Review Article

Uveitis in spondyloarthropathies

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ABSTRACT

Background: Uveitis is associated with several systemic disorders. It may be the initial presentation of a systemic disease. It is the most common ocular complication and is sometimes the earliest manifestation of spondyloarthropathies. This study aimed to review the current literature on spondyloarthropathies and associated uveitis.

Methods: A narrative review was performed using various combinations of the keywords *spondyloarthropathies*, *seronegative spondylarthritis-related uveitis*, and *human leukocyte antigen-associated uveitis* using PubMed/MEDLINE and Google Scholar from January 1, 2000, to September 30, 2022. We describe the disease mechanisms, genetics, and classification of spondyloarthropathies, the clinical patterns of their related ocular diseases, and the current modalities for the management of their ocular or systemic manifestations.

Results: Seronegative spondyloarthropathies are a group of rheumatic disorders including ankylosing spondylitis, reactive arthritis, psoriatic arthritis, inflammatory bowel disease-related spondyloarthropathy, juvenile-onset spondyloarthritis, and undifferentiated spondyloarthritis. These are characterized by enthesitis in the absence of serum rheumatoid factor and have a strong association with human leukocyte antigen B27. The clinical courses and features of spondyloarthropathies are remarkably diverse. Ocular inflammation is common in spondyloarthropathies, often precedes the onset or diagnosis of systemic disease, and responds well to topical therapy. Timely diagnosis of systemic diseases may improve quality of life and help avoid ocular and skeletal complications. Recurrence of ocular inflammation is frequent; on occasion, it may be associated with etanercept administration.

Conclusions: Eye care professionals should be able to recognize spondyloarthropathies, manage ocular disease, and collaborate with related specialties for modification of systemic treatment if associated with ocular complications. Timely referral and early management could attenuate or prevent ocular or systemic morbidities associated with spondyloarthropathies.

KEYWORDS

uveitides, uveitis, anterior uveitis, spondyloarthropathies, ankylosing spondylitis, reactive arthritis, psoriatic arthritis, human leukocyte antigens, etanercept-szzs, optometrist

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INTRODUCTION

Anterior uveitis is the most common form of intraocular inflammation involving the iris and ciliary body, presenting with corneal edema, anterior chamber cells and flare, keratic precipitates, synechiae formation, and a variable degree of ocular hypotony and vitritis [1]. Acute anterior uveitis (AAU) is the most frequent pattern of anterior uveitis, classically presenting as a sudden episode of anterior uveal inflammation lasting 6 – 8 weeks [2]. It may be infectious, autoimmune, or idiopathic; however, most cases of AAU have an idiopathic origin. In descending order, human leukocyte antigen (HLA)-B27, spondyloarthropathies, Fuchs heterochromic iridocyclitis, and herpetic uveitis are frequently associated [2, 3].

Seronegative spondyloarthropathies (SSpAs) are the most common systemic associations of anterior uveitis. Uveitis may precede the onset of systemic disease, in most instances by many years [4, 5]. The association between anterior uveitis and spondyloarthropathies is well established, and anterior uveitis is the most frequent pattern of ocular inflammation in ankylosing spondylitis (AS) [6]. AS is the most common and prototypical spondyloarthropathy and frequently presents with ocular involvement. The prevalence of AS in all forms of uveitis is 15%, whereas the prevalence of uveitis is 20 – 40% in AS, 12.4% in reactive arthritis, 7 – 16% in psoriatic arthritis, and 2 – 9% in inflammatory bowel disease [7].

Although most AAU cases are idiopathic [1], it is imperative to identify underlying systemic associations, which is challenging without a logical approach to each case of uveitis [8, 9]. Uveitis is frequent among carriers of HLA-B27 and patients with AS and other spondyloarthritides. Systemic disease-associated uveitis may be the reason a patient seeks initial medical advice, otherwise unaware of the underlying disease or the causal relationships between ocular and systemic diseases. In half of the cases, uveitis precedes the onset of systemic signs and symptoms [9].

