Theme:
HLA-B27 Associated Uveitis
Dear Friends,

It is with great pleasure we bring to you the 6th edition of the USI newsletter. This edition features HLA B27 related uveitis. Our editorial team has compiled some interesting articles in this newsletter. The panel discussions by our national and international faculty addresses many queries on this disease. In addition, there is a section by the rheumatologists providing us interesting tips, which I am sure will be useful in our clinical practice.

I thank all the authors, our national and international panel for this edition and the editorial team for their coordinated efforts in bringing this interesting issue on HLA B27 uveitis.

Dr. Kalpana Babu
Prabha Eye Clinic and Research Centre, Bengaluru
kalpanababumurthy@gmail.com
Dear Friends,

Greetings!

At the outset, I consider it an honour to thank the team behind our Newsletter headed by Dr Balamurugan (Editor in chief – USI Newsletter). His passionate efforts and the unwavering support of the editorial team have made sure that the current Newsletter has become slick, and pleasing to the eye but still academically as enriching or more than the previous ones.

Grateful to all those who have been part of this edition – authors/discussants/contributors – for their valuable time and intent to share their knowledge.

Hope this edition also is well received as were the others. We are confident that the knowledge from this newsletter will help everyone in managing better this potentially blinding disease.
Am sure you all will enjoy it, because we did.

Dr. Sudharshan S
Sankara Nethralaya, Chennai
drdharshan@gmail.com
From the Desk of the
Editor - Newsletter, Uveitis Society (India)

Pleasure is mine to be the part of the elegant editorial team in the field of uveitis who have actively contributed for this wonderful edition of USI Newsletter on HLA B 27 related uveitis. I sincerely thank all the motivating leaders, contributors, readers, critics for propelling us to improve and refine our sincere efforts. The level of enthusiasm from the new team of US(I) since 2022 on the making of this newsletter is unparalleled! In fact, it has a high degree of motivation transmission index too!

All the bouquets pertaining to this newsletter are surrendered to the almighty. All the brickbats concerning this newsletter are valuable pearls for us to refine and define ourselves in the future. Understand that you ask me why....It’s because otherwise it wouldn’t have been a lucid garland in the lotus feet of the Almighty and maketh you to smile....

Dr. S Bala Murugan
Arun Avind Eye Hospital, Pondicherry
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Thank You!
Image Courtesy
Front Cover Page Image
Dr. Reema Bansal, Professor, PGIMER, Chandigarh
"Fibrinous acute anterior uveitis as the presenting feature of HLA-B27 positivity in a 7-year-old boy"

Back Cover Page Image
Dr. Meera Mohanakumar, Consultant, Aravind Eye Hospital, Coimbatore
"The Masquerading Lens"
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<table>
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<tr>
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<tr>
<td>Dr. Dipankar Das</td>
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<tr>
<td>Dr. Vinaya Kumar Konana</td>
</tr>
</tbody>
</table>
CONTENTS

Preface: HLA B 27 Associated Uveitis
Dr. Radhika T, Dr. Anuradha V K

Dr. Parthopratim Dutta Majumder

Basic Science: Immunopathology of HLA-B27 Uveitis
Dr. Mayur R Moreker, Dr. Mamatha Ventakesh

Mini Review: Differential Diagnosis of HLA B27 Uveitis
Dr. Namita Dave

Rheumatologist: HLA-B27 mediated Uveitis: Rheumatology’s Perspective & Tips for Ophthalmologists
Dr. Ramesh Jois

Case Series: Atypical Presentations and Challenging Cases Of HLA B27 Anterior Uveitis
Dr. Anup Kelgaonkar, Dr. Bharat Panigrahi, Dr. Soumyava Basu

Uvea-Rheumatology Interface: Juvenile Spondyloarthritis - Focus on Uveitis - Twelve Things Every Ophthalmologist Must Know
Dr. Mayur R. Moreker, Dr. Archana Khan, Dr. Neepa Dave, Dr. Raju Khubchandani

Perspectives: HLA B-27 associated Uveitis: Practise Pattern & Management
Dr. Kessara Pathanapitoon, Dr. Amit Khosla, Dr. Soumyava Basu

Challenge Your Understanding: HLA B-27 associated Uveitis: MCQs
Dr. Suchitra Biswal

Recent Advances: Role of Microbiome in HLAB27 associated Uveitis
Dr. Gazal Patnaik

Crossword: The HLA B-27 Challenge
Dr. Vidya Mooss

Journal Scan: HLA B-27 associated Uveitis : Literature Review
Dr. Gazal Patnaik

Awards and Recognitions
CMEs conducted under the aegis of Uveitis Society (India)
Challenge Your Understanding & Crossword Answers
Acute anterior uveitis is the most common uveitis and accounts for nearly 90% of all cases.\(^1\) Half the number of patients with anterior uveitis are HLA B27 positive.\(^2\) The disease is typically unilateral, acute in onset and recurrent affecting young adults in the most productive years of their life. There is an association between Human leucocytic antigen HLA B27, its spectrum of associated systemic inflammatory diseases and acute anterior uveitis. This association was first described in 1973 and is the strongest HLA disease association known till date.\(^3\) Hence understanding the relationship between acute anterior uveitis and HLA B27 antigen is of great significance.

HLA-B27 uveitis is associated with well described systemic diseases. This spectrum of diseases includes ankylosing spondylitis, reactive arthritis, inflammatory bowel disease and psoriatic arthritis. These entities are grouped as seronegative arthropathies. HLA B27 anterior uveitis is often the first indication of a previously undiagnosed HLA B27 associated inflammatory disease. The presence of HLA B 27 is a predictor of disease severity in patients with anterior uveitis.\(^4\) Patients with HLA B27 have about 2% risk for developing uveitis in their life time. This risk increases to 40% if they are diagnosed with ankylosing spondylitis or reactive arthritis while it is 7% for psoriatic arthritis and 11% for inflammatory bowel disease.\(^5\) Studies have shown that environmental factors and microbial agents like gram negative bacilli and chlamydia play a role in the pathogenesis of HLA B27 anterior uveitis.\(^6\) The mechanism by which this happens is not yet ascertained. However in recent times there has been significant progress in our understanding of the genetics, clinical features and immunopathogenesis of HLA B 27 disease entities.

### Diagnostic Criteria For HLA B27 Uveitis

The standardisation of Uveitis Nomenclature (SUN) Working group has set out the diagnostic criteria for spondyloarthropathies/ HLA-B27 anterior uveitis(2).

#### Classification Criteria for Spondyloarthropathies/HLA-B27-associated Anterior Uveitis

**Inclusion Criteria**

1. Evidence of anterior uveitis
   a. anterior chamber cells
   b. 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. ASAS-defined spondyloarthritis (axial or peripheral) and/or HLA-B 27 positive OR
4. Chronic uveitis with both ASAS-defined spondyloarthritis (axial or peripheral) AND HLA-B27 positive

**Exclusions**

1. Positive serology for syphilis using a treponemal test
2. Evidence of sarcoidosis (either bilateral hilar adenopathy or chest imaging or tissue biopsy demonstrating non-caseating granulomata)
3. Aqueous specimen PCR X positive for cytomegalovirus, Herpes simplex Vrhu S Or Varicella zoster virus

*ASAS criteria for axial spondyloarthritis or peripheral spondyloarthritis.

*PCR = polymerase chain reaction.

### References

Evidence of ankylosing spondylitis in 1850, when a British Surgeon Sir Benjamin Collins Brodie described a 31-year-old man who had developed an ankylosed spine and occasionally suffered from ankylosing spondylitis.[1] However, there is no inscription or evidence that could suggest they also suffered from concurrent uveitis. Hippocrates (460 BC–370 BC), the father of medicine, described conditions such as spinal inflexibility and pain. He also outlined signs and symptoms of uveitis. However, there is no mention of any association between spondylitis and uveitis in his writings. The first clinical description of ankylosing spondylitis in modern medicine is credited to an Irish physician, Bernard Conner, who in 1691 documented the calcification of spinal ligaments, resulting in a fixed, fused spine in his MD thesis.[2] Over the time, numerous clinicians have highlighted various pivotal aspects of the disease, ultimately shaping its identity as a distinct, separate inflammatory disorder. The ailment was also referred to as Bekhterev's disease or Strümpell-Marie disease based on their respective depictions (Table 1).[2]

Earliest description of association of uveitis with ankylosing spondylitis can be found in 1850, when a British Surgeon Sir Benjamin Collins Brodie described a 31-year-old man who had developed an ankylosed spine and occasionally suffered from inflammations of the eye. The next landmark event was the simultaneous and independent research by Schlosstein et al. in Los Angeles and Brewerton et al. in London, who recognized the association of HLA B27 with this disease.[3] This remains the strongest known association between an MHC antigen and a disease.[4] However, to date, more than 100 ocular and systemic diseases have been associated with HLA B27.[5] In the 1980s, the association between the gut microbiome and ankylosing spondylitis was supported by the discovery of molecular mimicry between HLA-B27 and antigens found on Klebsiella, Yersinia, Salmonella, Shigella, and Klebsiella.[6] The mechanisms of how HLA B27 leads to spondyloarthopathies remain poorly understood. The increased expression of HLA-B27 on the surface of peripheral blood mononuclear cells is thought to facilitate the progression of ankylosing spondylitis or other spondyloarthopathies. HLA-B27 is believed to form a complex with B2 microglobulin, and this complex can attach to short antigenic peptides from intracellular microorganisms. Cytotoxic T lymphocytes can recognize these complexes on the cell surface which can attack and kill these cells.[4]

