteroid and mydriatic eye drops and without the need for additional therapy. Use of oral corticosteroids is reserved for patients, especially with associated chronic inflammatory bowel disease or psoriatic arthritis presenting with bilateral, chronic, anterior, and/or intermediate uveitis, and this treatment is rarely needed for more than a couple of weeks. A very small percentage may be more refractory to such treatment and require potential novel therapies, including the use of tumor necrosis factor blockers.

Keywords Uveitis · Acute anterior uveitis · Iritis · Spondyloarthritis · Ankylosing spondylitis · Psoriatic arthritis · Inflammatory bowel disease · HLA-B27 · DUET algorithm · Diagnosis · Treatment · Anti-tumor necrosis factor

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Introduction

Ocular inflammation is common in many rheumatologic diseases but with variable prevalence, and the major types include uveitis, conjunctivitis, scleritis, retinal vasculitis, dry eye syndrome, orbital inflammation, and neuro-ophthalmic lesions. Uveitis means an inflammation of the uvea, which is the middle layer of the eye and can be recognized as the pigmented layer of the eye ball. Uvea consists of the iris, ciliary body, and choroid. Iris pigment determines the eye color, and the iris reacts to light like a camera shutter. The ciliary body secretes aqueous humor and helps suspend the crystalline lens. The uvea is richly supplied with blood. Uvea is divided into anterior, intermediate, and posterior segments,

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and uveitis is classified by the location of inflammation into the following:

- anterior uveitis involving the iris (iritis) or the ciliary body (cyclitis) iritis or both (iridocyclitis)
- intermediate uveitis involving the vitreous humor and/or peripheral retina, which is known as the pars plana
- posterior uveitis involving the choroid or, by extension, the retina: choroiditis or retinochoroiditis
- panuveitis, which refers to an involvement of all three segments. If two adjacent segments are involved, descriptive terms such as anterior and intermediate uveitis or intermediate and posterior uveitis are used

Neither the aqueous humor nor vitreous humor is a part of the uveal tract. However, the detection of leukocytes in the aqueous or vitreous humor is the hallmark of an anterior or intermediate uveitis, respectively. Laterality defines uveitis as unilateral or bilateral, and the clinical course allows a further sub classification into acute (less than 3 months), chronic (more than 3 months), or recurrent uveitis (a flare after recovery from a first episode).

This review limits itself to the acute anterior uveitis (AAU) seen in association with inflammatory rheumatic diseases grouped under the term spondyloarthropathies or spondyloarthritis (SpA) that encompasses ankylosing spondylitis (AS), inflammatory bowel disease (IBD) associated arthritis, psoriatic arthritis (PsA), reactive arthritis, and undifferentiated SpA [1, 2•]. Uveitis is the most common extra-articular feature of SpA over the entire course of the disease, preferentially in HLA-B27-positive patients [2•]. AAU classically presents with a red, painful eye, photophobia, and blurring of the vision. Although infectious and neoplastic causes exist, the majority of cases are presumed to be immune in origin, and this is reflected in the high prevalence of systemic disease among patients with AAU [2•, 3]. However, there are similarities as well as distinct differences in the patterns of uveitis in the various regions of the world because of geographical, environmental, and genetic differences [4–8].There are many recent advances in the field of immunopathology, and several immunological pathways are now known to be involved in the development of uveitis. It may be caused by several mechanisms, such as infectious, inflammatory (no obvious infection), autoimmune, or idiopathic [4–9]. It is of interest that occurrence of uveitis, including anterior uveitis, has been reported after clearance of viremia from infection with Ebola virus [9]. New insights have been achieved by animal models and gene mapping, and a possible role of gut and skin microbiome is also being investigated [7, 10•, 11••, 12].