Optometrists may play a primary role in the early diagnosis of these spectra of disease. Often, the patients presenting with a first episode of AAU are diagnosed as having idiopathic AAU, as no workup beyond history taking is performed [9, 10]. Nonspecific questioning of the patient about general health may lead clinicians to falsely label them as otherwise healthy [9-11].

We aimed to review the current literature on spondyloarthropathies and associated uveitis. This paper describes the disease mechanisms, genetics, and classification of spondyloarthropathies, along with the clinical patterns and current treatments of systemic and ocular diseases related to these entities.

Pathogenesis and Genetics of Spondyloarthropathies

SSpAs are a group of arthritides characterized by enthesitis in the absence of serum rheumatoid factor and are strongly associated with HLA-B27 [12, 13]. Inflammatory lower back pain, dactylitis, and other extra-articular lesions are the characteristic manifestations. SSpAs include AS, reactive arthritis, psoriatic arthritis, inflammatory bowel disease-related spondyloarthropathy, juvenile-onset spondyloarthritis, and undifferentiated spondyloarthritis [12, 14-16]. The similarities in clinical manifestations and genetic predisposition suggest a common pathogenesis for these diseases [12-16].

The exact pathogenesis of SSpAs remains unclear [10]. However, compelling evidence supports the interplay between genetics and environmental factors triggering the release of pro-inflammatory cytokines. The interaction between HLA and environmental factors is a key driver in the pathogenesis of these arthritides. HLA is encoded by genes located within the major histocompatibility complex (MHC), mapped to the short arm of chromosome 6. MHC encompasses three classes of 220 genes, including class I, II, and III genes [17-21].

Human MHC, or HLA, is an MHC class I molecule composed of two polypeptide heterodimeric chains: an α chain and β2 microglobulin. The α chain has three domains, and β2 microglobulin binds noncovalently to the α3 domain [17-24]. The MHC is responsible for self-recognition by facilitating the binding, recognition, and tolerance of self-peptides by T cells. MHCs serve as chaperones for intercellular peptides, binding to and presenting them to T cell receptors [23-26].

HLA plays a pivotal role in the immunopathogenesis of spondyloarthropathies and the associated uveitis. HLA-B27 is the strongest known genetic risk factor for the development of spondyloarthritis [27-29] and AAU [27, 28].

The prevalence of HLA-B27 positivity varies significantly among different ethnicities. Prevalence was 7.5%, 4.6%, and 1.1% for non-Hispanic whites, Mexican Americans, and non-Hispanic Blacks, respectively [30]. HLA-B27 was present in up to 7% of the general Arab population, 9.2% of Caucasians, and 6.5% of Maori Polynesians of New Zealand [31-33]. Among the Chinese, HLA-B27 was present in 9.2% of Atayal Aborigines, 2.1% of Paiwan, and 5.6% of Han Chinese populations [34]. It is rare to nearly absent among the Japanese, South American Indians, sub-Saharan Africans, and Australian Aborigines [35].

Nonetheless, the presence of HLA-B27 in patients with AS and/or uveitis, as well as their families, is several-fold higher than that in the general population. Approximately 2% of the HLA-B27-positive population develops AS, while up to 90% of Caucasian AS patients and 60% of African Americans with AS are HLA-B27 positive [30-39]. These findings suggest a strong association between HLA-B27 and spondyloarthropathies. However, the mechanism(s) underlying this relationship are not fully understood [40, 41]. Some commonly known theories include arthritogenic/uveitogenic peptide [23, 26, 42], molecular mimicry [43-46], misfolding of HLA-B27 [23, 28, 47-50], and cell-surface HLA-B27 homodimer [25, 41, 42, 51-58].

In addition to HLA-B27, other class I and II MHC loci have been reported as associated with AS. These include HLA-A, HLA-B40, HLA-B60, HLA-DRB1, and others. These MHC genes interact with T-cell receptors and immunoglobulin-like receptors on natural killer cells and certain lymphocytes and also participate in antigen presentation [58-60].