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1500 BC</td>
<td>Evidence of ankylosing spondylitis in mummies recovered from ancient Egypt</td>
</tr>
<tr>
<td>460 BC–370 BC</td>
<td>Description of Spondyloarthropathy and Uveitis in writings of Hippocrates, but probably associations between these two were not known</td>
</tr>
<tr>
<td>1691</td>
<td>First clinical description of ankylosing spondylitis by Bernard Conner</td>
</tr>
<tr>
<td>1850</td>
<td>British Surgeon Brodie mention about the inflammation in eye of an young male with ankylosed spine</td>
</tr>
<tr>
<td>1893</td>
<td>Russian neurologist Vladimir Bekhterev recognized ankylosing spondylitis as a distinct inflammatory disease from rheumatoid arthritis (Bekhterev's Disease)</td>
</tr>
<tr>
<td>1897</td>
<td>Adolph Struempell from Leipzig, Germany, described two patients with complete ankylosis of the spine and hip joints.</td>
</tr>
<tr>
<td>1897</td>
<td>Similar descriptions of the disease by von Bechterew from St. Petersburg, Russia, and Pierre Marie from Paris, France.</td>
</tr>
<tr>
<td>1973</td>
<td>The first human leukocyte antigen (HLA) haplotype association with human inflammatory disease was discovered from simultaneous and independent research by Schlosstein et al. in Los Angeles and Brewerton et al. in London.</td>
</tr>
<tr>
<td>1983-89</td>
<td>Association between the gut microbiome and ankylosing spondylitis</td>
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Table 1: Historical Milestones in HLA-B27 associated diseases

HLA-B27 is a MHC class I molecule consisting of a MHC encoded alpha chain region on chromosome 6 and a non-MHC encoded beta chain, B2 microglobulin. Alleles represent diverse forms of a gene, distinguished by variations in the sequence of nucleotides and there are 260 known HLA B27 alleles, numbered from HLA- B*27:01 to HLA- B*27:260.[7] The prevalence of HLA-B27 differs widely between populations. While there is limited data on distribution of HLA-B27 alleles in various regions of India, the existing data shows considerable variation across populations, ethnicities, castes, and regions. Several studies have reported that HLA-B*2705-positive patients seem to have a stronger association with uveitis across various global populations. In a study conducted in Tamil population, uveitis was mainly associated with HLA-B*27:05.
However, in another study from Maharashtra, uveitis was observed more commonly in B*2704-positive patients with ankylosing spondylitis when compared to B*2705-positive patients.\[^{13}\]

The first report on HLA-B27 in ankylosing spondylitis from India was in 1977, published from PGIMER.\[^{14}\] Subsequently, numerous studies on both articular and extra-articular manifestations of HLA-B27-associated spondyloarthropathies have been published from India. However studies on ocular manifestations of HLA B27 positive spondyloarthropathies from India remain sparse.\[^{15,16,17}\]

Data from tertiary eyecare centres from India reveals that HLA-B27-associated spondyloarthropathies remains the most common cause of anterior uveitis, ranging from 8-27% cases of anterior uveitis.\[^{18,19,20}\] In another prospective study from India, ankylosing spondylitis was the most common identifiable cause (7.5%) of anterior uveitis. In a study conducted from Southern India, which examined shifts in uveitis trends over two different decades, it was observed that there was a notable increase in the proportion of anterior uveitis cases attributed to HLA B27 associated uveitis. Specifically, this proportion rose to 30%, a significant rise from the 14.5% reported in the year 1992.\[^{25}\]

Table 2: Studies published from India showing percentage of anterior uveitis cases due to HLA B27 associated spondyloarthropathies

<table>
<thead>
<tr>
<th>Authors</th>
<th>Region</th>
<th>Part of Anterior Uveitis</th>
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<tr>
<td>Borde et al.[^{18}]</td>
<td>Central India</td>
<td>15%</td>
</tr>
<tr>
<td>Sabhapandit et al.[^{19}]</td>
<td>South India</td>
<td>11.80%</td>
</tr>
<tr>
<td>Singh et al.[^{20}]</td>
<td>North India</td>
<td>13.2</td>
</tr>
<tr>
<td>Das et al.[^{21}]</td>
<td>North East India</td>
<td>23.40%</td>
</tr>
<tr>
<td>Dogra et al.[^{22}]</td>
<td>North India</td>
<td>20%</td>
</tr>
<tr>
<td>Das et al.[^{23}]</td>
<td>South India</td>
<td>8.60%</td>
</tr>
<tr>
<td>Pandurangan et al.[^{24}]</td>
<td>North India</td>
<td>27.30%</td>
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Table 3: Posterior Segment Involvement in HLA B27 associated Uveitis

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<tr>
<th>Vitritis</th>
<th>Macular Oedema</th>
<th>Retinal Vasculitis</th>
<th>Intermediate Uveitis</th>
<th>Vitritis with papillitis mimicking Panuveits</th>
<th>Optic Nerve Head edema</th>
<th>Ciliochoroidal Effusion</th>
<th>Serous Retinal Detachment</th>
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While global data show that the prognosis of HLA-B27-associated uveitis is rather favourable, with fewer than 2% developing legal blindness, the limited data from Indian patients with HLA-B27-associated uveitis showed that 6.6% to 7.4% of the patients with HLA-B27-associated uveitis developed severe visual impairment.\[^{29,31,32,33}\] Hence, it is imperative for ophthalmologists to familiarize themselves with the diverse clinical presentations and effective management approaches for this condition..
References:
**Introduction:**
A deeper understanding of the role of HLA-B27 (Fig. 1) in disease pathogenesis coupled with an understanding of the clinical spectrum of HLA-B27 anterior uveitis and its associated systemic diseases is essential to the ophthalmologist. This shall help to embrace the new therapies to suppress inflammation and control ocular and associated systemic inflammatory disease.  


**Results from genome-wide association studies**
Recent genome-wide association studies (GWAS) have revealed that there are a significant number of otherwise independent genetic associations of acute anterior uveitis (AAU) and Spondyloarthropathies (SpA). It is worth noting that most of these genetic associations involve immunologic pathways, including Interleukins like IL-17 and IL-23; which are involved in antigen processing/presentation, lymphocyte development and activation. Further patients with Ankylosing Spondylitis (AS) and AAU also share other genetic markers, such as endoplasmic reticulum aminopeptidase-1 (ERAP-1). This is a strong evidence for gene-gene interaction and direct/new mechanism in the pathogenesis of HLA B-27 AAU.  

![Peptide binding cleft](between alpha chain 1 and 2)

**Figure 1:** HLA B27 protein structure (Incorporated from: Alexander M. Ankylosing Spondylitis Pathogenesis and Pathophysiology. Ankylosing Spondylitis. Intech Open; 2023. Available from: http://dx.doi.org/10.5772/intechopen.109164)

**Table 1:** Genetic and clinical features of HLA-B27 AAU. (Incorporated from: Wakefield D, Yates W, Amjadi S, McCluskey P. HLA-B27 Anterior Uveitis: Immunology and Immunopathology. Ocul Immunol Inflamm. 2016 Aug;24(4):450-9)

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<th>AAU Association</th>
<th>Genetic associations</th>
<th>Clinical features</th>
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<tr>
<td>Idiopathic</td>
<td>HLA-B27, ERAP-1, EYS</td>
<td>Most often unilateral &gt; bilateral and AAU or recurrent disease (RAAU). Up to 50% of patients with AAU are HLA-B27-positive.</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>HLA-B27, ERAP-1, IL-23R and IL-6R Intergenic region 2p15 Chr. 1q32- KIF21B</td>
<td>AAU or RAAU occur in approximately 35% of patients with AS and increase with increasing age</td>
</tr>
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<td>Reactive arthritis</td>
<td>HLA-B27</td>
<td>AAU in 60% of patients. Severe AAU/CAU, especially associated with HIV infection. Rarely posterior uveitis and retinal vasculitis.</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Cw6, HLA-B27</td>
<td>AAU, RAAU, and BAAU, less common than in AS. 15% of patients have AAU</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>IL-10, IL-18R-ILR-1 HLA-B27</td>
<td>AAU, RAAU, or BAAU, in &lt;10% of patients with IBD. Occasionally severe disease with posterior uveitis and retinal vasculitis.</td>
</tr>
<tr>
<td>Juvenile spondyloarthritis</td>
<td>HLA-B27</td>
<td>AAU less common in children. AAU more common with increasing age</td>
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**Pathogenesis of HLA B27 related diseases:**
The pathogenesis of HLAB27 related diseases, such as AAU and AS are not clearly known resulting in several hypotheses being proposed to explain the role of HLA-B27 in these diseases. They include arthrogenic/ uveitic peptide hypothesis, HLA-B27 misfolding hypothesis and the innate immune recognition of aberrant HLA-B27 which is the dominant hypotheses (Fig. 2).
Main hypotheses for the contribution of HLA-B27 to the pathogenesis of uveitis and spondyloarthritis: schematic representation of the arthritogenic/uvetic peptide hypothesis, the HLA-B27 misfolding hypothesis, and the hypothesis of activation of the innate immune system by aberrant HLA-B27.