The pattern of uveitis seen in association with AS (sudden onset, anterior, unilateral, recurrent, more often male) tends to differ from the pattern often seen with either PsA or IBD (insidious onset, anterior and intermediate, bilateral, chronic, and more often female) [2•]. Occurrence of AAU episodes in AS has a 1- to 2-day prodrome with eye pain before cells in the anterior chamber can be detected by slit lamp examination. This inflammation can sometimes be intense and result in hypopyon (settling down of the inflammatory cells at the bottom of the anterior chamber of the eye), fibrin exudation, and even posterior synechiae (the pupil becoming attached to the lens posterior to it), but most patients recover full vision, usually within 2 months [2•]. The uveitis episodes have been reported to be unilateral in 52 % of the cases, "flip-flop," meaning that both eyes are involved but not simultaneously, in 42 %, and bilateral in 6 % in one study [2•]. But among patients with SpA associated with IBD, the uveitis was 19 % unilateral, 19 % flip-flop, and 63 % bilateral. AAU in association with AS is more frequent in males (65 %), but 88 % of AAU SpA patients with IBD are females. Females who develop uveitis may have less classic HLA-B27-associated uveitis (i.e., insidious rather than abrupt onset) as well as atypical SpA (perhaps because "typical" was initially defined in male patients) [10•].

Epidemiology

It has been shown consistently that AAU is the most common type of uveitis. For example, among 3000 new patients with uveitis attending a specialist uveitis clinic in England during a 22-year period, the anatomical distribution of uveitis was as follows: anterior 46 %, intermediate 11.1 %, posterior 21.8 %, and panuveitis 21.1 % [6]. Uveitis occurs in up to 50 % of patients with AS during course of their disease, and in contrast, it affects roughly 2 to 5 % of patients with IBD and approximately 7 % of patients with psoriatic arthritis [2•]. Uveitis occurrences do not appear to be related temporally with the activity or severity of underlying SpA [13].

The incidence of uveitis has been reported to range from 19 to 88 per 100,000 person-years [12]. A retrospective medical record review of 241 patients with AAU presenting to Sydney Eye Hospital in Australia between June 2009 and June 2011 was performed to evaluate the patterns of acute and recurrent AAU [14]. Only patients who underwent typing for the HLA-B27 antigen were included in this study; 95 patients were HLA-B27-positive, and 146 were HLA-B27-negative. SpA (n=26, 11 %) was the most common associated systemic disease in the HLA-B27-positive patients. Posterior synechiae were the most common complication, and occurrences of cataract, ocular hypertension, secondary glaucoma, and cystoid macular edema were more common in HLA-B27-negative patients with a recurrent disease course. This study adds further evidence that HLA-B27-negative patients have a poor visual prognosis [14].

In another report where 514 patients with anterior uveitis were evaluated, the most frequent form of SpA was AS

(64.1 %), and with regard to the type of uveitis, acute unilateral recurrent anterior uveitis was the most frequent clinical pattern in the group as a whole (68.3 %), observed in all subgroups, except for the IBD related SpA, which presented anterior and intermediate uveitis as the most frequent pattern [15]. Approximately 50 % of patients with sudden onset, unilateral, anterior uveitis that tends to be recurrent (and these recurrences sometimes affect the contralateral eye) possess HLA-B27 [4, 12]. The HLA-B27-positive AAU is the most common form of uveitis in Europe and North America, being roughly four times as common as intermediate or posterior uveitis [4].

The duration of the underlying SpA has also been shown to associate with the development of AAU [16, 17•]. Additionally, a recent French study evaluated the prevalence and the factors associated with uveitis in SpA patients in a nationwide cross-sectional study in which 202 participating rheumatologists recruited 902 patients (males 61 %), with a mean age of 45.3±13.4 years and a mean disease duration of 10.4± 9.6 years. Among these patients with SpA, 71 % had AS, 18 % had psoriatic arthritis, and 11 % had other types of SpA [18]. HLA-B27 was present in 76 % of the patients. Prevalence of uveitis was 32.2 % (95 % confidence interval (CI) 29.1–35.3 %) and was recurrent in 52.3 %. Uveitis was the most common extra-articular feature of SpA, and it occurred preferentially in HLA-B27-positive patients (adjusted odds ratio=2.97 [95 % CI 1.83–4.81]) and with longer disease duration (≥10 years; adjusted odds ratio=1.28 [95 % CI 1.16–1.41]). Similarly, the prevalence of uveitis in another French study was observed to be 32.7 % in a review of close to 2000 patients with SpA. This prevalence was even higher in HLA-B27-positive patients with an odds ratio of 4.2. The observed uveitis was acute in 88 %, anterior in 90 %, and unilateral in 87 %, with recurrence in 50 % [19].