The overall contribution of HLA-B27 to AS development is approximately 20%; many non-MHC genes contributing to spondyloarthropathies have also been identified [14, 22, 36, 61]. Endoplasmic reticulum aminopeptidase (ERAP) 1 and 2 genes are located on chromosome 5q15 and code for ERAP1 and ERAP2 proteins, which play a major role in the proteolysis of antigenic peptides before loading onto HLA class I molecules for presentation [19, 20, 24, 28, 47].

Different genome-wide studies have emphasized the roles of *ERAP1* and *ERAP2* in the pathogenesis of AS [62, 63]. *ERAP1*-associated variants affect peptide trimming prior to HLA class I presentation. Gene-to-gene interactions between *ERAP1* and *HLA-B27*, resulting in abnormal peptide presentation, are implicated in the pathogenesis of AS. Some *ERAP1* variants influence the risk of AS in HLA-B27-positive individuals. Alterations in *ERAP1*-derived cleavage of cytokine receptors affect receptor signaling and may trigger inflammatory processes [26, 36, 56, 64]. In addition, interleukin (IL)-23 and IL-17 pathways have been implicated in the pathogenesis of AS [36, 56].

Systemic Manifestations of Spondyloarthropathies

The clinical courses and features of spondyloarthropathies are remarkably diverse. Spondyloarthritis can be classified as axial [65] or nonaxial/peripheral [66]. Axial diseases have a predilection for the axial skeleton (sacroiliac joints, spine, chest wall, hip, and shoulder girdle), while peripheral or non-axial diseases include peripheral arthritis, enthesitis, dactylitis, psoriasis, uveitis, and inflammatory bowel disease [65, 66].

Diagnostic criteria are widely used for classifying SSpAs in research settings but are rarely adopted in clinical practice [65, 66]. Diagnosis is mainly based on history and physical examination findings. No specific laboratory tests exist for the diagnosis; however, a negative rheumatoid factor, elevated erythrocyte sedimentation rate or C-reactive protein concentration, and anemia of chronic disease may assist in the diagnosis and management. Despite its prime role in the pathogenesis and disease process [29, 67], most individuals possessing HLA-B27 are healthy, and only approximately 1% develop AAU [67].

Ankylosing Spondylitis: AS is the most common and prototypical SSpA, and uveitis is its most frequent extra-articular manifestation [68]. It typically affects young male individuals (aged 15 – 40 years) and is characterized by inflammatory back pain, sacroiliitis, and enthesitis. The inflammatory back pain is insidious in nature, dull in quality, and radiates to the buttocks [38]. It is described as a lower back pain/discomfort of insidious onset before the age of 40 that persists for over 3 months, worsens with rest/sleep, is associated with morning stiffness, improves with physical activity, and has a nocturnal component [15, 38]. Extra-articular manifestations include uveitis, aortic and mitral root dilatation with regurgitation/conduction defects, and pulmonary fibrosis in chronic cases [16, 69].

Sacroiliitis is a hallmark radiographic sign of AS, typically seen in the lower third of the sacroiliac joints [70-73]. The radiographic changes may range from blurring of the joint margins and bony erosion to bony bridge (syndesmophyte) formation between the neighboring vertebrae. In the initial stages, plain radiographs may appear normal. Magnetic resonance imaging of the sacroiliac joints offers sensitivity superior to that of plain radiography and computed tomography [70-73]. However, plain radiographs are the recommended first-line imaging modality, because sacroiliitis may be detected in 30 – 50% of cases, even in disease of short duration, rendering additional imaging unnecessary [72, 73].

Different criteria have been developed and validated to diagnose and classify the disease. The Rome and modified New York Criteria are commonly used, both of which are mainly based on radiography of the sacroiliac joints [74]. Both the Rome and modified New York Criteria consider many features except uveitis, and thoracic regional pain is excluded from the latter [74].

