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Review Article

Clinical Spectrum of HLA-B27-associated Ocular Inflammation

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ABSTRACT

Introduction: HLA-B27-associated anterior uveitis is the most common identifiable cause of anterior uveitis in adults worldwide. It is associated with significant ocular morbidity in young patients due to its typically recurrent attacks of inflammation and vision-threatening ocular complications.

Materials and methods: This review was compiled using articles identified by searching on PubMed with all relevant keywords such as HLA B27, HLA B27 uveitis, spondyloarthritis, Ankylosing spondylitis, HLA B27 systemic associations.

Results: We summarize the current knowledge on the HLA B27 associated uveitis epidemiology, genetics, clinical profile, systemic associations, laboratory investigations, complications and management.

Conclusion: HLA-B27-associated uveitis is a commonly encountered entity in the uveitic clinic. Its management must be in coordination with a rheumatologist. Early and appropriately intense treatment is essential for optimal visual prognosis.

Keywords: Ankylosing spondylitis, Anterior uveitis, HLA B27, Spondyloarthropathy, Uveitis.

INTRODUCTION

Inflammation of the uveal coats of the eye is referred to as uveitis. Anterior uveitis remains the most common type of uveitis (Chang et al., 2005), where inflammation is primarily involving the iris and ciliary body. Signs of inflammation such as cells and flare are prominently seen in the anterior chamber. The Standardization of Uveitis Nomenclature (SUN) system field (Jabs et al., 2005) has made it relatively easy to label and classify uveitic entities presenting to the clinic, but it remains a challenge for ophthalmologists to reach the correct etiological diagnosis of uveitis as it presents with a plethora of ocular as well as systemic signs and symptoms. Idiopathic uveitis is the most common form of uveitis,

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Table 1: Demography of HLA-B27-associated acute anterior uveitis (AAU).

Articles	Average age (in years)	Male to female ratio
(Woodrow et al., 1975)	41.8	1.42:1
(Tay-Kearney et al., 1996)	32	1.5:1
(Monnet et al., 2004)	31	1.3:1
(Chang et al., 2005)	30	2:1
(Braakenburg and Rothova, 2014)	36	1.1:1
(Dogra et al., 2016)	37	1.3:1
(Pathanapitoon et al., 2006)	38	1.94:1
(Lakra et al., 2021)	35.6	3.1:1

followed by HLA-B27-associated anterior uveitis. HLA-B27 AAU (acute anterior uveitis) is the most common identifiable cause of anterior uveitis. (Chang et al., 2005) (Bawazeer and Joharjy, 2013) (Kitamei et al., 2009) (Khan, 1995) It is associated with significant ocular morbidity in young patients due to its typically recurrent attacks of inflammation and vision-threatening ocular complications.

EPIDEMIOLOGY

The prevalence of HLA-B27 is highest in the Caucasian population, approximately 8% (Chang et al., 2005), while in Arab, African and East Asian populations, the prevalence is lower (1-5%) (Bawazeer and Joharjy, 2013) (Kitamei et al., 2009). Among Caucasians, the prevalence of HLA-B27 positivity among acute, alternating, and recurrent anterior uveitis is as high as 80%, and in acute unilateral, recurrent anterior uveitis is approximately 60%. (Rosenbaum, 1989)The range of prevalence of HLA-B27 across different racial groups in patients with acute anterior uveitis is 19-88% (Brewerton et al., 1973) (Woodrow et al., 1975)(Karaconji et al., 2013) (Torres et al., 2013)(Mishra and Bharucha, 2011). HLA-B27-associated uveitis most commonly affects the population between 20-50 years of age, and men are more commonly affected than women. Table 1 summarizes findings from various epidemiological studies on HLA-B27 from around the world.

GENETICS

The association between HLA-B27 and AAU was first demonstrated by Brewerton *et al.* in 1973 and remains one of the strongest genetic associations known. (Brewerton et al., 1973). HLAB27 positivity has been reported in 60% of individuals with recurrent acute unilateral uveitis and 80% of patients with recurrent acute unilateral alternating uveitis. (Rosenbaum, 1989) (Wang et al., 2014). HLA-B27 positivity and AAU are also strongly associated with ankylosing spondylitis, with studies showing the prevalence of HLA-B27 positivity as high as