**1. The arthritogenic/uvetic peptide hypothesis**

The basic concept is that HLA-B27 molecules present either “self-peptides” or “antigens” which share sequence homology with self-peptides to HLA-B27 restricted CD8+ T cells, which are autoreactive. Once activated; these T cells induce inflammation in the eye, joints, and other tissue as a result of a cross reactivity with peptides at these sites (eye, joints and other tissue).  

Indeed, Hermann et al, have shown HLA-B27 CD8 T cells have an antigenic specificity for certain gut bacteria including Yersinia Enterocolitica and Salmonella typhimurium; which have already previously been implicated in the pathogenesis of SpA.  

When one measures antibody levels to several bacteria including Chlamydia trachomatis, Chlamydia pneumoniae, Klebsiella pneumoniae, Salmonellae spp. and Yersinia spp, it has been found that patients with a history of recurrences are more likely to have raised antibody levels to one or more bacteria, indicating a possible link of HLA-B27 related diseases to recurrent (subclinical) infection or the persistent presence of the antigen from these bacteria.  

Helicobacter pylori implicated in peptic ulcer disease, has also been associated with AAU with patients of AAU having an overwhelming 40% rate of seropositivity to Helicobacter pylori compared with 0% in controls (0%) with about 50% patients showing anti-H. pylori antibodies in their aqueous humor; with overwhelming 40% rate of seropositivity to Helicobacter pylori implicated in peptic ulcer disease, has also been associated with AAU or SpA. The HLA-B27*05 subtype is associated with both SpA and AAU. But in this HLA-B27*05 subtype when an aspartate residue is changed to a histidine residue (making it the HLA B*2709 sub type); there is no disease.  

**2. HLA-B27 Misfolding Hypothesis:**

HLA-B27 heavy chains tend to misfold. Such misfolding has a role in the pathogenesis of HLA-B27-related disease.

This unfolding phenomenon is corrected, when six amino acid residues from within the B pocket (region of the peptide binding groove) of HLA-B27*05, are replaced with residues from a non-HLA-B27 gene. But this misfolding; when it occurs triggers a protein stress response. This protein stress response is known as the unfolded protein response (UPR) causing the production of proinflammatory cytokines such as Tumour Necrosis Factor TNF-α, IL-1 and IL-6, via a NF-kB pathway.

**3. Innate Immunity and Autoinflammation:**

In addition to the role of adaptive immunity in the pathogenesis of HLA-B27-related disease, innate immunity may also be involved. The term “autoinflammation,” is used to describe the innate immunity’s contribution to HLAB27-related disease. Autoinflammatory diseases are characterized by an activation of cells of the innate immune system in the absence of autoantibodies or autoreactive T cells. Since both innate and adaptive immune reactions contribute to HLA-B27-related disease; it falls somewhere along the continuum between autoimmune and autoinflammatory disease.  

Role of natural killer cells: HLA-B27 molecules are ligands for activating natural killer (NK) cell receptors that are expressed on NK cells and T cells. Engagement of these receptors modulates NK cell responses and T-cell antigen receptor (TCR)-dependent T-cell activation.

The role of natural killer cells (NK cells) and killer immunoglobulin receptors (KIRs) in the pathogenesis of uveitis is established. HLA-B27*05 (which is associated with disease) stimulates reporter T cells transduced with KIR3DL2CD3ε, a KIR known to bind to HLA-B27, more effectively compared with HLA-B27*09 (which is not associated with disease). Indeed, KIR2D and KIR3D polymorphisms, KIR2DL1 and KIR2DL5 are significantly higher in patients with HLA-B27-positive AS compared with HLA-B27-positive healthy controls.  

**Animal studies and its clinical applications**

1. Transgenic rats raised in a germ-free environment do not develop inflammatory joint or gut disease.  
2. These animals also do not develop anterior uveitis.  
3. But endotoxin injected into them induces an acute anterior uveitis.  

This endotoxin-induced uveitis (EIU) model highlights the role of environmental factors in AAU and also the potential role of toll-like receptor (TLR) ligands in inducing disease.

Benham et al used SKG strain of BALB/c mice, which harbours a mutation of ZAP-70, an important adapter protein signaling downstream of the T-cell receptor, found that the otherwise spontaneously developing arthritis; did not develop, when the mice were raised in a germ-free environment. However, even in germ-free conditions, the intraperitoneal injection of the β-1,3 glucan (which is present in fungal cell walls, bacteria, and also in plants, and which is a ligand for the dectin-1 receptor increasing the production of IL-12 and IL-23); was shown to induce arthritis in these animals. Injection
of anti-IL-23 into these animals a day before the β-1,3 glucan injection suppressed the development of disease. IL-17, one of the major cytokines acting downstream from IL-23, also increased in the ileum after induction of disease in this animal model. This has an important therapeutic implication for the treatment of SpA and AAU. 23

To wrap up, there are the above and many more exciting new developments in the study of HLA-B27-related diseases. These beyond doubt herald new therapeutic approaches in the management of HLA-B27 AAU prevention of the disease and its complications.

References


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Differential Diagnosis of HLA-B27 Uveitis

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While considering the differential diagnosis, uveitic entities causing non granulomatous uveitis with plasmoid aqueous/hypopyon or associated with arthropathy should be included. Spondyloarthritis is not the only condition associated with both uveitis and arthritis. HLAB27 associated uveitis is diagnosed after ruling out both non-infectious and infectious disease entities. Since therapy differs significantly, it is essential to consider infectious causes of acute anterior uveitis as part of the differential diagnosis.

Arthropathies associated with uveitis:
HLA-B27-related uveitis (ankylosing spondylitis, reactive arthritis syndrome)

a. Anterior uveitis associated with ankylosing spondyloarthropathy is often unilateral and alternating (flip-flop), non-granulomatous (fibrinous, often with posterior synechiae). Systemic symptoms are marked by lower back pain due to sacroilitis. The presence of the HLA B27 gene with raised inflammatory markers are observed.

b. Anterior uveitis associated with reactive arthritis (ReA): Anterior uveitis in 60% of ReA patients is often severe, associated with signs/symptoms of urethritis. HLA-B27 may be present, and inflammatory parameters are raised. It could be post-infectious and follow nongonococcal urethritis (chlamydia, ureaplasma) or infectious dysentery. Reiter's syndrome is characterized by Achilles tendonitis, plantar fasciitis, and rarely, aortic incompetence. It is also associated with a systemic condition known as keratoderma blenorrhagicum, which causes brown aseptic abscesses on the palms and soles of the feet.

c. Inflammatory bowel disease (IBD)-associated uveitis: Anterior uveitis is typically with acute onset and nongranulomatous. Other ocular features of episcleritis, scleritis, and glaucoma are noted in patients with IBD. History of diarrhea, hematochezia, and abdominal pain can be present. Referral to the gastroenterologist for further colonoscopy biopsy may be done to confirm the diagnosis.

Laboratory workup including perinuclear anti-neutrophil cytoplasm antibodies (p-ANCA) and anti-Saccharomyces cerevisiae antibodies (ASCA) can be done.

d. Anterior uveitis associated with psoriatic arthropathy3 also known as arthritis mutilans, severe destructive arthritis that affects the small joints of the hands. Distinctive skin and nail lesions are seen in psoriasis. Uveitis can develop in patients with psoriatic arthropathy, not only in those with psoriatic skin lesions. Anterior uveitis may initially manifest as bilateral and progress into a chronic condition. Keratitis, dry eye, conjunctivitis may be other ocular findings.

e. JIA-associated uveitis is typically non granulomatous, unilateral/bilateral, sero positive, pauciarticular arthropathy in children. On laboratory investigations Antinuclear antibody (ANA) is positive. Rheumatoid Factor and CCP antibodies typically negative.

f. Miscellaneous uveitis with arthritis:
Behcet’s disease and sarcoidosis are differential diagnoses that should be considered, as they can also involve joints, eyes, and other organ systems (skin, lung, or central nervous system).

Behcet’s syndrome may present initially as hyperacute anterior uveitis with a “cold hypopyon”-a characteristic transient mobile hypopyon in a relatively white eye. Often affecting both eyes.13 Bilateral uveitis with a longer clinical course in contrast to SpA-associated AAU (anterior uveitis), is seen. Posterior segment findings of occlusive retinal vasculitis and vitritis is predominant. Systemic features of joint, skin, and CNS involvement, as well as recurrent oral/genital ulcers (> 95%) are diagnostic of Behcet’s disease. HLA-B51 is present along with raised inflammatory parameters.