Reactive arthritis: also known as Reiter's syndrome, is the classical triad of arthritis, urethritis, and conjunctivitis. It is assumed to be triggered by the genitourinary or gut microbiome in genetically susceptible individuals [75, 76], with an incidence ranging from 0.6 to 27 per 100 000 [77].

Acute diarrhea or cervicitis/urethritis may precede arthritis by many weeks [75, 76]. Reactive arthritis is diagnosed if there is monoarthritis or asymmetric oligoarthritis involving the lower limbs following symptomatic enteritis (diarrhea for at least 1 day, occurring 3 days to 6 weeks before the onset of arthritis) or urethritis (dysuria or discharge for at least 1 day, occurring 3 days to 6 weeks before the onset of arthritis), in the presence of at least one of the two minor criteria [76]. The minor criteria are evidence of triggering infection (positive urine ligase reaction for *C. trachomatis* or positive stool culture for associated enteric pathogens) and evidence of persistent synovial infection (contributing immunohistology or polymerase chain reaction for *Chlamydia*) [4, 76].

Other frequently encountered manifestations include circinate balanitis, keratoderma blennorrhagicum, plantar fasciitis, keratitis, cystitis/prostatitis, psoriasiform eruptions, aortic regurgitation, heart conduction disturbances, and pericarditis [4]. Onycholysis, oral ulceration, and amyloidosis are also encountered [16]. Up to 50% of men with reactive arthritis of urogenital origin and 75% of those with enteric origin have ocular involvement [4].

Psoriatic Arthritis: Arthritis may occur in up to 20% of patients with psoriasis. Dermatological manifestations precede spondyloarthropathy in most cases; however, an inverse pattern is observed in up to 20% of cases [4, 16].

Five distinct patterns of psoriatic arthritis have been described: the most common oligoarticular type, polyarticular pattern, predominant distal interphalangeal joint involvement, and psoriatic spondylitis. Both enthesopathy and dactylitis are quite common in psoriatic arthritis [12, 14]. Dermatological lesions are typically dry, pruritic, red papules, ranging from small localized lesions to involvement of the entire body. Nail changes, including onycholysis and pitting, are observed in 80% of patients [12, 14]. Uveitis, occurring in 7 – 20% of psoriasis cases, has a chronic nature with a tendency for bilateral involvement and may be seen in psoriasis with or without arthritis [4, 67].

Ocular Disease in Spondyloarthropathies

SSpAs are the most frequent systemic associations of non-infectious uveitis, and AS is the most common. Multiple reports have suggested SSpAs as the etiological origin of anterior uveitis in 9 – 22% of all new uveitis cases [78-83]. In a 7-year, single-clinic study of 514 patients with new-onset uveitis, 23% were diagnosed with some type of spondyloarthropathy, of whom 64% received a diagnosis of AS. Uveitis preceded the diagnosis of spondyloarthropathy in half of the cases [78]. In a Singapore-based epidemiological study of 552 new uveitis cases, 5.1% were associated with AS [84]. It is noteworthy that these data were extracted from the overall population with uveitis. Nonetheless, uveitis may affect 18 – 32% of the HLA-B27-positive population [67, 35].

Uveitis in patients with HLA-B27 positivity and those with AS typically manifests as unilateral or alternating bilateral episodes of recurrent acute anterior segment inflammation, characterized by limbal hyperemia, fine keratic precipitates, and marked cellular reaction manifesting as fibrin exudation, fibrinous clot, and hypopyon [85-87] (Figures 1, 2, and 3). Posterior segment manifestations, including vitritis (Figure 4), retinal edema, vasculitis, papillitis, and pars plana exudation, are also seen [85, 86, 88].

Most patients present with unilateral or alternating bilateral attacks of anterior segment inflammation [87, 89]. The disease is unilateral in 52 – 87% of patients and bilateral in up to 47% [88, 90]. The definition of laterality varies among the published studies. Many authors have reported unilateral patterns as alternating bilateral disease. Simultaneous bilateral involvement is observed in 10 – 14% of cases [80, 85, 87-89, 91, 92]. The disease is 1.1 – 2.5-fold more frequent in male individuals. Male sex is a predictor of more severe disease and more frequent relapses [85, 86, 90, 93].