92% in individuals with AS and AAU (Robinson et al., 2015) (Robinson et al., 2016). A British study of patients using biologics also concluded that HLA- B27 was associated with an increased risk of AAU complicating AS (Derakhshan et al., 2020). Although AAU in HLA-B27 positive individuals does not operate along simple Mendelian genetic principles, it nevertheless shows a strong familial tendency. Derhaag *et al*. (Derhaag et al., 1988) have shown that the prevalence of AAU in HLA-B27-positive first-degree relatives of AAU patients was 13%, significantly higher than the frequency of 1% in the HLA-B27-positive individuals without affected relatives. That is to say that HLA-B27 positive individuals with a family history of AAU are more likely to develop AAU than HLA-B27 positive individuals without any family history of AAU. Other possible factors in modifying the development of AAU include the gut microbiome (Rosenbaum and Asquith, 2018) and specific HLA-B27 subtypes, some of which are protective for AS, and some are protective for AAU. Genome-wide association studies (GWAS) have shown new susceptibility gene associations at 11 loci, including ERAP1, NOS2, MERTK, KIFAP3, CLCN 7, ACAA2, and five intergenic loci (Huang et al., 2020). Many genetic factors critical to the immune response to microorganisms, such as IL10, IL18R1-IL1R1, IL6R, and KIF21B, are also shown to be associated (Robinson et al., 2015).

CLINICAL PROFILE

The diseases linked to the allele HLA-B27 include spondyloarthritis (SpA), a group of inflammatory arthritis including ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and arthritis related to inflammatory bowel disease (IBD). All of these are variably associated with uveitis (Figure 1).

Table 2: Classification criteria for spondyloarthritis/HLA B-27-associated anterior uveitis. Table adapted from (Standardization of Uveitis Nomenclature (SUN) Working Group, 2021).

Criteria	Exclusions
1. Anterior Uveitis: Anterior chamber cells and if anterior vitreous cells are present, severity is less than anterior chamber inflammation AND either (both #2 and #3) OR #4 2. Characteristic uveitis course a. Acute or recurrent acute, unilateral or unilateral alternating course OR b. Chronic course with a history of a recurrent acute, unilateral or unilateral alternating course evolving into chronic course AND 3. Assessment of SpondyloArthritis international Society (ASAS)-defined spondyloarthritis (axial or peripheral) AND HLA-B-27-positive OR 4. Chronic uveitis with both ASAS-defined spondyloarthritis (axial or peripheral) AND HLA-B27-positive	1. Positive serology for syphilis 2. Evidence of sarcoidosis 3. PCR from Aqueous specimen positive for cytomegalovirus, herpes simplex virus or varicella zoster virus

