



Recent Developments in HLA B27 Anterior Uveitis

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There has been steady progress in understanding the pathogenesis, clinical features, and effective treatment of acute anterior uveitis (AU) over the past 5 years. Large gene wide association studies have confirmed that AU is a polygenic disease, with overlaps with the seronegative arthropathies and inflammatory bowel diseases, associations that have been repeatedly confirmed in clinical studies. The role of the microbiome in AU has received increased research attention, with recent evidence indicating that human leukocyte antigen B27 (HLA B27) may influence the composition of the gut microbiome in experimental animals. Extensive clinical investigations have confirmed the typical features of acute AU (AAU) and its response to topical, regional and systemic immunosuppressive treatment. Increased understanding of the role of cytokines has resulted in studies confirming the value of anti-cytokine therapy [anti-tumor necrosis factor (anti-TNF) and interleukin 6 (IL-6) therapy] in severe and recurrent cases of AAU, particularly in subjects with an associated spondyloarthropathy (SpA) and in juvenile idiopathic arthritis (JIA)-associated AAU.

Keywords: acute anterior uveitis, HLA B27, pathogenesis, microbiome, review

INTRODUCTION

Uveitis is a common vision threatening inflammatory eye disease with a reported annual incidence of between 17 and 52 per 100,000 and prevalence of between 38 and 370 per 100,000 of the population (1–4). The disease is most common in children, young and middle-aged adults. Uveitis and its complications account for up to 10% of those with severe vision impairment and blindness (5). Anterior uveitis (AU) is present in up to 90% of cases of uveitis and approximately 50% of all patients with acute AU (AAU) are human leukocyte antigen B27 (HLA B27) positive. HLA B27 is also strongly associated with ankylosing spondylitis (AS), reactive arthritis (ReA), and other spondyloarthropathies (SpA) (6). These associations are among the strongest of any HLA antigen to a human disease, although the pathogenetic mechanism(s) involved remain unknown (7). There has been relatively little research devoted to the immunopathogenesis of HLA B27 AAU, compared with the numerous studies of the immunopathogenesis of the SpA's.

Evidence that HLA B27 is directly involved in the pathogenesis of this group of diseases is supported by the fact that HLA B27 is associated with AAU and SpA in many populations and ethnic groups, in the context of over 140 haplotypes (the HLA B2705 subtype is the most common

in Caucasians). Secondly, some HLA B27 subtypes are not associated to AAU or SpA, suggesting that subtype polymorphism modulate disease susceptibility, and thirdly, HLA B27 transgenic rats and mice develop a disease that strongly resembles human SpA, although these animals do not spontaneously develop AAU (8).

CLINICAL FEATURES OF HLA B27 ANTERIOR UVEITIS

In a large study of over 2000 patients with axial SpA from 83 rheumatology centers in the United Kingdom 23.5% of the patients in the cohort reported at least 1 episode of AAU. The mean age of patients was 51 years with a male to female ratio of 2:1. The factors associated with increased prevalence of AAU in this cohort were HLA B27 positivity, university education, age, and the presence and duration of axial spondylo-arthritis (9). There is a well-defined clinical phenotype for patients with AAU associated with spondyloarthritis which was confirmed in a study by Peizeng et al. in a large Chinese population (10). Typical symptoms include: acute onset of blurred vision, ocular redness, pain and photophobia. Important clinical descriptors include: unilateral episodes, alternation between eyes, sudden onset and limited duration. HLA B27 AAU is non-granulomatous and characterized by flare and cells in the anterior chamber that commonly spills over into the anterior vitreous. Other clinical features such as hypopyon and posterior synechiae may occur. HLA B27 associated uveitis is nearly always confined to the anterior uvea as AAU, although uncommonly there can be prominent intermediate uveitis and involvement of the posterior segment (11). A Chinese study also found that asymptomatic previously unrecognized, retinal vascular involvement often involving the peripheral retina is not uncommon (10). HLA B27 associated AAU is further characterized by recurrences, which are more frequent early in the course of the disease and become less frequent with the duration of disease (12).

Severe and/or recurrent episodes of AAU may result in structural complications such as cataract, elevated intraocular pressure, glaucoma and cystoid macular oedema, which become increasingly common with multiple episodes of uveitis (13). Some patients develop chronic AU following very severe attacks or frequent recurrences. D'Ambrosia and colleagues performed a literature-based meta-analysis to characterize the clinical features and complications associated with HLA B27 AU. The results confirmed the strong association of AU with AS, increased male prevalence, unilateral alternating episodes of uveitis often characterized by a fibrinous inflammatory reaction with or without hypopyon, and occasionally optic disc swelling. The prevalence of raised intraocular pressure and glaucoma were more common in the HLA B27 negative cases of AAU. Interestingly, they concluded that there is no significant difference between HLA B27 positive and HLA B27 negative AAU with regard to final visual acuity and structural complications, such as posterior synechiae, cataract, and macular oedema (14).