Differential diagnosis of Non arthritis HLA B27 associated uveitis

- Idiopathic anterior uveitis is one of the commonest cause of anterior uveitis differentiated from HLA B 27 associated uveitis by the absence of arthropathy /HLA B27 gene
- Fuchs’ uveitis syndrome is diagnosed with the presence of diffuse stellate keratic precipitates, absence of posterior synechiae, with or without iris changes.
- Traumatic uveitis—diagnosed with the history of trauma and associated ocular signs of angle recession, iridodonesis damage and commotio retinae in the posterior segment.
- Tubulointerstitial nephritis and uveitis syndrome (TINU) can have uveitis which is often bilateral acute/chronic and non-granulomatous. Systemic features of nephritis, proteinuria, and fever and Laboratory investigations may show proteinuria and B2 microglobulin in urine.
- Viral uveitis, unlike HLA-B27-positive linked AAU, is mostly unilateral (non-alternating). Similar to SpA-associated AAU, it can involve non-granulomatous inflammation, elevated IOP, iris atrophic patches, and non/granulomatous KPs. However, a history of dermatomal vesicular rash (as in VZV) can aid in diagnosis. Aquous specimen PCR for cytomegalovirus, Herpes simplex virus, or Varicella zoster virus can also aid in diagnosis.
- Sarcoidosis with non-granulomatous manifestations:
  - Anterior uveitis (AAU)/chronic anterior uveitis associated with sarcoidosis can be of acute onset, often bilateral, in contrast to HLA-B27-associated uveitis. However, it may frequently present as panuveitis. Notable associated symptoms/signs of general illness (skin, lung, liver) may be observed. A chest X-ray/HRCT scan can reveal bilateral hilar adenopathy or biopsy may reveal non-caseating granulomata, along with lab tests such as IL-2R, serum ACE, calcium and phosphate levels in serum, and a raised CD4/CD8 ratio in the aqueous.6 Serum lysozyme can also aid in confirming the diagnosis.
- Syphilis: Infectious causes of AAU should be considered as important differential diagnoses since their treatment approaches differ fundamentally. Syphilis, known as the "great imitator," can present as unilateral/bilateral acute anterior uveitis or panuveitis. Primary symptoms/signs include a chancre, while secondary symptoms include a skin rash. Tertiary symptoms may include malaise, joint involvement, and CNS involvement. Lab tests used to exclude syphilis in the differential diagnosis include TPHA, FTA-ABS, VDRL, HIV 1&2 tests, and CSF analysis.

- Tuberculosis must be ruled out before starting systemic immunosuppressive therapy. Tuberculosis can manifest as AAU/CAU with granulomatous keratic precipitates. Panuveitis and chorioretinitis are common manifestations. Before initiating immunosuppressive treatment, tuberculosis should be ruled out, especially in patients living in endemic countries like India, those with a history of exposure, or those who are immunocompromised. Lab tests such as the Mantoux test, quantiferon-test, HIV testing, a chest CT scan, sputum analysis, and consultation with a pulmonologist are recommended. Molecular diagnostic tests like polymerase chain reaction (PCR) for MTB and tissue biopsy can help confirm the diagnosis of tuberculosis.

- Borrelia or Lyme disease is another differential diagnosis for HLA-B27-associated anterior uveitis. Anterior uveitis may be unilateral/bilateral and non-granulomatous as in HLA B27 related uveitis. Ocular findings of keratitis, viritis, exudative retinal detachment, multifocal chorioretinitis, and panophthalmitis may be present.7-8 However a history of insect/tick bite provides a clue, along with associated symptoms/signs of general illness, such as erythema migrans, joint involvement, and CNS involvement help clinch the diagnosis. Lab tests such as ELISA and immunoblot for IgG and IgM can aid in confirming the diagnosis.

- Leptospirosis is characterized by acute, non-granulomatous panuveitis, hypopyon, vasculitis, optic disc edema, membranous vitreous opacities, and the absence of choroiditis or retinitis.9-10 The patient’s geographic location, occupation, socioeconomic position, risk factors related to exposure, and a history of fever or jaundice can help in diagnosis.

- Lens-induced uveitis may present with unilateral non-granulomatous anterior uveitis with a hypopyon as seen in HLA B27 related uveitis. Lens-induced uveitis occurs when the lens capsule is ruptured or when lens proteins leak out through an intact capsule, leading to ocular inflammation.11 Lens-induced uveitides (LIU) are often associated with progressive cataracts. Clinical indicators include conjunctival hyperemia, corneal edema, large anterior chamber cells and flare, an open anterior chamber angle, a pseudohypopyon, and a hypermetropic or Morgagnian cataract.

- Drug-induced anterior uveitis is known to be caused by drugs such as NSAIDs, Cidofovir, Rifabutin, and biphosphonates.12 This type of uveitis is often non-granulomatous and bilateral, sometimes with a hypopyon. It usually responds to topical steroids and discontinuation of the causative drugs. A history of the drug intake is present to aid the diagnosis.

- Parasitic diseases can mimic unilateral AAU. They may have presence of live or dead worm in the eye with eosinophilia.

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**Differential Diagnosis**

<table>
<thead>
<tr>
<th>Clinical features</th>
<th>Diagnostic tests</th>
</tr>
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<tbody>
<tr>
<td><strong>Spondyloarthropathy associated Anterior uveitis</strong></td>
<td>- Unilateral - alternating (flip-flop) Fibrinous Non granulomatous - Inflammatory back pain (Saccroilitis)</td>
</tr>
<tr>
<td><strong>ReA associated AU</strong></td>
<td>- Severe NGAU</td>
</tr>
<tr>
<td><strong>IBD associated AU</strong></td>
<td>- NGAU</td>
</tr>
<tr>
<td><strong>Psoriatic arthritis associated AU</strong></td>
<td>- NGAU-Bilateral</td>
</tr>
<tr>
<td><strong>Behcets Disease</strong></td>
<td>Hyperacute AU</td>
</tr>
<tr>
<td><strong>Sarcoidosis</strong></td>
<td>- Simultaneous bilateral anterior uveitis Granulomatous -Skin/lung/liver involvement</td>
</tr>
<tr>
<td><strong>TINU syndrome</strong></td>
<td>- Simultaneous bilateral AU -Nephritis/ proteinuria, fever</td>
</tr>
<tr>
<td><strong>Tuberculosis</strong></td>
<td>Mostly bilateral</td>
</tr>
<tr>
<td><strong>Syphilis</strong></td>
<td>Uni/bilateral NGAU/ panuveitis -Systemic- chancre, skin rashes, joint CNS involvement</td>
</tr>
<tr>
<td><strong>Viral</strong></td>
<td>- Unilateral NGAU</td>
</tr>
</tbody>
</table>
**Borreliosis**
- Uni/bilateral NGAU
- Often panuveitis
- History of tick bite
- Systemic: erythema migrans, joint and CNS involvement

| Lab: ELISA, immunoblot IgG, IgM |

**Leptospirosis**
- -NGAU
- -Often panuveitis, retinitis
- History of fever, jaundice

| IgM ELISA MAT (microscopic agglutination test) |

**Lens induced**
- -Unilateral NGAU, hypopyon (pseudo-hypopyon)
- Progression cataract

**Drug induced Uveitis**
- Bilateral NGAU
- History of drug intake

**Table 1:** Differential Diagnosis of HLA B27-associated Uveitis


**Conclusion**
Anterior uveitis is a common clinical condition that is frequently related with HLA B27. It is the most common extraarticular symptom of SpA which can have an impact on disease activity and quality of life by early detection and treatment. Differentiating from other causes of non-granulomatous uveitis with arthritis help initiate timely systemic intervention and improve prognosis.

**References**
HLA-B27 mediated Uveitis, refers to ocular inflammation particularly acute anterior non-granulomatous uveitis, sometimes intermediate and rarely posterior, occurring in patients who are often positive for HLA-B27 gene. Generally mild and unilateral, HLAB27-mediated uveitis sometimes can be severe, fibrinous or bilateral.

HLA-B27 is generally associated with a variety of extra-ocular diseases which includes spinal/axial inflammation, peripheral inflammatory arthritis (usually affecting large joints – hips, knee, ankle or shoulder), psoriasis, inflammatory bowel disease (Ulcereative colitis and Crohn’s Disease) and Reiter’s Syndrome. The uveitis can either precede or follow extra-ocular disease.

It is well known that there is a delay of around 4 – 11 yrs from the onset of symptoms to making a diagnosis of axial spondyloarthtitis. Extra-ocular manifestations can go unnoticed for a long duration of time. Hence screening patients for extra-ocular disease at the time of presentation for uveitis at the ophthalmology out-patient clinic is important.

What should an ophthalmologist look for in a patient who presents with HLA-B27 related Uveitis?