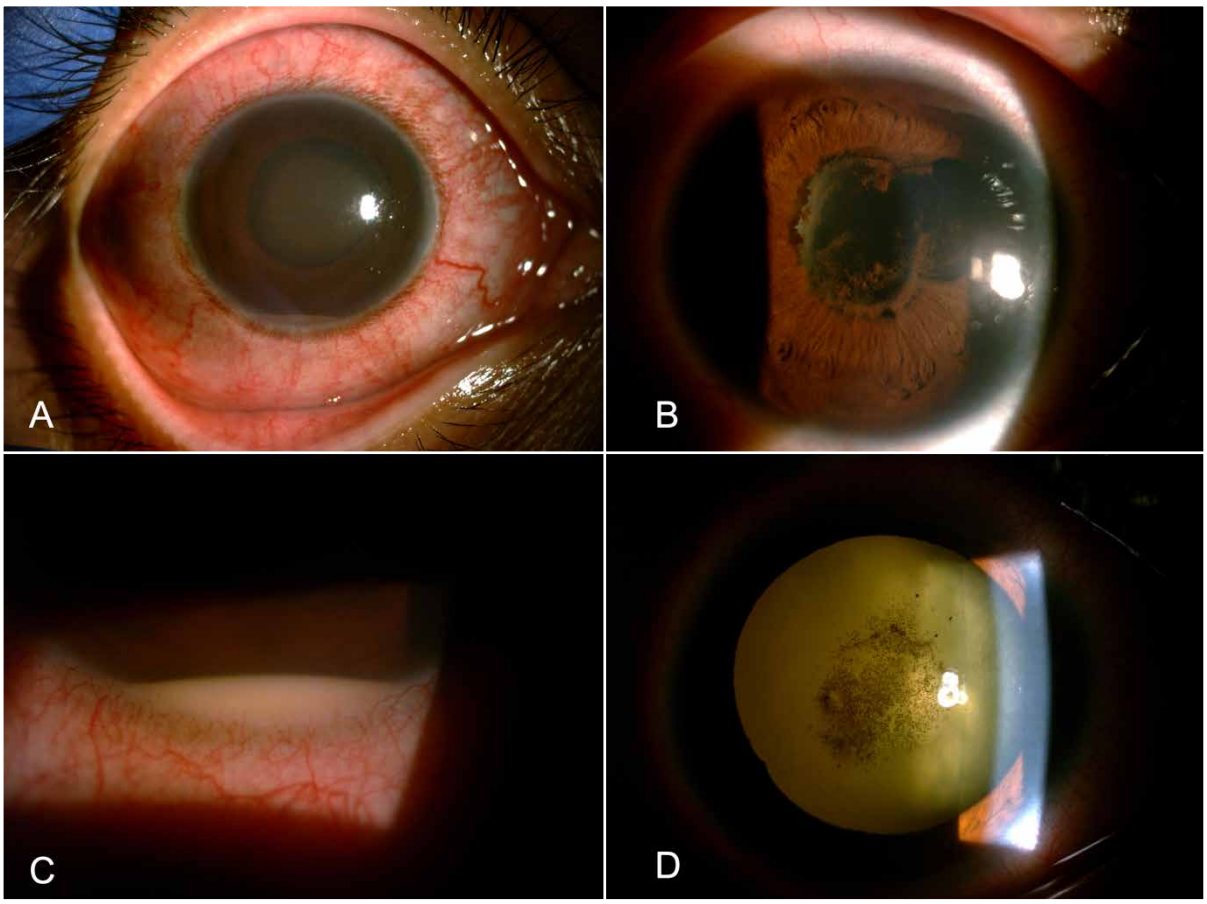

Figure 1: Slit-lamp photographs of HLA B-27-associated uveitis showing (A) circumciliary congestion associated with acute anterior non-granulomatous uveitis; (B) synechiae, and areas of partially broken synechia in response to topical cycloplegic in a case of fibrinous anterior uveitis; (C) hypopyon; (D) severe vitritis in a patient with HLA B-27-associated uveitis.

The most typical findings of HLA-B27 AAU include acute or recurrent acute unilateral or unilateral alternating anterior uveitis. Tay-Kearney et al. reviewed records of 148 HLA-B27 positive patients with uveitis and described the ocular involvement as unilateral in 93%, bilateral in 10% with up to 3 recurrences in 1 year follow-up period (Tay-Kearney et al., 1996). The pattern of the disease is recurrent, with complete remission between the attacks (Tay-Kearney et al., 1996). The interval between acute attacks is highly variable, with a range of 1 month to 35 years (Monnet et al., 2004). Patients present with a painful, red eye associated with photophobia, lacrimation, and a drop in vision. On examination, the keratic precipitates are never mutton fat; they are usually monocellular but may become conglomerates over time. The anterior chamber reaction is usually severe, with cells reaching SUN classification grade 3 or 4, hypopyon being a frequent finding (Tuncer et al., 2005) (D'Alessandro et al., 1991). According to D'Alessandro et al., HLA-B27 positive uveitis is the most common cause of endogenous

hypopyon formation (D'Alessandro et al., 1991) (Figure 1). The flare is also significant, with fibrin formation common (Tuncer et al., 2005). HLA B-27 associated episcleritis and scleritis are uncommon but have been documented. (Sainz de la Maza et al., 2012). Table 2 shows the recently published SUN working group classification criteria for HLA B27-associated anterior uveitis (Standardization of Uveitis Nomenclature (SUN) Working Group, 2021) .

Vitritis is common, mostly observed in the anterior vitreous as a spill-over uveitis (Lakra et al., 2021). However, severe vitritis and clinical picture mimicking panuveitis or endogenous endophthalmitis are rare but have been reported (Toh and Agrawal, 2020)(Lakra et al., 2021). Posterior segment involvement in HLA B-27 AAU is an under-recognized phenomenon. Multiple case studies and series have reported the association of HLA-B27 with posterior segment findings, including chorioretinitis, retinal vasculitis, and posterior scleritis, among others (Monnet et al., 2004) (Dodds et al., 1999) (Rodriguez et al., 1994)(Kim et al., 2009) (Anshu and Chee, 2007) (van der Veer et al., 2014). The reported frequencies of posterior segment involvement with HLA-B27 positivity range between 0% to 21%. Intermediate uveitis has been reported in patients with HLA-B-27-associated uveitis (Rodriguez et al., 1994) (Lee et al., 2020) (Lakra et al., 2021). There has been an increase in literature on retinal vasculitis in patients with HLA B-27-associated uveitis in the last few decades. Hemorrhagic ischemic retinal vasculitis was reported in a 12-year-old with *alopecia areata* who presented with acute and severe vision loss, and subsequent investigation could attribute it to the positive HLA B27 (Sharma and Randhawa, 2018). However, the reported incidence of retinal vasculitis may be much more than what has been reported in the literature as the majority of the time, detailed evaluation of the fundus, including fundus fluorescein angiography (FFA), is not routinely carried out in patients with HLA-B-27-associated uveitis (Lakra et al., 2021). Similarly, optic nerve head involvement is rare, but papillitis has been reported in the literature by several authors (Rodriguez et al., 1994)(Dodds et al., 1999) (Kim et al., 2009). Orbital involvement in HLA-B-27-associated uveitis is extremely uncommon. A 41-year-old lady who presented with painful diplopia with a history of recurrent attacks of AAU and spondyloarthropathy was found to have myositis secondary to HLA-B27-associated uveitis (Dutta Majumder et al., 2020). In another case reported by Sachdev et al. a 29 year old female with HLA-B27-associated spondyloarthropathy presented with recurrent orbital pain, periorbital edema, and proptosis. The orbital inflammation was attributed to enthesitis (Sachdeva et al., 2012).