Genetic Predisposition

HLA-B27 is the major genetic factor associated with AAU in SpA, and AAU is significantly more common in HLA-B27-positive than in HLA-B27-negative patients with AS [8, 20, 21]. We had studied 175 consecutive patients with AS, the first 131 patients were tested for HLA antigens of the A and B loci, and the remaining 44 patients were typed only for HLA-B27 [21]. AAU was significantly more common in HLA-B27-positive patients, occurring in 40 of 144 HLA-B27 positive (27.7 %) and in only 3 of 31 HLA-B27-negative patients (9.7 %) ($p<0.05$). Among the HLA-B27-positive AS patients, AAU occurred in 24 of 68 patients (35 %) who also possessed HLA-A2 and in only 5 of 35 patients (14 %) who lacked HLA-A2 ($p<0.025$). We had concluded that associations in the MHC region with AS are not completely explained by HLA-B27 [21]. This has now been amply confirmed by high-intensity genotyping [22••].

Moreover, an association of HLA-A2 (now called HLA-A*0201) with AS at genome-wide significance level has also been reported [22••]. We had also observed that individuals apparently homozygous for HLA-B27 are about three times more susceptible to developing AS than are B27 heterozygotes [23]. This has now been confirmed [22••, 24], and HLA-B27 homozygosity was more prevalent in HLA-B27-positive cases than in HLA-B27-positive controls (OR= 2.07; $P=0.0025$) [22••]. But homozygosity for HLA-B27 does not influence clinical manifestations, functional disability, or radiographic damage in AS [25, 26].

A high-density genotyping to investigate the genetic associations of AAU has recently been investigated in 1711 patients with AAU (either primary or combined with AS), 2339 AS patients without AAU, and 10,000 control subjects [27••]. In addition to the known strong association with HLA-B27, significant association with three non-major histocompatibility complex loci, *IL23R*, the intergenic region *2p15*, and *ERAP1*, was also observed. Moreover, five loci harboring the immune-related genes *IL10-IL19*, *IL18R1-IL1R1*, *IL6R*, the chromosome 1q32 locus harboring *KIF21B*, as well as the eye-related gene *EYS*, were also associated at a suggestive level of significance. These findings of both novel AAU-specific associations and associations shared with AS demonstrate overlapping but also distinct genetic susceptibility loci for AAU and AS, and the associations with *IL10* and *IL18R1* are shared with IBD suggesting common etiologic pathways.

Undiagnosed SpA Common Among Patients Presenting with Uveitis

Undiagnosed SpA is quite common in patients presenting with AAU. For example, one study has shown that about one quarter of 514 anterior uveitis patients had SpA, and among these SpA patients, 53 % had undiagnosed SpA when they presented to their ophthalmologists. In other words, among more than half of them (53 %), the diagnosis of SpA was arrived at after an episode of uveitis [15]. So, uveitis can be an important initial manifestation of underlying SpA. For example, in a study, 18 % of 394 anterior uveitis patients had SpA, and for 41 % of these SpA patients, uveitis was the first interaction with medical care for underlying SpA [27]. Now, if we look at the prevalence of underlying SpA in HLA-B 27-positive uveitis patients only, it has been reported to be very high, and two recent studies have shown this to be as high as 76 % [28, 29].