GENETICS AND ANTERIOR UVEITIS

The heritability of HLA B27 AAU has a strong association with the major histocompatibility complex (MHC) type 1 allele which over 50% of those with primary AAU possess (7). In an examination of 152 first degree relatives of 42 randomly selected HLA B27 AAU patients, 6% were found to develop the condition (15). The same Dutch study also identified that there may be other genetic factors influencing inheritance, with higher rates of proband first degree relatives developing AAU than in the normal HLA B27 population (15). Recent genotyping studies have supported this observation with several non MHC loci demonstrating genome wide association significance. In one study comparing AAU subjects to healthy controls using the Illumina ImmunoChip, associations were established with ERAP1, IL23R, and the intergenic region 2p15 (16).

The first genome wide association study (GWAS) of patients with AAU with or without AS identified new susceptibility genes and confirmed the strong association of HLA B27 AAU with SpA (17). Gene associations were observed for 11 loci, including the previously reported ERAP1 and NOS2. Associations were also found at previously unrecognized sites for AS and AU including MERTK, KIFAP3, CLCN 7, ACAA2, and five intergenic loci (17). A number of genetic factors critical to the immune response to microorganisms, such as IL10, IL18R1-IL1R1, IL6R, and KIF21B, were previously reported in a GWAS study of patients with AS and AAU (16).

Despite the association of the ERAP1 gene with HLA B27 SpA and AAU the role of this gene in peptide selection and processing in the pathogenesis of these diseases has not been defined. Barnea et al. examined the effect of ERAP1 deletion in HLA B27 transgenic rats. The male HLA B27 transgenic rats develop a spondylo-arthritic type of disease, but not AU, and have been used as a model of spondylo-arthritis. Deletion of the ERAP1 gene did not affect the development of SpA (18). Interestingly, examination of the peptidomes of rats susceptible to arthritis was similar to those of non-susceptible rats and no peptides were found to be uniquely associated with arthritis.

Using next generation sequencing to identify T-cell receptor beta motifs and amino acid sequences specific to HLA B27 positive patients with AS. Faham et al. recently reported sequences specific to AS, indicating that specific antigens possibly related to the pathogenesis of AS may be identifiable using such an approach (19). Such studies have not been reported in patients with HLA B27 associated AAU but could yield results strengthening the argument that CD8 positive T cells are pivotal in the pathogenesis of this disease.

INFECTION AND HLA B27 AAU

There is considerable epidemiological, clinical, and experimental evidence in patients with AU implicating the role of microbial infections as part of the molecular mimicry or arthritogenic peptide hypothesis. In particular, infection with *Chlamydia Trachomatis* and gram negative bacteria including *Klebsiella*,

Salmonella, *Yersinia*, *Shigella* species, and *Campylobacter jejuni*, has been reported to trigger AU and SpA (20–22). Furthermore, there is compelling evidence implicating *Chlamydia trachomatis* in the pathogenesis of ReA and undifferentiated spondylarthroses (19, 20, 22–24). More recently, epidemiological evidence has emerged implicating *Ureaplasma Urealyticum* (25) and a yet to be identified fungus (26) with the occurrence of uveitis. We have previously provided evidence for the role of microbial triggers in the pathogenesis of HLA B27 AAU, by demonstrating humoral and cellular immune responses to *C. trachomatis* and *Yersinia* (26, 27).

Schofield et al. have delineated potential inciting peptide sequences common between enteric bacteria capsules and the third hypervariable region of the HLA B27 molecule (28). Further studies in this vein have found that *Klebsiella* nitrogenase shares six consecutive amino-acids with HLA B27 (29) and surface proteins of *Salmonella*, *Yersinia*, and *Shigella* have homologous sequences (30). Investigating mice models of disease Horai and colleagues demonstrated that the presence of enteric bacteria triggers retinal specific auto reactive T cells and subsequently spontaneous uveitis (31). Unfortunately, attempts to further localize the effect to self-peptides or self-antigens have thus far failed.