Fibrinous exudation and hypopyon can occur in HLA-B27- and SSpA-related uveitis. Fibrinous exudation occurs in the absence of mutton-fat keratic precipitates [94, 95]. The incidence of hypopyon among HLA-B27-positive patients is higher than that among HLA-B27-negative patients [94]. Studies have documented a higher frequency of hypopyon in SSpA-related uveitis than in Behçet's disease and other uveitides manifesting with hypopyon [85, 86, 96]. The incidence of hypopyon in HLA-B27-positive uveitis with or without SSpAs is 12 – 15% [67, 94]. However, regardless of the presence or severity of systemic disease, hypopyon is entirely associated with HLA-B27 positivity [86]. Several studies have reported other ocular features including vitritis, retinal vasculitis, macular edema, pars plana exudates, and papillitis [87, 88, 90, 95, 97].

Between 50% and 70% of patients experience recurrences of uveitis. Recurrence is more common early in the disease course, and the frequency of exacerbations declines over time [86, 92]. The mean (standard deviation [SD]) number of recurrent attacks during the first 5 years after the initial episode is 1.1 (0.8) per year and diminishes to 0.8 (0.6) thereafter [88, 90, 97].

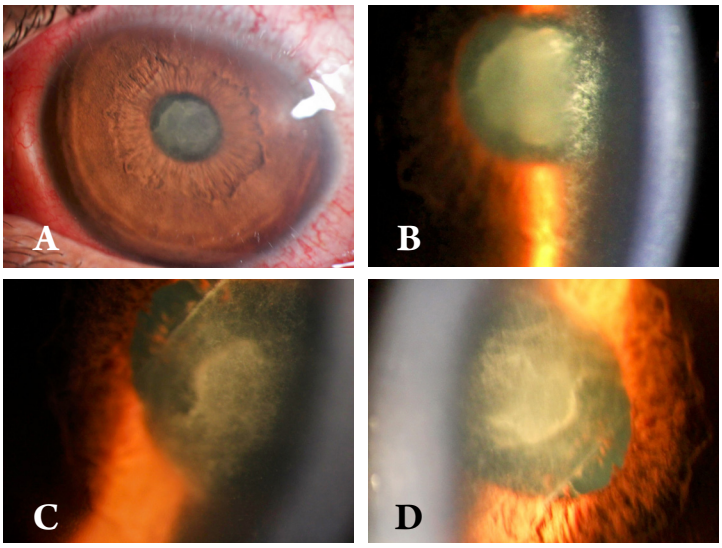

Figure 1. Anterior segment slit-lamp photographs (A-D) of acute anterior uveitis in a young male patient with ankylosing spondylitis, showing intense diffuse conjunctival hyperemia, flare, fibrinous exudate in the anterior chamber, corneal edema, and multiple posterior synechiae.

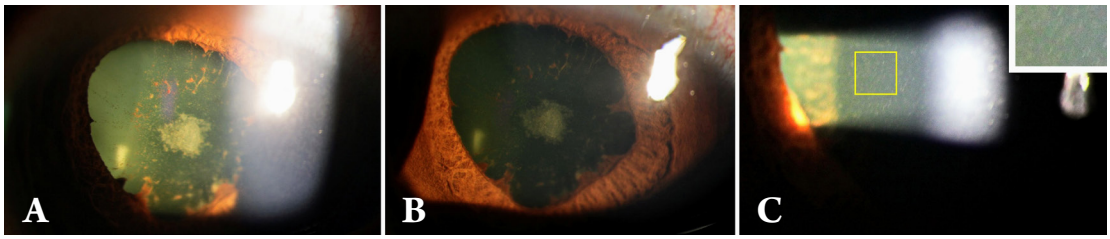

Figure 2. The same patient 48 hours after treatment with topical cycloplegia and topical corticosteroids [105, 106], resulting in multiple broken synechiae (A and B) with pigment deposits on the crystalline lens (A and B) that indicate where the iris was attached to the crystalline lens when posterior synechiae was developed. Yet, severe anterior chamber cells and flare are present (C).