Braakenburg and Rothova reported that these atypical presentations of HLA-B27-associated uveitis are more common in females than males (Braakenburg and Rothova, 2014).

Table 3 summarizes the posterior segment findings in HLA-B27 associated uveitis.

Table 3: Posterior segment involvement in HLA-B27-associated uveitis.

Case Series (year)	Total Number of Patients	Posterior Segment involvement	Vitritis (%)	CME (%)	Papillitis (%)	Retinal vasculitis (%)	Epiretinal membrane (%)	Pars plana exudates (%)	Choroidal folds (%)	Retinal Detachment (%)	Posterior scleritis (%)	Choroidal effusion (%)
(Dodds et al., 1999)	114	24	18 (75%)	7 (29%)	2 (8.3%)	-	-	-	-	-	-	-
(Rodriguez et al., 1994)	166	29	27 (93%)	11 (37.9%)	24 (82%)	7 (24.1%)	5 (17.2%)	2 (6.8%)	-	-	-	-
(Monnet et al., 2004)	175	44	44 (25.1%)	22 (12.6%)	8 (4.6%)	-	-	-	-	-	-	-
(Kim et al., 2009)	78	23	18 (78.3%)	10 (43.5%)	3 (13.0%)	5 (21.7%)	-	1 (4.3%)	-	-	-	-
(Anshu and Chee, 2007)	5	5	-	5 (100%)	-	-	-	-	3 (60%)	2 (40%)	5 (100%)	2 (20%)
(Lakra et al., 2021)	431 eyes of 255 patients		203 (47.1%)	19 (4.4%)		4 (0.9%)	27 (6.3%)			3 (0.7%) RRD		
(van der Veer et al., 2014)	242	5	-	4 (80%)	-	-	-	-	-	3 (60%)	-	1 (20%)

ASSOCIATED SYSTEMIC DISEASES

Acute anterior uveitis may be the first symptom of a systemic disease, preceding the onset of other clinical manifestations, or it may be the clinical manifestation that completes the clinical picture of the systemic disease in conjunction with other previously existing but non-specific and/or mild symptoms. They are mostly associated with spondyloarthritis (SpA). The prevalence of SpA in patients with HLA-B27 uveitis is predicted to be between 58% and 78%.(Tay-Kearney et al., 1996) (Monnet et al., 2004) (Linssen and Meenken, 1995). The axSpA is a group of chronic inflammatory diseases characterized by typical clinical features, such as axial inflammation, enthesitis and extra-articular manifestations associated with HLA B-27 positivity. The rheumatic symptoms usually precede the first attack of uveitis in more than 80% of the cases (Pathanapitoon et al., 2016), but AAU can still be the first sign of HLA-B27 associated SpA in a number of patients. According to a recent observational study, patients with AAU who were referred because of persistent back pain had a significant prevalence of axSpA. (23% had definite SpA, and 40% had high suspicion of SpA) (van Bentum et al., 2022). They also noted that there was a substantial diagnostic delay in the majority of patients with recurrent AAU as patients had symptoms of chronic back

pain in the previous attacks but were not referred for further evaluation. The paper concluded that ophthalmologists need to be more aware of the need to refer cases of AAU with chronic back pain to rheumatologists. A simple algorithm called the DUET (Dublin Uveitis Evaluation Tool) has been devised to simplify referral characteristics to rheumatologists for the ophthalmologists (Haroon et al., 2015). Ankylosing spondylitis is the most common of the associated SpA (54.2%), followed by Reiter's syndrome (27.6%) and inflammatory bowel disease (12.7%) (Monnet et al., 2004). The Assessment of SpondyloArthritis international Society (ASAS) classification criteria provides a guide for how to diagnose a patient with back

Table 4: Assessment of SpondyloArthritis international Society (ASAS) Classification criteria for axial and peripheral spondyloarthritis. Modified from (Rudwaleit et al., 2009), (Rudwaleit et al., 2011).