Many patients presenting with HLA-B27-positive AAU have undiagnosed AS or related SpA. Rheumatologic evaluation of 175 consecutive such patients revealed that 136 cases (77.7 %) had an HLA-B27-associated extra-articular disorder

(46.3 % with associated AS, 9.7 % presumed AS, 12.0 % undifferentiated SpA, and 9.7 % with other HLA-B27-associated disease). The male-to-female ratio was 1.3 to 1, and the median age at the time of the first attack of uveitis was 31 years. Among 117 patients (66.9 %) with more than 1 episode of uveitis, same eye attacks were observed in 48 of 117 patients (41.0 %). The median +/− SD frequency of active episodes of uveitis was 0.8+/−0.6 per year and decreased as the duration of the disease lengthened [30]. Thus, AAU is an important clue to the diagnosis of SpA.

A Chinese retrospective study of 504 HLA-B27-associated AAU patients found that 387 patients (76.8 %) had SpA (214 had AS (42.5 %) and 150 (29.8 %) had undifferentiated SpA). These 387 patients with SpA had an earlier onset of uveitis (p=0.01) and a greater number (six or more) of flares (p= 0.03) when compared with the 117 AAU patients without SpA [28]. Interestingly, Munoz-Fernandez et al. evaluated presence of enthesis lesions in patients with idiopathic recurrent AAU and noted that a high percentage of patients with HLA-B27-positive recurrent AAU without features of SpA showed evidence of enthesis lesions similar to those observed in patients with SpA. Therefore, they have suggested that patients with recurrent, HLA-B27-positive AAU may suffer from an abortive or incomplete form of SpA [31].

The majority of studies on the prevalence of SpA among patients with AAU have relied on radiographic evidence for sacroiliitis in order to diagnose AS. However, it is common to have symptomatic sacroiliitis without changes on plain x-ray. The prevalence of uveitis in these patients with non-radiographic axial SpA is equal to the prevalence in those with radiographic disease [32]. Accordingly, studies based on radiographic changes underestimate the relationship between AAU and SpA. Thus, the relatively recent criteria suggested by Assessment of SpondyloArthritis international Society (ASAS) indicate that the combination of inflammatory back pain, anterior uveitis, and positivity for HLA-B27 is sufficient to classify a patient as having axial SpA [33].

When an Ophthalmologist Should Make a Rheumatology Referral

Since a significant delayed diagnosis is common among SpA patients [34], uveitis presents a unique opportunity for identifying such undiagnosed SpA patients, and studies clearly show that AAU may frequently be the first interaction with medical care [15, 27]. A need for a close collaboration between rheumatologists and ophthalmologists cannot be overestimated. No one should wonder why rheumatologists might be interested in uveitis patients attending ophthalmology clinics. However, unfortunately, the major hurdle in this cross talk of specialties has been a lack of formal guidelines or referral pathways to help select appropriate AAU patients for referral from ophthalmology to rheumatology. A novel evidence-based algorithm called Dublin Uveitis Evaluation Tool (DUET) has been recently proposed to guide ophthalmologists to refer appropriate AAU patients to rheumatology [35••] (see Fig. 1) that will aid the early detection of undiagnosed SpA in patients presenting with AAU. In this large two-phase study, approximately 40 % of patients presenting with idiopathic AAU were noted to have undiagnosed SpA, and DUET algorithm was noted to have excellent sensitivity (96 %) and specificity (97 %). It has a positive likelihood ratio (LR) 41.5 and negative LR 0.03 [35••].

Impact of Uveitis Among Patients with SpA

Uveitis, like AS and related SpA, more commonly affects the working population, with onsets of symptoms earlier in life than those with age-related eye diseases such as cataracts, glaucoma, and age-related macular degeneration. [36] In western countries, uveitis accounts for approximately 10 % of visual disability, and up to 35 % of patients with uveitis have been reported to have significant visual impairment or legal blindness. [37, 38] Many patients without such decrease in visual acuity may experience floaters, increased light sensitivity, alteration of depth and color perception, and decreased contrast sensitivity that result in impaired quality of life [39].

Presence of AAU in AS patients may be a prognostic marker for worse outcome, as it has been shown to associate with higher disease activity, poorer functional ability, and physical mobility in a report from Taiwan [40]. Similarly, the 12-year follow-up data from the Outcome in Ankylosing Spondylitis International Study (OASIS) show that the history of AAU is associated with more radiographic damage (OR 1.02 (95 % CI 1.00, 1.04)) [41].