1. Ask for history of Inflammatory back pain (IBP). IBP is the presenting complaint in majority of patients who present with axial / spinal inflammatory arthritis (often referred to as Axial Spondyloarthtitis AxSpA). It is important to differentiate IBP from mechanical back pain, which is more prevalent in the community.

Clinical features suggestive of Inflammatory back pain include:
- Onset in age group < 45 yrs (Peak onset 2nd or 3rd decade)
- Low Back Pain lasting for > 3 months duration.
- Insidious onset.
- Not relieved on rest and improves with exercise.
- Nocturnal awakening (later part of night).
- Morning stiffness > 30 minutes.
- Alternating buttock pain.
- Relieved with NSAID’S.

2. Ask for history of inflammatory bowel disease: abdominal pain, diarrhoea, weight loss, mucus or blood in stools.

3. Ask or Look for peripheral arthritis: Majority of the times HLA-B27 related arthritis affects large joints such as hips, knee, ankle and shoulders. Rarely rheumatoid-like polyarthritis is seen especially in the context of psoriatic arthritis.

4. Look for Psoriasis and arthritis: Patches of erythematous flaky skin visible over elbows, knee, shin, torso, gluteal area, umbilicus, scalp, nail and other sites. Approximately 40% of patients with psoriasis develop psoriatic arthritis. Psoriatic arthritis can present as either oligo (< 3 joints) or polyarticular disease and patient complains of joint pains, swelling, stiffness and loss of joint function. Psoriasis may precede or follow arthritis. For patients with no current psoriasis, a careful family history of psoriasis in first-degree relatives is an important history.

5. Look for Dactylitis (Sausage Digits) : Uniform or diffuse swelling of a digit (finger or toe) is a unique feature of spondyloarthtitis-spectrum disorders. (Figure 1)

6. Ask or look for Enthesitis: pain or swelling at tendon-insertion sites such as plantar fascia, Achilles insertion in heel, anterior knee over tibial tubercle, lateral hip over greater trochanter, lateral epicondyle tip on the elbow, tip of the shoulder etc.

7. Genito-urinary or gastrointestinal infection in the preceding one month (Reiter’s syndrome)

8. Ask for history of arthritis, psoriasis, IBD or Uveitis amongst other family members.

If any of the above features are present referral to a rheumatologist is warranted.

What are the Investigations generally done?

1. ESR and CRP:
- Raised in 75% of patients with AxSpA & generally not raised in patients with isolated eye involvement. It is high in majority of patients with peripheral arthritis.
- A normal value does not rule out spondyloarthtitis.
- Baseline high CRP: suggests an increased risk of progression of spinal disease and a better response to immuno-suppressive therapy.
2. HLA-B27:
- Prevalence and disease association varies among racial / ethnic groups.
- Not a diagnostic test (neither 100% sensitive or specific) but when positive supports the diagnosis of Ankylosing spondylitis or other B27-related diseases.
- HLA-B27 is detected by either Flow cytometry (less sensitive method, higher false negative’s) or Polymerase Chain Reaction –PCR (higher sensitivity and specificity).
- 83 - 94% of Indian AS patients are positive for HLA-B27.
- Prevalence of HLA-B27 in various diseases is described in Table 1.
- 10% of unaffected individuals in the general population are positive for HLA-B27 on routine testing. Hence presence of a positive HLA-B27 test alone in the absence of relevant clinical features is not diagnostic of spondyloarthritis.

<table>
<thead>
<tr>
<th>Disease</th>
<th>HLA-B27 ASSOCIATION(%)</th>
</tr>
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<tbody>
<tr>
<td>Ankylosing Spondylitis</td>
<td>90</td>
</tr>
<tr>
<td>Acute Anterior Uveitis alone</td>
<td>50</td>
</tr>
<tr>
<td>Reiter’s Syndrome</td>
<td>40-80</td>
</tr>
<tr>
<td>Psoriatic psoriatic arthritis</td>
<td>50</td>
</tr>
<tr>
<td>Psoriatic Peripheral Arthritis</td>
<td>15</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>35 - 75</td>
</tr>
</tbody>
</table>

3. X-ray:
- Sacroiliac joints most commonly are the joints to be affected first in AxSpA. X-ray of the sacro-iliac joint shows narrowing, erosions, peri-articular sclerosis, bony-bridges in the joint and obliteration or fusion. (Figure 2A and B)
- New bone formation might bridge adjacent vertebrae eventually leading to fusion / ankylosis of the spine, termed as “bamboo spine”. (Figure 3B)

**Figure 2 A:** Bilateral sacroilitis: erosions, irregularity, narrowing of sacroiliac joint along with periarticular sclerosis. 2B: Fused sacroiliac joints

- Lateral spine radiographs are taken to screen for axial disease. A lateral radiograph of dorso-lumbar spine shows squaring of the vertebrae, ossification of anterior longitudinal ligament (seen as syndesmophytes or new bone growth at anterior vertebral corners), posterior longitudinal ligament, facet joints and spinous processes. (Figure 3A).

**Figure 3A:** Syndesmophytes at anterior vertebral margins. 3B: Complete Ossification of anterior longitudinal ligament (Bamboo spine)
- The disease is referred to as Radiographic Axial Spondyloarthritis (r-AxSpA) or Ankylosing spondylitis when these X-ray changes are present.
- It takes few years from onset of symptoms for these changes to appear on X-ray and a normal X-ray in the early stages of the disease hence, does not rule out a diagnosis of Spondyloarthritides.
- X-rays of peripheral joints are done in Psoriatic arthritis which in established cases demonstrate marginal erosions, joint space narrowing, ankylosis, erosion and destructive arthritis (pencil-in-cup deformity).

**Figure 4:** Psoriatic arthritis: X-ray showing erosion and pencil-in-cup deformity in right index PIP joint, bony ankylosis in right second and third MCP joint, subluxation of DIP of left thumb, erosions left fifth PIP joint

**Figure 5:** MRI sacroiliac joints: T2-weighted STIR image showing bilateral sacroilitis (edema around the sacroiliac joint)
4. MRI Scan of Sacroiliac joint and Spine:
   - The earliest sign of inflammation are visible on MRI scan and is particularly useful in symptomatic patients with normal X-rays.
   - MRI with T1 and T2 weighted STIR sequences of sacroiliac joints and spine are required to demonstrate inflammation which is seen as bone-marrow edema.
   - Bone marrow edema or inflammatory lesions at vertebral corners, para-discal area (spondylodiscitis), facet joints and costo-vertebral articulations are seen in patients with spinal disease.
   - The term Non-radiographic axial spondyloarthritis (nr-AxSpA) is used for a patient with positive MRI changes and normal spinal X-rays.

What is the treatment?

1. **Extra-ocular disease treatment is decided by the Rheumatologist based on predominant disease phenotype.**
   - Peripheral arthritis: NSAIDS, Sulphasalazine, Methotrexate, Apremilast (in psoriatic arthritis) are first-line drugs. In resistant disease anti-TNF biologics (such as infliximab, etanercept, adalimumab, golimumab) or JAK-kinase inhibitor Tofacitinib is used.
   - Axial disease: NSAIDS, Anti-TNF agents or Tofacitinib or Seckikunumab
   - Cutaneous disease: Topical therapy, Photo therapy, Methotrexate, Cyclosporin, Apremilast are first line measures. Anti-TNF drugs or Tofacitinib or Seckikunumab are indicated for resistant cases.
   - Dactylitis alone: Methotrexate and NSAIDS are first line drugs. Anti-TNF drugs are used for resistant cases.
   - Enthesitis: NSAIDS are used as first-line agents. Anti-TNF drugs are used in resistant cases.

2. **Uveitis:**
   - Topical steroids are the preferred first-line anti-inflammatory drugs.
   - If uveitis is severe, vision threatening, fibrinous, intermediate / posterior, oral steroids would be required in addition. The dose of prednisolone varies depending on the severity of ocular disease. Generally prednisolone 0.5 mg/kg/day should suffice with slow tapering based on eye status.
   - If uveitis is recurrent (probably more than 3 attacks per year), relapse on tapering oral / topical steroids, unable to tolerate oral or topical steroids due to toxicity refer patient to a Rheumatologist to consider adding a steroid-sparing immunosuppressive drugs

3. **General principles of immunosuppressive medications:**
   - They are SLOW to work (need 2-3 months for maximum benefit).
   - Periodic DOSE ESCALATION is required provided blood count and SGPT are normal.
   - Monitor for DRUG TOXICITY (Complete blood count, SGPT, Creatinine)
   - Concomitant topical / systemic steroid to be CONTINUED till systemic drugs are effective
   - Steroid dose is gradually reduced while immunosuppressive medication dose is escalated.
   - If response to treatment is inadequate then change to an ALTERNATE AGENT.
   - Drugs commonly used for B27-mediated Uveitis are: Methotrexate (upto 25mg per week oral or subcutaneous), Mycophenolate mofetil (1 gm twice daily), Azathioprine (2mg/kg/day). Amongst these methotrexate is the most preferred drug. A switch between these drugs is attempted in patients who do not respond to first-line drugs. Second-line biologic drugs such as anti-TNF drugs (Adalimumab, Infliximab or Golimumab) are indicated for patients who have severe, resistant or even persistent low-grade disease who continue to require oral prednisolone or topical steroids. Etanercept and Seckikunumab, which are effective in extra-ocular disease are not effective for ocular inflammation. Paradoxically worsening of existing uveitis or occurrence of new uveitis is described with these agents. Evidence for use of Tofacitinib in uveitis is still lacking.
   - Aim to keep ocular inflammation in remission: asymptomatic, no signs of ocular inflammation and not requiring oral or topical steroids.
   - Duration of immunosuppressive drugs: No data to suggest how long to continue these drugs. However a decision has to be taken on a case to case basis. In patients with extra-ocular disease treatment is long-term. In patients with isolated ocular disease who have no flares for at least two years, an attempt at slow tapering of immunosuppressive drugs can be made with an eventual aim to stop treatment. Abrupt stopping of immunosuppressive drugs should be avoided. Close follow-up is advised for patients who stop treatment.