The most common ocular complications are posterior synechia and cataract formation, affecting up to 20% of the eyes. Transient intraocular pressure spikes during attacks, iris rubeosis, secondary glaucoma, and hypotony may affect a small proportion of eyes [87, 88, 90, 95, 97].

Most HLA-B27- and SSpA-related uveitis precedes the onset of systemic disease, and most patients are diagnosed with idiopathic uveitis during the first episode. Approximately 40% of uveitis cases have an underlying undiagnosed SSpA [98-100]. In a series of 91 AS patients with uveitis, the mean (SD) age at the first uveitis episode was 32.8 (11.3) years, whereas it was 33.8 (11.6) years at the time of spondylitis onset [88]. Furthermore, uveitis has been identified as a risk factor for AS among at-risk individuals. The delay between the diagnoses of uveitis and AS was 6 months to 8 years [98-101].

Recommendations have been devised for eye care providers to avoid delays in the diagnosis of SSpA. The Dublin Uveitis Evaluation Tool is 96% sensitive and 97% specific for diagnosing spondyloarthropathies in uveitis patients [102-104]. The algorithm recommends testing for HLA-B27 in any case of AAU if there is inflammatory back pain for more than 3 months or joint pain requiring medical care. Rheumatology referral is warranted if a patient either tests positive for HLA-B27 or is seronegative for HLA-B27 but has evidence of psoriasis [102-104]. Nonetheless, the authors believe that any case of acute or recurrent uveitis with a history of inflammatory back pain, joint pain, or psoriatic lesions should be referred to a rheumatology department for additional workup and HLA testing.

Treatment

Treatment of ocular disease: The treatment of acute ocular inflammation is typically similar to that of idiopathic AAU, involving cycloplegia and topical corticosteroids [105, 106] (Figure 2). However, more severe cases and eyes with vitreous involvement may require peribulbar injections or systemic administration of corticosteroids [88].

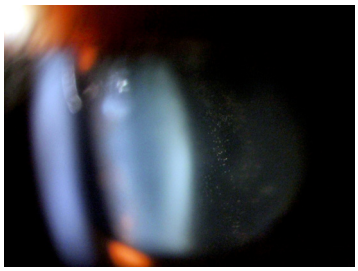

Figure 3. Slit-lamp photography of the same patient 48 hours after treatment with topical cycloplegia and topical corticosteroids [105, 106], with vitreous inflammation at high magnification.

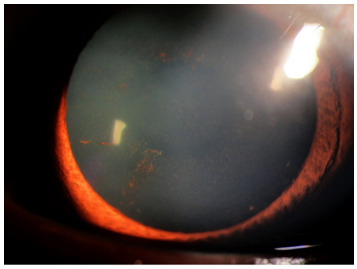

Figure 4. Anterior segment slit-lamp photographs following resolution of acute anterior uveitis in another patient with ankylosing spondylitis, showing pigment deposits on the crystalline lens indicating where the iris was attached to the crystalline lens when posterior synechiae was developed.

Topical therapies for AAU include dexamethasone 0.1%, prednisolone acetate 1%, and difluprednate 0.05% [107]. Both difluprednate and prednisolone acetate achieve higher and more prolonged aqueous concentrations than dexamethasone [108]. Difluprednate 0.05% four times daily was non-inferior to prednisolone acetate 1% eight times daily. Difluprednate clears the anterior chamber reaction more quickly than prednisolone, and in a greater proportion of patients [109].

Treatment of systemic disease: The mainstay of systemic disease management includes non-steroidal anti-inflammatory drugs (NSAIDs) and tumor necrosis factor-alpha inhibitors (TNFIs) [22]. Other pharmacological options include analgesics, glucocorticoids, non-TNFI biologics, and disease-modifying anti-rheumatic drugs (DMARDS) [22, 67, 110].