Schittenhelm and colleagues have searched for the existence of disease inducing peptides, the so-called arthrogenic or uveitic peptide(s) proposed to be important in the pathogenesis of HLA B27 related diseases (32). Using sophisticated Mass Spectroscopy they examined 1,500 epitopes across several different HLA class I allotypes (HLA B27:02- HLA B27:09). Analysis of this large data set identified 26 peptides, which were present in lower abundance by non-disease-related HLA B27 allotypes compared with the disease associated HLA B27 subtypes. It is yet to be ascertained whether these peptides represent the arthrogenic peptide proposed to cause SpA's. The high amount of overlap found in the absolute peptide binding preferences of the HLA B27 allotypes (:02 to :09) has shifted the focus of the arthritogenic peptide hypothesis to quantitative analysis of peptide binding conformation, self-peptide presentation and T cell activation (33). It would be of great interest to use similar technology to identify potential peptides related to HLA B27 AU.

THE ROLE OF THE MICROBIOME

There is considerable recent interest in the role of the microbiome in influencing immune responses and susceptibility to diseases such as Crohn's disease, ulcerative colitis, SpA's, and uveitis (34–36). Studies in HLA B27 transgenic rats demonstrate an altered microbiome compared to non-transgenic animals (37). The mechanisms by which the microbiome may influence immune responses are poorly understood. One theory is that gut microbes or their products may alter the permeability of the gut wall allowing translocation of bacteria and/or microbial products to regional lymph nodes, which generate a systemic immune response. Such increased gut permeability has been described in

patients with AS and inflammatory bowel disease. Patient with ReA have had microbial antigens detected in joint fluid and subsequently been shown to have a clinical response to antibiotic therapy (38). Additionally, endotoxin, which is a component of Gram negative bacteria cell-walls has been shown in experimental animals to induce AU when injected into the foot pad of rodents (39). Similarly, we have shown that patients with active AU have increased expression of Toll like receptors 4 (which binds endotoxin) in the peripheral blood during acute attacks of AU (40). An alternative theory holds that there is molecular mimicry between microbial and self-antigens. Such microorganisms and their associated antigens may generate an immune response whereby antibodies or T cells cross-reacts with self-antigens as is known to occur in diseases such as rheumatic fever and post-infection Gilliam Barré syndrome (41). Thirdly, it has been shown that the microbiome may affect the immune response by influencing T cells to synthesize increased amounts of IL-17 and the number of regulatory T cells that express the transcription factor fox P3 (42). Furthermore, it has been shown that a large number of microbial peptides bind the HLA B27 molecule and such microbial peptides may induce an immune response in certain target organs such as the eye and joint (43). We have recently shown, for example, that peptides derived from *Chlamydia trachomatis* bind the HLA B27 molecule and when such peptides are injected with adjuvant into experimental animals they induce an arthritis and less frequently AU (27).

An immune response to peptides derived from gut microorganisms (microbiome) could cross-react with endogenous peptides leading to the development of AU (34). This concept is strengthened by the results of the recent studies indicating that a large number of peptides derived from microorganisms bind to the HLA B27 molecule as well as our studies showing increased affinity of chlamydia and derived peptides for the HLA B27 molecule (27, 28, 44–46). We have also shown that immunizing rats with chlamydia derived peptides leads to a polyarthritis and occasional uveitis in these animals (47). Furthermore, a peptide (C34) derived from type VI collagen was shown to be recognized by CD8⁺ T cells from patients with AS (48). Additionally, cross-reactivity between *chlamydial* peptides and homologous peptides from the heart muscle-specific protein -myosin was shown to be involved in the pathogenesis of autoimmune myocarditis in mice (49).

The microbiome of the aqueous humor has not been examined in patients with acute and recurrent AU. The anterior chamber of the eye is usually considered to be sterile, although a recent study indicated that in fact the aqueous humor may have a microbiome that was previously unrecognized (50). Examination of the aqueous humor for evidence of microorganisms during acute attacks of AU could reveal valuable information with regard to the microbial and immunological mechanisms underlying this common inflammatory disease. If the gut microbiome does play a key role in diseases induction, a variety of therapeutic strategies could be developed to alter the microbiome or the immune response to particular microorganisms implicated to prevent or ameliorate the development of immune mediated diseases such as AAU and SpAs.

IMMUNE MECHANISMS AND ANTERIOR UVEITIS

Immune mechanisms involved in the pathogenesis of AU have been investigated in human and animal studies. It was recently reported that in patients with HLA B27 AAU the aqueous humor concentration of CC chemokines, including CCL8, CCL13, and CCL20, were upregulated, compared with patients with granulomatous uveitis and control subjects (51). Such chemokines play a key role in attracting inflammatory cells to the eye during attacks of uveitis and may represent potential therapeutic targets.