ASAS Classification Criteria		
Classification Criteria for Axial SpA		**Classification Criteria for Peripheral SpA**
Sacroiliitis on Imaging Plus ≥1 SpA Feature	Or HLA-B27 Plus ≥2 SpA Features	Arthritis (peripheral) or enthesitis or dactylitis
SpA features: • Inflammatory back pain • Arthritis • Enthesitis (heel) • Uveitis • Dactylitis • Psoriasis • Crohn disease/ulcerative colitis • Good response to NSAIDs • Family history for SpA • HLA-B27 • Elevated CRP	Sacroiliitis on imaging: • Active inflammation on MRI highly suggestive of sacroiliitis with SpA • Definite radiographic sacroiliitis according to the modified New York criteria	PLUS ≥1 Spondyloarthritis feature • Uveitis • Psoriasis • Crohn disease/ulcerative colitis • Preceding infection • HLA-B27 • Sacroiliitis on imaging OR ≥2 other spondyloarthritis features • Arthritis • Enthesitis • Dactylitis • Inflammatory back pain • Family history for SpA

Table 5: Ocular involvement in various systemic conditions.

Disease	Ocular manifestation
Ankylosing Spondylitis (Haroon et al., 2015) (Khan et al., 2015) (Barisani-Asenbauer et al., 2012)	Acute anterior uveitis Conjunctivitis
Reactive Arthritis (Kiss et al., 2003)	Conjunctivitis Anterior uveitis Keratitis Scleritis Cystoid macular edema Papillitis
Inflammatory Bowel Disease (Lyons and Rosenbaum, 1997) (Troncoso et al., 2017) (Singh et al., 2004)	Scleritis/episcleritis Conjunctivitis Anterior uveitis Retinal vasculitis
Psoriatic Arthropathy (Rehal et al., 2011) (Kolomeyer et al., 2014)	Panuveitis uveitis Scleritis Conjunctivitis Dry eye Keratitis Corneal melt
Undifferentiated Spondyloarthropathy	Anterior uveitis (acute or chronic) Vitritis Retinal Vasculitis

pain and/ or joint pain and HLA B 27 positivity with axial or peripheral spondyloarthritis (Table 4). Table 5 outlines the ocular involvement in various systemic conditions.

Ankylosing Spondylitis (AS)

The prevalence of AS in the general population is estimated to be between 0.5%-1.0% (Rudwaleit and Taylor, 2010). Among Caucasian patients with AS, almost 90-95% will be HLA-B27 positive. The cumulative risk of uveitis among patients with ankylosing spondylitis is estimated variably, with some as high as 55% but usually reported as approximately 25%. Classification criteria for AS were first attempted in 1961 with the Rome criteria, followed by the New York criteria in 1984. These relied on radiographic demonstration of sacroiliitis. Computerized tomography and magnetic resonance imaging are more sensitive than conventional radiography and are hence more useful in demonstrating early sacroiliitis. According

to the classification criteria proposed by the Assessment of SpondyloArthritis international Society (ASAS), spondyloarthritis is now divided into axial SpA (spinal and/ or sacroiliac involvement), or peripheral SpA, axial SpA is further divided into radiographic or non-radiographic axial SpA (Rudwaleit et al., 2009) (Rudwaleit et al., 2011). Here it is important to note that classification criteria are different from diagnostic criteria in that classification criteria are more specific and devised for research purposes rather than clinical scenarios. Among the most common extra-articular features of SpA is uveitis.

Reactive Arthritis (ReA)

This entity was formerly called Reiter's disease. It was classically diagnosed by a clinical triad of non-specific urethritis, arthritis and conjunctivitis and/or iritis (Brewerton et al., 1973). It is the second most commonly associated SpA (Monnet et al., 2004). Similar to AS, it is more common in males than females and tends to occur in the age range of 16- 60 years, with the mean age of diagnosis being 29 years. The mean age of presentation to a uveitis clinic has been reported as 37.3 years (Kiss et al., 2003). It may be post-infectious, following nongonococcal (chlamydia, ureaplasma), urethritis or infectious dysentery. Systemic conditions associated with ReA include the characteristic skin condition where brown aseptic abscesses occur on palms and soles of the feet (*keratoderma blenorrhagicum*), mouth ulcers, circinate balanitis, Achilles tendonitis plantar fasciitis and aortic incompetence. Ocular involvement is very common; in a retrospective study of 25 patients with ReA, it was seen that all patients demonstrated ocular involvement at the time of diagnosis (68% with unilateral and 32% with bilateral disease), 84% had evidence of uveitis, 3% had scleritis, 2% had conjunctivitis, and 1% had pars planitis and iridocyclitis (Kiss et al., 2003). The cumulative risk of uveitis in these patients is about the same as in AS (up to 55%, but typically around 25%).