Data from the French national cohort DESIR were used to study the impact of uveitis in patients with inflammatory back pain (IBP) suggestive of recent SpA [16, 17•]. This is a prospective, multi-centered cohort of 708 patients with early IBP suggestive of SpA. Uveitis was defined by an ophthalmological episode diagnosed as uveitis by an ophthalmologist or a history of medical diagnosis of uveitis given to the patient. Data on the baseline demographic characteristics, functional status and quality of life, imaging features, bone mineral density (BMD), and blood tests were compared in patients with and without uveitis. Factors associated with the presence of uveitis were identified both by uni- and multivariate analysis (logistic regression). The prevalence of uveitis at inclusion in the DESIR cohort was 8.5 %. Uveitis occurred after the first symptoms of IBP in 45 %. Presence of uveitis was significantly associated in univariate analysis with pain in the cervical spine, infection preceding inflammatory disease, previous diagnosis of IBD, some domains of the SF36, Achilles enthesitis, elevated leukocyte count, and radiological hip

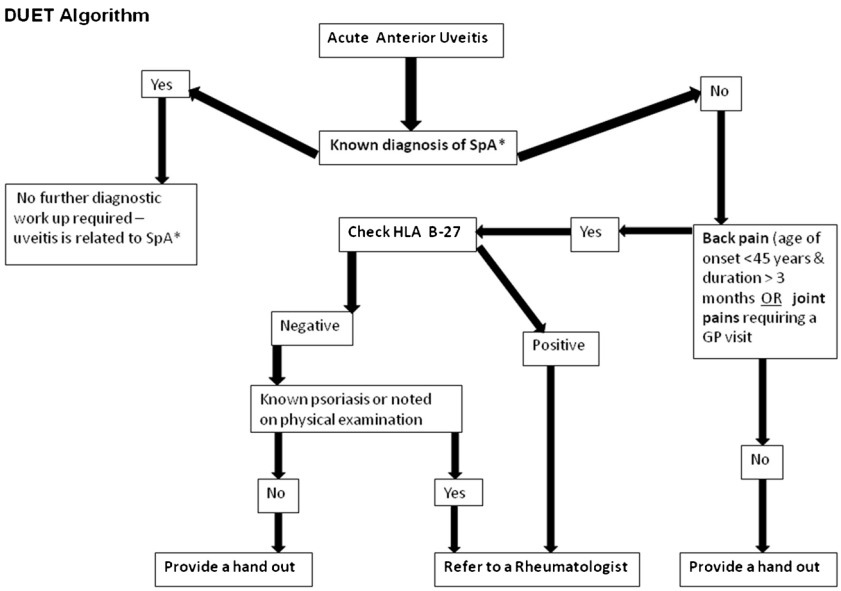

Fig. 1 A simple-to-apply DUET algorithm for patients diagnosed with AAU by ophthalmologists that will facilitate appropriate and timely referrals of such patients to rheumatologists to achieve early detection of associated AS or related SpA

involvement but not with fulfillment of classification criteria, HLA-B27, BASDAI, BASFI, ASDAS, and BMD [17•]. However, it is worth pointing out that multiple studies have shown an association of AAU per se with HLA-B27 [8]. Stepwise multivariate analysis found an association between uveitis and pain in the cervical spine, infection preceding inflammatory disease, previous diagnosis of IBD, and physical health limitation of SF36 ($p<0.05$) [17•]. These results argue that in recent IBP suggestive of SpA, uveitis is associated with IBD and infection. This might suggest, from an epidemiological basis in early stages of the disease, that there is a role of environmental factors in the incidence of uveitis in SpA.