The pro-inflammatory cytokine IL-6 has previously been shown to be produced by ocular parenchymal cells and to promote the differentiation of B cells to plasma cells (52). Recently Kumar et al. demonstrated that tear levels of IL-6 and IL-10 are elevated during acute and multiple episodes of uveitis (53) building on previous work identifying elevated IL-6 levels in human aqueous (54), vitreous and monocyte culture supernatant (55). In a study examining cytokine profiles of specific uveitic entities Abu El-Asrar et al. discovered elevated GM-CSF, IL-11, and IL-35 levels in HLA B27 AAU (56). IL-11 is classed within the IL-6 family, based on its shared use of the glycoprotein-130 receptor β -subunit (57) and in the study had a particularly strong association with disease activity. The coupled elevation of inhibitory cytokines IL-35 and IL-10 with IL-6 and IL-11 may represent an immunoregulatory response in uveitis (53, 56).

A recent study by Zhao et al. reported increased levels of IL37 mRNA and protein expression by peripheral blood mononuclear cells from patients with active AAU compared with control (58). There was no difference between HLA B27 positive and negative patients with AAU. Interestingly IL37 was shown to inhibit the production of pro-inflammatory cytokines, including IL-1, IL-6, IL-10, IL-21, IL-23, TNF, and gamma interferon in the supernatant of dendritic cells (58). Thus, IL37 may inhibit pro-inflammatory cytokines in patients with AAU and may be a new therapeutic approach to treating this disease.

It has previously been demonstrated that HLA B27 homodimers on the surface of T-cells, monocytes and natural killer cells may trigger innate immune mechanisms through binding to killer immunoglobulin-like receptors (KIR) (59). Specifically, KIR3DL2 receptor expression has been found to be increased on NK cells in the peripheral blood of patients with HLA B27 AAU, associated with higher active numbers and increased cytotoxicity (60). Using flow cytometric methods Huang et al. have now also implicated mucosa associated innate lymphoid (MAIT) cells, which in the study produced more IL-17A than controls (61), an important proinflammatory cytokine seen in HLA B27 AAU (62, 63).

In a comparison of peripheral monocytes in patients with idiopathic uveitis against those with HLA B27 AAU using ELISA methods, increased expression of S100A8/A9 was found in patients with HLA B27 AAU outside of uveitis episodes accompanied by heightened numbers and activity of monocytes and T cells (64).

NEW DEVELOPMENTS IN THE TREATMENT OF HLA B27 ANTERIOR UVEITIS

A better understanding of the pathogenesis of AAU will provide new avenues for management of uveitis with the possibility of specific therapy that can alter the natural history or even cure uveitis. At present, treatment options consist of local or systemic anti-inflammatory or immunosuppressive drugs, which may be associated with treatment limiting side effects.

Current first line therapy for acute episodes of HLA B27 AAU is a cycloplegic, typically atropine 1%, and very frequent administration of potent topical corticosteroids (1–2 hourly) which are then slowly tapered over 8–10 weeks (65). The so called “steroid response” leads to elevated intraocular pressure in up to 30% of patients using topical corticosteroids, often requiring the addition of pressure lowering medication and requiring cessation of topical corticosteroid therapy in some patients. Corticosteroid therapy is also associated with increased rates of posterior subcapsular cataract (66). Although a large randomized clinical trial of 193 subjects failed to achieve non-inferiority of iontophoresis as a method to increase anterior chamber corticosteroid levels compared to topical therapy, there was a promising signal that should be tested using larger data sets (67).

In patients with vision threatening uveitis, periocular corticosteroid injections are safe and efficacious, either alone or as adjuncts to systemic therapies (68). Peri- and intra-ocular injections reduce macular oedema which is the major inflammatory mediated cause of visual loss in uveitis patients (69). Regional corticosteroid therapies have a relatively short duration of effect necessitating 3 to 6 monthly injections. The development of both bioerodible (Iluvien) and non-biodegradable (Retisert) intravitreal implants of polymers allow the controlled release of fluocinolone acetate into the vitreous for up to 3 years. Both the multicenter uveitis steroid treatment (MUST) study and a recent Cochrane review that compared Retisert implants to systemic combination immunosuppressive therapy, showed that systemic therapy resulted in superior visual outcomes and lower rates of raised intraocular pressure, cataract formation, retinal detachment and endophthalmitis (70). There was no difference in systemic side effects such as weight gain, diabetes and hypertension in the two groups and the only significant adverse outcome was increased use of antibiotics for infections in those on systemic therapy (71). Nearly two thirds of the patients in the systemic therapy arm of the MUST study required intermittent local corticosteroids.