Inflammatory Bowel Disease (IBD)

IBD includes Crohn's disease and ulcerative colitis (UC). It is a chronic, relapsing, inflammatory disorder of the gastrointestinal tract. The frequency of HLA-B27 among these patients is lower, around 7%. They are characterized by recurrent, often bloody diarrhea associated with abdominal cramping (Ye et al., 2015) (Silva et al., 2016). There is a female preponderance among patients with IBD (Lyons and Rosenbaum, 1997). Ocular involvement is infrequent, occurring in less than 10% of cases, but can be associated with significant morbidity, including blindness (Mintz et al., 2004). Episcleritis, uveitis and scleritis are frequent ocular manifestations. Anterior uveitis in these patients has an insidious onset; it is longstanding and bilateral and not related to intestinal disease activity (Troncoso et al., 2017). Occurrence of isolated retinal vasculitis is also seen in these patients, most often due to Crohn's disease (Ruby and Jampol, 1990) (Duker et al., 1987) (Sykes and Horton, 1997) (Khan et al., 2015). The cumulative risk of uveitis in these patients is around 10-20%.

Psoriatic Arthropathy (PsA)

Psoriasis is a chronic autoimmune condition with many extra-articular manifestations, of which ocular are common but subtle (Rehal et al., 2011). Ocular manifestations included panuveitis (50%), scleritis (25%), keratitis, corneal melt, peripheral ulcerative keratitis, iritis (17%), and inflammatory glaucoma, uveitic cataract, uveitic papillitis, pigmentary retinopathy, epiretinal membrane, and phthisis (8.3%). (Kolomeyer et al., 2014) The frequency of HLA-B27 among patients with psoriatic arthritis is around 24%, and the cumulative risk of uveitis is 10-20%.

Undifferentiated Spondyloarthropathy

This condition is diagnosed in patients with spondyloarthropathy that does not fall clearly into one of the categories mentioned above. Uveitis may occur in both eyes simultaneously in these conditions and may be chronic. Vitritis, retinal vasculitis and exudative retinal detachment may also occur.

LABORATORY INVESTIGATIONS

All patients with recurrent non-granulomatous AAU or recurrent anterior uveitis, which has evolved into chronic anterior uveitis, should undergo HLAB-27 testing, preferably using the polymerase chain reaction method as serological techniques such as flow cytometry are rapid and relatively inexpensive but lack specificity (Chheda et al., 2018).

Haroon *et al*. have validated an algorithm (DUET- Dublin Uveitis Evaluation Tool) for referral from ophthalmologists of appropriate AAU patients to the rheumatologist, which will lead to early diagnosis of spondyloarthritis (Haroon et al., 2015). This uses the ASAS criteria for diagnosing SpA.

ANCILLARY INVESTIGATIONS

These are usually indicated in cases of atypical presentation like posterior segment involvement. Optical coherence tomography (OCT), ultrasonography (USG) and fundus fluorescein angiography (FFA) being the most commonly used investigations to detect posterior segment involvement (Monnet et al., 2004) (Braakenburg and Rothova, 2014) (Dodds et al., 1999) (Rodriguez et al., 1994). Retinal vascular involvement was confirmed by using FFA in a 36-year-old male with ankylosing spondylitis after cataract surgery (A. K. Majumder et al., 2018). USG B scan is recommended in HLA-B27-associated uveitis in long-standing media opacities with severe inflammation to look for serous retinal detachment (van der Veer et al., 2014) (Preusser et al., 2012) (Belcon et al., 1984). USG B scan can be a valuable tool in the diagnosis of posterior scleritis in HLA B27 patients (Anshu and Chee, 2007).

OCULAR COMPLICATIONS

Studies from tertiary referral centers report a complication rate of over 65% in HLA B-27 positive AAU patients (Linssen and Meenken,

1995) (Power et al., 1998) (Lakra et al., 2021). The most common ocular complication of HLA B-27 positive AAU is posterior synechiae, the prevalence of which has been variably reported between 13% and 91% (Monnet et al., 2004) (Linssen and Meenken, 1995) (Power et al., 1998) (Lakra et al., 2021). Other frequently reported complications include cataract, ocular hypertension, glaucoma, cystoid macular oedema, epiretinal membrane, hypotony and phthisis (Tay-Kearney et al., 1996) (Monnet et al., 2004) (Linssen and Meenken, 1995) (Power et al., 1998) (Lakra et al., 2021).