Further Reading

1. Ritchlin C, Adamopoulos IE. Axial spondyloarthritis: new advances in diagnosis and management. BMJ. 2021 Jan 4;372:m4447. doi: 10.1136/bmj.m4447. PMID: 33397652
HLA B-27-associated uveitis, although most commonly characterized by bilateral alternating non-granulomatous fibrinous anterior uveitis, can present with atypical manifestations.

**Case one:**
**Acute anterior uveitis with dense vitritis: a diagnostic dilemma with endogenous endophthalmitis at first presentation.**
A 34-year-old gentleman presented with first episode of redness, photophobia, pain, and diminution of vision in right eye with best corrected visual acuity (BCVA) of hand movements. Right eye conjunctival congestion, circumcorneal congestion, anterior cells of grade four, flare, dense fibrin, and streak hypopyon.

The fundus was not visible due to dense vitritis, and B-scan was done which showed dot, clump and membranous echoes.

**Case Series**
By third day, the vision improved to 20/50 and fundus with visible a vitreous haze. The patient was treated with oral steroids to further decrease the vitritis.

The differentiation of cases of HLA B27 uveitis from endogenous endophthalmitis is an important one from treatment point of view. HLA B27 is known to have significant vitreous haze or vitritis rarely necessitating the use of oral steroids.

Case two: Acute anterior uveitis with hyphema and neovascularization-like vessels of the iris

A 33-year-old gentleman presented with a sudden diminution of vision in his left eye. He had multiple episodes of redness, photophobia in both the eye and was already diagnosed as a case of seronegative spondylarthritis with HLA B27 positivity. Right eye had BCVA of 20/20 for distance and N6 for near, anterior, and posterior segment examination was essentially normal.

Left eye had conjunctival congestion, circumcorneal congestion, anterior chamber reaction of grade four with dense fibrin and streak hypopyon. Hemorrhages were noted on the surface of iris along with neovascularisation of iris like vessels. Central dense fibrin with contraction was noted. Fundus was not visible clearly. On treatment, with intense hourly topical steroids, cycloplegics the anterior chamber reaction, iris vessels and hemorrhages resolved. The patient was continued on ADALIMUMAB/ ORAL METHOTREXATE dual therapy in view of multiple and frequent recurrence during the further course of the disease.

Though rare, either spontaneous or secondary hyphema in HLA B 27 are known. The dilated and fine vessels that are seen on the surface of the iris look like new vessels but are possibly dilated vessels secondary to the inflammation. The breakdown of the anterior blood aqueous barrier at may further increase the propensity of hemorrhage through these vessels.

The presence of hemorrhages and NVI like vessels in a case of hypopyon anterior uveitis though rare should be considered in cases of HLA B27 uveitis.

Case three: Recurrent anterior uveitis in either eye with HLA B 27 negative with flowcytometry

35-years old gentlemen presented to the uveitis OPD with sudden drop in vision in left eye with redness and photophobia. He had a history of multiple such episodes in either eye over the past 3-4 years. HLA B 27 was done earlier and was negative by flow cytometry. He also had complaints of left hip joint and neck pain with occasional stiffness.

We treated this episode with intense topical steroids and cycloplegics. But also investigated the patient for HLA B27 by PCR which was noted to be positive and MRI of Sacro-iliac joint showed subarticular erosion in the left SI joint with narrowing of the joint space.

HLA B27 by flowcytometry is a easily available and relatively cheaper than other methods. However, it had lower specificity, sensitivity and is influenced by expression and/or conformation changes in the antigens in the blood cells. In cases such as the one illustrated above checking for HLA B27 positivity by one of the molecular methods and confirmation of structural changes in joints is one of the confirmatory tools for the diagnosis.

Case Four: Complicated cataract as a presenting sign in a lady with HLA B27 positivity.
A 38-year-old lady presented with left eye complicated cataract and right eye active anterior non granulomatous anterior uveitis. She had multiple episodes of uveitis in either eye and was thoroughly investigated elsewhere and found out to be positive for both HLA B27 and Tuberculin skin test.

Figure 9: Complicated cataract in lady with HLA B27 and tuberculin skin test positivity.

We performed a lensectomy, vitrectomy in this lady since this was a quiet eye to known the posterior status of the eye. A multifocal choroiditis was noted during the surgery with inferior large snowbanking. On further history it was revealed that her sister had pulmonary tuberculosis. QuantiFERON TB gold was done which was positive along with Chest imaging showing evidence of old tuberculosis. She was initiated on anti-tubercular therapy with steroids.

Figure 10: Fundus photo after lensectomy of tubercular panuveitis with multifocal choroiditis lesions and large snowbanking. She had incidental HLA B27 positivity.

The careful examination of posterior segment of the eye in case of complicated cataract and recurrent anterior uveitis is often needed to rule out alternative pathologies like tuberculosis in this particular case.

References


1. What is Spondyloarthritis?
Spondyloarthritis (SpA) is a group of inflammatory arthritides affecting both children and adults. It is characterized by presence of enthesitis, and the potential involvement of spine and sacroiliac joint (axial skeletal), has a strong association with HLA-B27 and development of uveitis, which is more often acute onset and/or symptomatic.¹

2. What does Juvenile Spondyloarthritis include?
Juvenile SpA (JSpA) begins before the age of 16. International League of Associations for Rheumatology (ILAR) classification of juvenile idiopathic arthritis (JIA) does not recognize a specific category for JSpA patients.² Yet, Spondyloarthritis includes enthesitis-related arthritis (ERA), juvenile psoriatic arthritis (PsA), undifferentiated arthritis (UA), reactive arthritis (ReA), and the arthropathies associated with inflammatory bowel disease (IBD-A).²

Conditions such as chronic non-infectious osteomyelitis, SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis), and hidradenitis suppurativa are sometimes clustered with spondyloarthritis.³

3. Is it pertinent to consider Juvenile Spondyloarthritis on a continuum with adult Spondyloarthritis?
Yes. Considering JSpA on a continuum with adult spondyloarthritis is crucial for long-term care. This is so because, most children with JSpA can progress to ankylosing spondylitis and may continue to have active disease well into adulthood. It also simplifies adaptation of new treatments.³

4. What are gender and age characteristics of Juvenile Spondyloarthritis?
In a study from Pennsylvania, in the JSpA cohort, as well as in patients with UA, gender was equally distributed. The ERA sub-cohort had the higher male prevalence (59% male), whereas the PsA subset showed a female preponderance (80% female).⁴

Stoll ML et al. found children with JPsA classically to be separate into 2 subgroups.⁵ The first group included those less than 4–5 years of age, similar to children with early onset oligoarticular and polyarticular JIA with a female preponderance, dactylitis and higher incidence of ANA positivity and uveitis. The second group included children with a later age at onset are more likely to be male and have enthesitis, sacroiliitis and psoriasis. HLA-B27 is positive in only 10.6–12% with JPsA with similar distribution in early onset and late onset JPsA and does not correlate with axial disease.⁶,⁷

Other studies have found that mean age at diagnosis is 3.1 years for early onset JPsA and 8.2–11.2 years for late onset JPsA.⁶ Early-onset JPsA has a female preponderance of 78%. Late onset JPsA also has a modest female preponderance of 57.7%.⁶,⁷

Patients with uveitis had a median age at diagnosis of 7.8 years. Half of the children with uveitis were male, both in the entire JSpA cohort and the ERA sub-cohort (46 and 50%, respectively), whereas PsA patients with uveitis were mostly female (67%).⁴

5. What are the characteristics of uveitis in Juvenile Spondyloarthritis?
Uveitis is a frequently occurring extra articular manifestation of JSpA and is thought to be mostly symptomatic acute anterior uveitis.⁸ It occurs with varying frequency according to the SpA subtype (33% in AS, 6–9% in PsA, 25% in ReA, 13% in undifferentiated SpA and 2–5% in IBD), the presence of HLA-B27 and with increasing duration of disease.