A recent important study has investigated the economic burden of uveitis in French and German AS patients and found a substantial cost associated with the development of AAU among patients with AS. Clinician-estimated medical costs of AS-related uveitis were €1410 (Germany) and €1812 (France). This study highlights a very important point that any future economic evaluation of anti-TNF agents should incorporate extra-articular manifestations of SpA and subsequent treatment costs [42]. Uveitis is one of the variables recommended by ASAS to be collected in epidemiological studies or clinical trials dealing with SpA. For such purpose, and current clinical practice, uveitis is defined as a diagnosis arrived at by an ophthalmologist or an episode suggestive of uveitis in a patient with a previous history of an episode diagnosed as uveitis by an ophthalmologist [43].

Psoriatic Arthritis and Uveitis

Psoriatic arthritis (PsA) is a progressive inflammatory musculoskeletal disease, which if untreated leads to joint damage and disability. PsA was formerly considered a milder form of arthritis, but an inception cohort study has shown that 47 % of the PsA patients who presented within 5 months of onset of symptoms had ≥1 erosion by the second year of follow-up, despite the fact that the majority had been treated with disease-modifying anti-rheumatic drugs (DMARDs) [44]. Despite the increasing awareness of PsA by primary care physicians and dermatologists, the prevalence of undiagnosed PsA remains high. A recent study of psoriasis patients attending a dermatology clinic has shown that 29 % of patients had undiagnosed PsA [45]. Uveitis affects approximately 7 % of patients with PsA [46, 47]. There is some data to support that the presence of PsA in patients with psoriasis increases their risk of uveitis [48, 49]. Uveitis associated with PsA is usually atypical in that it follows a more insidious course, more likely to be continuous, bilateral, and to be situated behind the crystalline lens compared to cases of uveitis among AS patients [50]. It has also been shown that axial disease affects about one fifth of patients with PsA but accounted for 50 % of the patients with PsA and uveitis [51].

Treatment

In general, a good prognosis is anticipated among SpA patients who develop AAU, but ideally, the treatment should be started within 24 h of onset. A combination of topical corticosteroids (such as 1 % prednisolone acetate) and mydriatics (such as 1 % cyclopentolate) is effective in such patients, and the frequency for the prednisolone eye drop use depends upon the severity of inflammation [52]. Use of oral corticosteroids is reserved for patients not responding to topical treatment, especially those with chronic inflammatory bowel disease or psoriatic arthritis presenting with bilateral, chronic, anterior, and/or intermediate uveitis, and this treatment is

rarely needed for more than a couple of weeks. A very small percentage may be more refractory to such treatment and require potential novel therapies, including the use of tumor necrosis factor blockers.

Treatment with sulfasalazine (SSZ) can be effective in reducing recurrences of AAU in SpA; this has been shown in a prospective longitudinal open label study and also in a randomized study with a 3-year follow-up. [53, 54]. Methotrexate may have a similar affect, but it was observed in a prospective open label study in only 10 patients with 1-year follow-up [55]. Non-steroidal anti-inflammatory drugs (NSAIDs) can also help to reduce the frequency or intensity of attacks of uveitis in B27-positive patients [2•, 56].

Anti-TNF therapy improves rheumatologic symptoms and can also be effective in those with refractory severe AAU, but they are rarely required. They also reduce the frequency of uveitis recurrences, especially in AS. In this regard, monoclonal antibodies seem to have greater efficacy as compared to etanercept; for example, a recent study has shown that the average rates of AAU flare (per 100-PYs) were 3.4, 3.7, and 5.7 for infliximab ($p=0.26$ vs etanercept; $p=0.86$ vs adalimumab), adalimumab ($p=0.033$ vs etanercept), and etanercept, respectively [42]. This differential response from TNF inhibitors (TNFi) for AAU is intriguing.