The systemic treatment for eye diseases (SITE) cohort study retrospectively examined the efficacy of systemic therapies in 7,957 patients across five centers from 1979 to 2005 who had non-infectious ocular inflammatory disease. For patients with AU corticosteroid sparing success (tapering to 10 mg or less) was achieved over a 6-month period in 47.2% with mycophenolate mofetil, 16.6% with azathioprine, 28.5% with cyclosporine, and 46.1% with methotrexate (72–75). The role of disease modifying agents (DMARDs) have now been examined specifically in HLA B27 AAU with methotrexate and sulfasalazine both shown to

reduce relapse rates and methotrexate additionally proven to reduce AU related macular oedema (76).

There is significant evidence that anti-TNF alpha therapy is of benefit in patients with HLA B27 uveitis (77–80). In a retrospective analysis of 717 patients with SpA those who were treated with either infliximab or etanercept had 6.8 AAU recurrences per hundred patient years versus 15.6 in the placebo group (81). Data from the use of adalimumab in another cohort of 1,250 patients with SpA demonstrated an overall 51% reduction in uveitis recurrence rate (82). Further analysis of these cohorts showed that of the anti-TNF therapies available, anti-TNF antibodies appear to have greater efficacy than soluble TNF receptor blockers (83). Adding weight to this preference is a collection of case reports and new data from a large Swedish rheumatology study suggesting that in AS etanercept may induce new uveitis (84, 85). Prospective studies of anti-TNF antibodies have now been performed on small cohorts of patients with frequent and/or refractory AAU. The use of infliximab led to the complete resolution of HLA B27 AAU in 6 of 7 patients following an average of 8 days (86). The new anti-TNF alpha agent golimumab induced the remission of uveitis in 12 of 15 eyes with significant improvements in visual acuity (87). Certolizumab pegol has been used in AAU cases refractory to even previous biologic therapy and achieved quiescence in 5 of 7 patients (88).

The success of the antibiotic sulfasalazine as a DMARD in HLA B27 AAU adds weight to the prospect of targeting the microbiome for disease control. Clinical studies are currently underway evaluating faecal microbial transplants in AS and it will be interesting to see whether this influences rates of uveitis in these patients (89). If the gut microbiome does play a key role in diseases induction, a variety of therapeutic strategies could be developed to alter the microbiome or the immune response to particular microorganisms implicated to prevent or ameliorate the development of immune mediated diseases such as AAU and SpA's.

ADVANTAGES IN STUDYING HLA B27 ACUTE ANTERIOR UVEITIS

There are significant advantages in studying the immunopathogenesis of AAU as a pathophysiological model for HLA

B27 related disease. AAU is well defined disorder, that is readily and reliably diagnosed clinically by slit lamp bio-microscopy. Importantly there are agreed objective grading systems to determine the severity and changes in the grade of the protein exudation and cellular infiltration in the anterior chamber that characterize AU (90). Additionally, aqueous humor can be easily sampled for analysis. The natural history of AAU has been extensively studied and has a recurrent, relapsing and remitting course. Importantly, there is a group of subjects with a similar clinical phenotype, who are HLA B27 negative and form a relevant critical disease control group. The recurrent nature of the disease also has advantages for investigators studying environmental factors, such as the gut microbiome, that may trigger relapses of uveitis. There is a large number of patients with recurrent AAU, not on systemic therapy or immunosuppressive medication, which can influence immunological and bio-molecular investigations. As 50%–70% with HLA B27 AU have an associated systemic disease, usually a SpA or inflammatory bowel disease, subjects without confounding systemic disease can be studied and compared with subjects with systemic disease (91, 92).

CONCLUSION

AU is a relatively common polygenic disease, strongly associated with HLA B27 and a number of other inflammatory diseases that share a common gene pool. The function of HLA B27 and the other recently described genes predisposing to AAU is poorly understood. The role of infection and in particular the microbiome remain active areas of research, as does the importance of innate immunity in the pathogenesis of this disease. New insights into genetic, microbial, and immune mechanisms has the potential to lead to more effective preventative and suppressive forms of therapy.

AUTHOR CONTRIBUTIONS

All authors contributed to writing, editing, and reviewing the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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