Secondary involvement of the posterior segment can present as vitritis, macular oedema, or papillitis (Monnet et al., 2004) (Dodds et al., 1999) (Rodriguez et al., 1994) (Lakra et al., 2021). Severe cases of HLA B-27 associated uveitis with protracted hypotony have also been reported (Pathanapitoon et al., 2016) (Lakra et al., 2021) (Roe et al., 2008) (P. D. Majumder et al., 2018).

MANAGEMENT

The first line of treatment for acute anterior uveitis is topical steroids with cycloplegics. Intense topical steroid application in the initial period is important to control inflammation. HLA-B27-associated uveitis is often thought to be easy to control, but recurrences are more frequent than in idiopathic recurrent uveitis, and the complication rate is higher. Therefore, many patients require additional therapy to prevent recurrences of the uveitis and the complications associated with repeated topical steroid use. Systemic NSAIDs may be invaluable in these patients both for preventing recurrences and in controlling joint inflammation.

When long-term systemic therapy is required, oral steroids are not the ideal agent due to the multiple systemic side effects associated with it. Immunosuppressive agents are preferred in such situations. In the case of failure to control the recurrence of inflammation with adequately high doses of immunosuppressives (such as methotrexate and azathioprine), a combination of immunosuppressives can be considered.

The introduction of biological treatments, especially those targeting tumour necrosis factor α (anti-TNF α), has dramatically improved the management of rheumatic diseases, such as rheumatoid arthritis and juvenile idiopathic arthritis (JIA) and spondyloarthritis (SpA). Anti-TNF α agents have become a valuable addition to the therapeutic armamentarium for patients with associated uveitis that is refractory or intolerant to conventional treatment. Biologic agents are a class of therapeutic drugs that target different mediators involved in the pathogenesis of human diseases; in inflammatory diseases, the therapeutic target of a biologic is often a specific protein of the immune system related to inflammatory processes. Biologics include monoclonal antibodies, soluble receptors, cytokines themselves (such as interferons), and natural cytokine antagonists (Pasadhika and Rosenbaum, 2014).

ANTI-TNF α AGENTS

TNF α has been implicated as a pro-inflammatory mediator in the pathogenesis of various forms of uveitis, including AAU, in both human and experimental animal studies, thus recognised as a potential therapeutic target. Five anti-TNF α agents are currently available: infliximab, etanercept, adalimumab, certolizumab pegol, and golimumab.

Infliximab: A murine human chimeric monoclonal antibody directed against human TNF-α, it neutralizes the soluble and membrane-bound form of cytokine and has shown to be a rapid, effective and relatively safe therapy of sight-threatening ocular inflammation in Behçet's disease and refractory posterior uveitis.

Adalimumab: It is a fully human monoclonal antibody targeting TNF α. Adalimumab has been approved by the United States Food and Drug Administration (FDA) for treating non-infectious intermediate, posterior, and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing therapy, or in whom corticosteroid treatment is inappropriate (Jaffe et al., 2016) (Ming et al., 2018). It has proven to be effective and relatively safe in the treatment of various inflammatory diseases associated with HLA-B27, such as anterior uveitis, AS, Crohn's disease, psoriatic arthritis and juvenile rheumatoid arthritis. It is also a first-line agent in the management of Behçet's disease; and a second-line immunomodulatory agent for the treatment of uveitis associated with JIA and for the treatment of severe posterior uveitis or panuveitis who have failed with or are not candidates for immunomodulation with antimetabolite or calcineurin inhibitor (Levy-Clarke et al., 2014).

Etanercept: It is a genetically engineered fusion protein consisting of a ligand binding portion of human TNF receptor p75 and the Fc domain of human IgG1, which binds and inactivates both TNF α and TNF β. Substantial data suggest that etanercept has lower efficacy for treating uveitis than other anti-TNF antibodies and should not be used in AS patients with uveitic symptoms (Levy-Clarke et al., 2014). A possible reason is the less stable bond formation of etanercept with TNF α, particularly the transmembrane form, while both Infliximab and Adalimumab bind effectively to the soluble and transmembrane forms (Scallon et al., 2002).