Many reports document uveitis flares or new onset occurring during TNFi treatment (potential "paradoxical" effect), more often with etanercept [57–60]. Although in some cases, uveitis resolved without discontinuation of the anti-TNF agent, in other cases, it only resolved when treatment was stopped. Sometimes, a recurrence of uveitis has occurred upon rechallenge. In some patients, switching to another TNFi agent did not result in recurrence of uveitis. Drug registry data show that after excluding patients with an underlying diseases, such as AS, IBD, or PsA, that are known to be associated with uveitis, there were 21 cases of uveitis associated with etanercept, vs 10 cases with infliximab ($p<0.001$), and 2 cases with adalimumab ($p<0.05$) [61]. Similarly, a French nationwide study of the cases of new onset of uveitis during anti-TNF treatment of patients with rheumatologic diseases has also confirmed rare triggering of uveitis by such therapy [62].

Data regarding other biologic agents in their ability to treat or to reduce recurrences of uveitis in patients with SpA are meager [63]. IL-23/IL-17 pathway is also involved in the pathogenesis of SpA, and IL-17 blockade may become a new option for treating both SpA and uveitis. IL-17 is produced by a unique subset of T cells potentially responsible for many immune-mediated diseases, and its release is induced by IL-23. In a mouse model of uveitis (induced by bacterial peptidoglycan), increased production of IL-17 and IL-23 was documented in the inflamed eye tissue [64]. Moreover, neutralization of IL-17 ameliorates uveitis in this murine model [65]. However, in three randomized controlled trials that evaluated a monoclonal antibody, secukinumab that neutralizes IL-17 as a treatment for uveitis (not specifically for the uveitis associated with SpA), the primary efficacy end points were not met [66]. Tocilizumab has been described to be effective in two patients with refractory uveitis accompanied with macular edema, but a new onset of acute anterior uveitis occurred in one patient with AS [67]. Rituximab has been shown to be effective in 7 out of 10 patients with juvenile idiopathic arthritis (JIA) who had uveitis refractory to topical corticosteroids, immunosuppressives, and anti-TNF agents [68]. Abatacept efficacy has also been explored in seven JIA patients with severe uveitis refractory to conventional and anti-TNF therapy, and it led to sustained improvement [69].

Concluding Remarks

Uveitis, like AS and related SpA, more commonly affects the working population, with onsets of symptoms earlier in life than those with age-related eye diseases such as cataracts, glaucoma, and age-related macular degeneration. Presence of AAU in patients with AS may be a prognostic marker for worse outcome, as it has been shown to associate with higher disease activity, poorer functional ability and physical mobility, and greater radiographic damage. High-density genotyping to investigate the genetic associations of AAU with SpA has found that in addition to the known strong association with HLA-B27, there is significant association with three non-major histocompatibility complex loci, *IL23R*, the intergenic region *2p15*, and *ERAP1*. Patients with AAU, especially those who are HLA-B27-positive, should be questioned about inflammatory low back pain and also evaluated for other clinical features of SpA. Since a prolonged delay in diagnosis is common among SpA patients, and occurrence of AAU may be the reason for their first interaction with medical care, a novel evidence-based algorithm, named DUET, has been proposed to guide ophthalmologists to refer appropriate AAU patients to rheumatologists. Approximately 40 % of patients presenting with idiopathic AAU in a large study were noted to have undiagnosed SpA, and DUET algorithm was found to have excellent sensitivity (96 %) and specificity (97 %). Moreover, this algorithm has a positive LR of 41.5 and negative LR of 0.03. In most instances, the eye inflammation responds to mydriatic eye drops and topical corticosteroids without the need for additional therapy. A small percentage of patients, mostly with associated IBD or PsA with bilateral, chronic, anterior, and/or intermediate uveitis, may be more refractory to conventional therapy, and they may require a short course of oral corticosteroids or more therapy, primarily the use of TNF inhibitors.

Compliance with Ethics Guidelines

Conflict of Interest Muhammad A. Khan has consulted for Abbvie, Amgen, Novartis, Celgene, Janssen, and Crescendo Bioscience.

Muhammad Haroon is a member of advisory boards for Abbvie and Celgene Ireland.

James T. Rosenbaum has consulted for Abbvie, UCB, Allergan, EMD Serono, Novartis, Regeneron, Xoma, Santen, Genentech, Sanofi, Portage, Topivert, Cavtherx, and Auventx.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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