Studies have found majority of patients to have both pain and light sensitivity, although more patients report red eyes more than of eye pain/light sensitivity (79 and 71%, respectively).⁴

In majority of cases (83%), uveitis is unilateral during the course of disease. Uveitis is classified most frequently as anterior uveitis (88%) and less frequently involved primarily the posterior eye segments (12%). The latter is more frequently complicated by cystoid macular oedema (CMO) and sight loss.

The course of uveitis episodes after initial manifestation are usually acute in majority of patients (46%, with sudden onset and limited duration), recurrent (28%), repeated episodes separated by periods of inactivity without systemic and topical treatment ≥ 3 months.⁹

6. What is the rate and role of HLA-B27 positivity in Juvenile Spondyloarthritis?
SpA tends to run within families. The most significant genetic risk factor for axial SpA is HLA-B27. While the presence of HLA-B27 is the most significant risk factor for axial SpA, the vast majority of HLA-B27+ individuals are healthy, highlighting the role of additional genetic factors.

In the Pennsylvania study the rate of HLA-B27 positivity of the whole cohort of JSpA is 38%; those with ERA had the highest rate of HLA-B27 positivity whereas non-ERA patients had a significantly lower rate (46% vs. 21%).⁴
Other published JSpA cohorts, one from France and one from Germany share similar features: ERA patients as the prevalent subset (69 and 52%), male predominance (63 and 73%) and high rate of HLA-B27 positivity (43 and 66%). Another study of JIA from Poland reported an HLA-B27 prevalence of 71, and 87% for ERA and UA, respectively. HLA-B27 positivity in ERA is associated with prolonged disease course, higher incidence of acute anterior uveitis, a family history of spondyloarthritis, and higher erythrocyte sedimentation rate.

7. What is the role of ANA in Juvenile Spondyloarthritis?

The prevalence of chronic idiopathic uveitis and ANA positivity in early onset JPsA (18.8%) is similar to that of oligoarticular JIA. Patients with ERA, late onset JPsA and undifferentiated JIA generally develop acute anterior uveitis (79%) which is typically associated with HLA-B27 positivity.

Contrary to idiopathic uveitis, acute anterior uveitis in JSpA classically presents with pain, photophobia and redness. Thus ophthalmology screening should occur every 3 months for children with JPsA and undifferentiated arthritis who are ANA positive and less than 7 years of age. Patients with JPsA and undifferentiated arthritis who are older than 7 and are ANA negative and patients with ERA should be screened every 6–12 months.

8. What is Juvenile Spondyloarthritis Disease Activity Index?

The Juvenile Spondyloarthritis Disease Activity Index (JSpADA) is the only validated disease activity measure specific for JSpA. It is a composite measure including history, physical exam, laboratory markers and pain visual analog scale where each item is equally weighted and summed. The score can range from 0–8 with higher scores indicating higher disease activity. A modified version of this scoring system excluding back mobility was validated in ERA.

9. What are treatment recommendations of Juvenile Spondyloarthritis?

The 2019 American College of Rheumatology guidelines for treatment of JIA includes recommendations for saccroiliitis and enthesitis. Use of TNF inhibitors is strongly recommended in those with saccroiliitis and conditionally recommended over conventional disease-modifying anti-rheumatic drugs (DMARDs) in those with enthesitis. Sulfasalazine is conditionally recommended in those who fail TNF inhibitors or have contraindications to their use in sacroiliitis. Methotrexate monotherapy is strongly discouraged for the management of sacroiliitis, and glucocorticoids are recommended only as bridging therapy. Biologics such as IL-17 blocking agents and small molecules such as JAK inhibitors have shown promise in treatment of adult and now JSpA.

The treatment for uveitis in SpAs is predominantly with topical corticosteroids for acute episodes. DMARD treatment is associated with a reduced risk for developing uveitis; corticosteroid intake decreases the odds for developing uveitis. Among the conventional DMARDs, methotrexate and sulfasalazine decrease the risk for uveitis onset. Regarding biologics, infliximab, adalimumab and certolizumab are effective in reducing the frequency of uveitis; but etanercept is not.

10. What is the role of treatment with NSAIDs for Juvenile Spondyloarthritis?

NSAID treatment do not decrease, but rather increase the risk for developing uveitis; this has been the only significant effect observed in a study. In that study treatment with NSAIDs was (significantly) associated with an increased risk for developing uveitis. Given the fact that most ERA patients are initially treated with NSAID therapy only, this might require some reconsideration of strategy.

11. What is the Indian scenario with Juvenile Spondyloarthritis?

The enthesitis-related arthritis (ERA) category of JIA is the most common category found in Asia including India. HLA B27 presence is included as one of the criteria for categorizing patients as ERA. The prevalence of HLA B27 in ERA varies from 60 to 85 % in different studies and in India the prevalence is about 87 %. The common HLA B27 alleles seen in Indian ERA population are HLA B*2705 and B*2704.

12. What should be the ophthalmological screening schedule in Juvenile Spondyloarthritis?

The ophthalmological screening schedule for JIA patients currently employed in Germany recommends yearly examinations in ERA, assuming that these patients characteristically experience acute symptoms of flare onset, prompting immediate ophthalmological consultation. But, the British guidelines suggested a 3- to 4-monthly screening of children diagnosed with ERA, similar to what is recommended for patients with other JIA subtypes, for which onset of the vast majority of uveitis cases is insidious. This approach is found to be more appropriate by Walscheid K et al, especially in children younger than 10 years at ERA onset, as those children have a particularly high risk for developing uveitis.


## HLA B-27 associated Uveitis: Practice Pattern & Management

### Dr. Kessara Pathanapitoon
Chiang Mai University Hospital, Faculty of Medicine, Chiang Mai, Thailand

### Dr. Amit Khosla
Senior consultant Sir Ganga Ram Hospital New Delhi

### Dr. Soumyava Basu
Senior consultant L V Prasad Eye Hospital Hyderabad

### 1. How do you differentiate between HLAB27 related uveitis, endogenous endophthalmitis and Behcets disease in a hypopyon presentation?

<table>
<thead>
<tr>
<th>Dr. Kessara Pathanapitoon</th>
<th>Behcet’s disease</th>
<th>Endogenous endophthalmitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternating bilateral</td>
<td>Bilateral</td>
<td>Unilateral or bilateral immunocompromised host (chemotherapy, DM, etc) Fever, associated with systemic symptoms and extraocular infection</td>
</tr>
<tr>
<td>Marked ciliary injection</td>
<td>+/- ciliary injection</td>
<td>+/- ciliary injection</td>
</tr>
<tr>
<td>Frequently fibrinous</td>
<td>Rarely fibrinous</td>
<td>+/- fibrinous</td>
</tr>
<tr>
<td>Sticky hypopyon</td>
<td>Shifting hypopyon</td>
<td>Hypopyon</td>
</tr>
<tr>
<td>presence of pigmentation on central anterior lens capsule</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20% vitritis</td>
<td>90% vitritis</td>
<td>90% vitritis</td>
</tr>
<tr>
<td>+/- response to topical steroid Rx</td>
<td>Rapid response to topical steroid Rx</td>
<td>+/- response to topical steroid Rx; later worsening if not received antimicrobial</td>
</tr>
</tbody>
</table>

### Dr. Amit Khosla
Hypopyon can occur with inflammatory disease, infective, disease or tumours. Before making a diagnosis, a complete eye evaluation needs to be done, especially after pupillary dilation. In HLA B 27 uveitis one may see signs of uveitis. A diagnosis of anterior uveitis after doing a complete posterior segment evaluation. If fundus is not fully visualised an USG Bscan should be done and patient examined again after 24 hrs

### Dr. Soumyava Basu
HLA-B27 – red eye, fibrin, recurrent alternating presentation, inflammatory back pain Endogenous – red eye, yellow glow, ±choroidal lesion, suggestive history Behcets – white eye, mobile hypopyon, FFA features, oral±genital ulcers
2. How often do you find HLAB27 related intermediate and posterior segment inflammation in your clinic and what is your preferred management in these cases?

Dr. Kessara Pathanapitoon
I find 10-15% of patients had intermediate and posterior segment inflammation. My preferred management is systemic steroids with or without immunosuppressive agents.

Dr. Amit Khosla
Posterior segment involvement in HLA-B27 Uveitis is in less than 10% cases. It is important to rule out other causes of posterior Uveitis. See attached flow chart for management. Presence of HLA-B 27 report does not mean that the Uveitis is related to HLA-B 27 many HLA-B 27 patients are on long term immunosuppressive therapy and in a country like India. Can have TB

Dr. Soumyava Basu
Commonly, since the cyclitis component of iridocyclitis will cause vitreous inflammation. If mild, I treat the anterior uveitis, and vitritis settles down. If severe, I prefer oral steroids over periocular injections. Posterior segment inflammation other than vitritis (e.g. retinitis, retinal vasculitis) should be treated with caution since it could be a non-B27 pathology – B27 is positive in up to 6% of population. However, IBD and psoriatic arthritis may rarely have retinal vasculitis.
3. What are the panel of investigations you order at the initial presentation?