Golimumab: It is a fully human anti-TNFα monoclonal antibody; studies have shown successful control of severe uveitis is seen in JIA, Behçet's disease and severe forms of HLA-B27 uveitis using golimumab (P. D. Majumder et al., 2018) (Cordero-Coma et al., 2011) (Mesquida et al., 2013) (William et al., 2012) (Lanz et al., 2021) (Faez et al., 2014). It also offers the advantage of subcutaneous injection only once a month compared to fortnightly injections in adalimumab.

Certolizumab pegol: This consists of a PEGylated recombinant humanized antibody

Fab fragment against TNF α. Pegylation of the antibody delays the elimination. Certolizumab pegol is an effective option for the treatment of axial spondyloarthropathy and psoriatic arthropathy (Dhillon, 2014). Table 6 encapsulates the biologics available for clinical use in HLA B27 SpA.

ADVERSE EVENTS

Anti-TNF α agents carry a specifically increased risk of tuberculosis (TB), usually reactivations of latent disease (Keane et al., 2001). The risk is higher with infliximab and adalimumab than with etanercept (Dixon et al., 2010). Screening for latent tuberculosis is necessary for patients starting biologics. Other opportunistic infections, especially caused by intracellular microorganisms, may develop in patients receiving anti-TNF α treatment. Several demyelinating and neurologic events, including exacerbations of pre-existing multiple sclerosis, have been reported in patients receiving anti-TNF α agents (Cunningham and Zierhut, 2010). Use of Anti TNF α has been estimated to increase the risk of non-melanoma skin cancer (Atzeni et al., 2015), paradoxical exacerbation of sarcoidosis and psoriasis (Wendling and Prati, 2014), paradoxical scleritis (Gaujoux-Viala et al., 2012). Anti-TNFα agents can induce the formation of neutralizing antibodies, resulting in loss of efficacy and the appearance of infusion reactions (Van den Bosch and Deodhar, 2014).

ANTI TNF α AGENTS FOR ACUTE HLA B-27 UVEITIS ATTACK

Role of Infliximab in treating an acute attack of uveitis has been reported (Van den Bosch and Deodhar, 2014). Use of golimumab in a case of refractory HLA B-27 uveitis has also been recently reported (Calvo-Río et al., 2014).

ANTI TNF α AGENTS IN PREVENTING HLA B-27 UVEITIS RELAPSES

The primary role of anti-TNF α agents in clinical practice lies in preventing relapses of uveitis. Infliximab, adalimumab and golimumab are better at reducing rates of uveitis flare-ups when compared to etanercept (Guignard et al., 2006).

Table 6: Biological agents used in the treatment of HLA B27-associated uveitis with or without systemic involvement.

Name	Composition	Directed against
Infliximab	Murine human chimeric monoclonal antibody	TNF-α
Adalimumab	Fully human monoclonal antibody	TNF-α
Etanercept	Genetically engineered fusion protein	TNF α and TNF β
Golimumab	Fully human monoclonal antibody	TNF-α
Certolizumab pegol	PEGylated recombinant humanised antibody Fab fragment	TNF-α

OTHER BIOLOGIC MODIFIER DRUGS IN HLA B-27 ASSOCIATED UVEITIS

ANTI-INTERLEUKINS (IL): Therapies targeting the IL-23 / IL-17 axis are being explored to treat HLA B-27-associated uveitis.

Anti- IL17 therapy: Secukinumab is a fully humanized, anti-IL-17A monoclonal antibody. Phase III studies showed reduced clinical and biologic signs of active AS and psoriatic arthritis (Van den Bosch and Deodhar, 2014).

Anti-IL 12/23 therapy: Ustekinumab is a fully-humanized monoclonal antibody with a high affinity for the common p40 subunit of IL-12 and IL-23. Recent studies have reported a beneficial effect of ustekinumab in the treatment of SpA and axial disease in AS patients (Baeten et al., 2015).

Other molecules like anakinra (IL-1receptor antagonist), Tocilizumab and sarilumab (Humanized monoclonal antibodies targeting IL6, cytotoxic T-cell and B-cell targeted therapies like Rituximab (CD 20-directed cytolytic antibody), abatacept (soluble fusion protein which blocks CD 80, CD 86) have been tried but have failed to show good clinical efficacy in AS (Sieper et al., 2014)(Song et al., 2011).

CONCLUSION

HLA-B27-associated uveitis is a commonly encountered entity in the uveitic clinic. Its management must be in coordination with a rheumatologist. Early and intense steroid treatment for acute uveitis along with appropriate immunomodulatory and/ or biologic therapy, when indicated, can prevent significant ocular and systemic morbidity. Newer agents continue to be explored for cases which are recalcitrant to or intolerant of more traditional immunomodulation.

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