Both traditional and selective cyclooxygenase 2 (COX-2) inhibitors are first-line agents for the treatment of active AS. Non-selective NSAIDs, including naproxen, flurbiprofen, and ketoprofen, and selective COX-2 inhibitors are administered for reduction in pain and disease activity [22]. Disease activity is determined using laboratory (erythrocyte sedimentation rate, C-reactive protein level), clinical, and imaging features [6, 22]. Continuous administration has not shown superior clinical outcomes over on-demand treatment but may result in more drug-related adverse events [6, 22]. Analgesics (such as opioids and acetaminophen) are administered concomitantly in cases of suboptimal pain relief with NSAIDs [22, 67, 110].

Short-term oral administration and local injections of corticosteroids are used in active cases of AS for improved control of inflammation and symptoms. Intra-articular steroid injections into the sacroiliac and peripheral joints have been previously described [54].

DMARDs include methotrexate, sulfasalazine, thalidomide, and leflunomide. Despite the arguable efficacy of some of these drugs, they are widely used as second-line treatments for SSpAs [22, 54, 111]. Nonetheless, these agents are beneficial in cases resistant to conventional therapy and provide better outcomes in peripheral than in axial arthritis. Patients with contraindications to TNFIs may benefit from sulfasalazine or pamidronate [111].

Considering the role of the gut microbiome, multiple studies have investigated the role of antibiotics in the treatment of SSpAs. Both moxifloxacin and co-amoxiclav have demonstrated significant and durable improvements in all AS parameters in small patient groups [112, 113].

TNFIs have emerged as a cornerstone treatment of AS and other spondyloarthropathies. These are warranted in patients with high disease activity despite treatment with NSAIDs [15, 22, 114]. The use of TNFIs for AS is based on their indications and contraindications in individual cases, as there are no specific recommendations

Table 1. Different tumor necrosis factor inhibitors, routes of administration, and dosages in management of spondyloarthropathies

Drug	Dosing (route of administration)	Frequency
Etanercept [115, 116]	50 mg (SC)	Every week
Adalimumab [116, 117]	40 mg (SC)	Every two weeks
Certolizumab pegol [118]	400 mg (SC)	Loading dose
	200 mg (SC)	Every 2 weeks (maintenance)
Infliximab [116, 119, 120]	5 or 7.5 mg/kg (IV)	Weeks 0, 2, and 6 followed by every 6 weeks

Abbreviations: SC, subcutaneously; mg, milligram; kg, kilogram; IV, intravenous.

regarding the selection of TNFIs for AS. Etanercept, adalimumab, certolizumab pegol, and infliximab are commonly used in the treatment of SSpAs [15, 22, 114]. A summary of the different TNFIs, their dosing, and routes of administration is provided in Table 1.

Studies have found greater incidence, recurrences, and severity of uveitis in patients treated with etanercept; alternative agents such as adalimumab should be considered in cases with more active/recurrent uveitis [121, 122]. Infliximab and adalimumab have shown great efficacy in controlling non-infectious uveitis and in reducing disease activity and recurrence [122, 123].

CONCLUSIONS

Uveitis may be the first manifestation of SSpAs in more than half of cases, although it develops or recurs over the course of a diagnosed spondyloarthropathy. Optometrists, as a first line, may help establish an early diagnosis of AS and other spondyloarthropathies by initiating directed investigations and making appropriate referrals. Whereas, known cases of SSpAs may be monitored for ocular involvement along the disease spectrum. Spondyloarthropathy-related uveitis is recurrent and is associated with an array of ocular complications. Topical corticosteroids are an effective treatment option in most cases and help to control inflammation. Etanercept, one of the most commonly administered TNFIs for axial disease, is associated with higher severity and rates of recurrence of uveitis, and optometrists should consider this association in cases of recurrent SSpA-related uveitis.

ETHICAL DECLARATIONS

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Conflict of interests: None

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