Dr. Kessara Pathanapitoon
CBC, UA (look for urine sugar, WBC and proteinuria), CXR, anti-HIV, VDRL, TPHA, HLA B27

Dr. Amit Khosla
Investigations are ordered based on the history and clinical examination. History of back pain, joint involvement psoriasis, bowel symptoms will give clue to HLA B27 involvement. Investigations include CBC/CRP may give general clues to systemic infection or inflammation. Patient with spondylarthropathy with uveitis can be HLA B27 negative also. HLA B 27 test should be ordered by PCR technique.

Dr. Soumyava Basu
I advise only B27 (flow cytometry) in patients with non-granulomatous uveitis with other ocular signs (fibrin, hypopyon, alternating recurrent). X-ray SI spine is added if inflammatory back pain. I almost never combine B27 with tests for granulomatous uveitis – TB and sarcoid, although these could be non-granulomatous as well. Testing syphilis in these patients is open to debate.

4. When is a rheumatologist referral sought in HLA B27 related uveitis?

Dr. Kessara Pathanapitoon
When patients complain of eyes symptoms or patients were treated with chloroquine

Dr. Amit Khosla
AAU does not always have a cause-and-effect relationship. In patients with bilateral uveitis, granulomatous uveitis or with chorioretinitis, HLA B27 testing is not recommended. The ophthalmologist should keep in mind that the majority of the patients of acute anterior uveitis may have associated undiagnosed spondyloarthropathy. They should follow the DUET algorithm, which helps them decide when to refer the patient to the rheumatologist.

Dr. Soumyava Basu
Whenever the patient has history of inflammatory joint pain, bowel or skin symptoms.

5. When do you consider immunomodulatory therapy in HLAB27 related uveitis?

Dr. Kessara Pathanapitoon
- Uncontrolled inflammation with oral prednisolone 1 mg/kg/day
- Intolerant to oral prednisolone
- Recurrence attack of uveitis (more than 3 times/year)
- Required more than 10 mg/day to prevent relapse
- Required topical steroids more than 2 drops/day to prevent relapse
- My preferred IMT is methotrexate starting with 10 mg/week and gradually increase to 20 mg/week as needed

Dr. Amit Khosla
Long term inflammation leads to breakdown of aqueous blood barrier leading to chronic flare, which does not disappear with treatment. Acute anterior uveitis leads to lowering of intraocular pressure, but the pressure can increase due to turbid aqueous, adhesions/synechiae and steroid overuse. Chronic use of oral steroids can lead to cataract and glaucoma formation. It is advisable to shift to disease-modifying antiinflammatory drugs (DMARDs), if the uveitis is chronic, that is more than 3 months, has more than 3 attacks a year, high intraocular pressure due to steroids (steroid responder) or intolerance to oral steroids. It is important to remember that cataract surgery can cause aggravation of uveitis. Cataract surgery is done when uveitis is quiescent for 3 to 6 months and under cover of oral steroids or DMARDS. There are no clear-cut guidelines or recommendations for the management of AAU in SpA. This could stem from the fact that acute monophasic and recurrent acute uveitis would need treatment only of the acute attacks. The other issue is that the AAU may or may not be associated with clinically active SpA or the latter may be undiagnosed in 40% of patients when uveitis is treated by the Ophthalmologist. Adding to the conundrum is the fact that the conventional drugs used systemically for AAU (Methotrexate, Sulphasalazine, Azathioprine, Mycophenolate) are unlikely to have any bearing on the musculoskeletal component, at least the axial and enthesis part. The scenario would change with the usage of Biologics in AAU with or without active features of SpA minus the eye.

Dr. Soumyava Basu
Immunomodulatory therapy is rarely needed in patients with isolated B27 uveitis (without systemic disease). If recurrences happen 2-3 times a year, I prefer treating with topical steroids. If recurrences are more frequent (despite adequate topical therapy), I initially suggest lifestyle changes for possible triggers, and then consider immunomodulatory therapy.
6. If an individual with HLA-B27 seropositivity develops hypopyon 1 month after cataract surgery, how would you proceed?

Dr. Kessara Pathanapitoon

- Review medications whether patient under controlled of inflammation before surgery and current medication
- First rule out the infection (post cataract surgery endophthalmitis), look at vitreous if there are any cells and perform B-scan to see whether vitreous haze.
- If there is only anterior inflammation, I will give topical steroid, topical and systemic antibiotics
- If there is posterior involvement, I will manage as endophthalmitis (tap vitreous for gram stain, culture/sensitivity, intravitreal injection of cefuroxime and vancomycin, topical and systemic antibiotic

Dr. Amit Khosla

Hypopyon after cataract surgery should be considered as infection unless proved otherwise. In case of HLA B 27 uveitis with cataract, the patient should be oral steroids or IMT therapy should be given for few months after surgery

Dr. Soumyava Basu

I would initially investigate thoroughly for infectious endophthalmitis. Look for lid edema, wound infection, yellow glow, and then consider B27 uveitis (provided there is past history of uveitis). In any doubt, I would err towards endophthalmitis and get a vitreous biopsy.

7. What differentials do you consider for unilateral, alternating, non granulomatous anterior uveitis in a HLA-B27 negative individual with no signs of systemic spondylisis

Dr. Kessara Pathanapitoon

- HLA B27 like anterior uveitis (HLA B27 can be negative in this presentation)
- Look for psoriasis

Dr. Amit Khosla

Differential diagnosis is all the disease associated with HLA B 27 like psoriasis, IBD, Reiter's disease, Disease like sarcoidosis and TB can also present as non granulomatous uveitis

Dr. Soumyava Basu

Up to 20% B27 type disease may test negative for B27. So that remains my first differential even in the absence of SpA. I will test for TB, sarcoid or syphilis in acute unilateral, alternating, non-granulomatous anterior uveitis only if there is a clinical suspicion for those conditions.

8. What is the role of UBM in the setting of a non-dilating/ festooned pupil in HLAB27 associated chronic uveitis?

Dr. Kessara Pathanapitoon

- Identify cyclitic membrane/atrophy in those with ocular hypotony
- In pseudophakic uveitis, UBM help to assess IOL position

Dr. Amit Khosla

UBM helps us pick up ciliary body membranes or traction, sometimes it may give clues of pars planitis, indicating that systemic treatment is required

Dr. Soumyava Basu

UBM helps differentiating ciliary atrophy from ciliary membranes in hypotony with chronic uveitis.

9. How do you manage hypotony in HLA B27 related uveitis, both in the acute as well as the chronic phase?

Dr. Kessara Pathanapitoon

- Acute: intensive anti-inflammatory treatment (topical, periocular injection, systemic steroid)
- Chronic: Immunosuppressive agents/Biologic, identify whether there is cyclitic membrane, if so PPV, remove membrane and silicone-oil injection and intensive anti-inflammatory treatment

Dr. Amit Khosla

Hypotony indicates inflammation. Hypotony in the acute disease gets corrected with topical and systemic treatment with steroids and Immunosuppressives, Chronic Hypotony can be caused by inflammation and membranes over the ciliary body, which is diagnosed clinically and with UBM, treatment is targeted at the cause

Dr. Soumyava Basu

Acute hypotony usually responds to oral steroids or sometimes even topical steroids. In chronic hypotony, I usually add difluprednate eye drops 4 times/day without tapering periocular steroids, and wait for at least two months. If IOP remains below 6, I consider surgical intervention including silicon oil injection.
10. Where do you place biologic therapy role in the management of the HLAB27 related uveitis?

Dr. Kessara Pathanapitpon

- Uncontrolled inflammation or relapse with conventional immunosuppressive agents
- Systemic side effect of conventional immunosuppressive agents and chronic steroid usage

Dr. Amit Khosla

Biologic response modifiers (BRM) or Biologics have revolutionized treatment of eye disorders, specifically uveitis, in patients who fail corticosteroids or conventional immunosuppressants. More importantly they take care of the musculoskeletal, skin and gut features including the difficulty to treat inflammatory back pain and enthesitis that may be associated with uveitis. There are no specific guidelines or recommendations and one has to rely on case reports, expert opinions and FOCUS & SHARE initiatives. At present the indications of their use could be as suggested below:

1. Recalcitrant eye disease not or inadequately responding to corticosteroids and conventional immunosuppression.
2. Intolerance to conventional immunosuppressive therapy or in whom corticosteroid treatment is inappropriate.
3. Significant extra ocular morbidity, musculoskeletal, skin, IBD

The treatment depends on the activity of the joints or extra articular disease like IBD Psoriasis and whether the eye disease has become chronic with breakdown of aqueous barrier

Dr. Soumyava Basu

Biologics are almost never required in isolated uveitis, but may be needed for the systemic disease.

11. In the setting of active iritis in HLA B27 uveitis, if there is an indication for urgent surgical intervention, how would you proceed?

Dr. Kessara Pathanapitpon

- Acute angle closure attack with pupillary block may require surgical peripheral iridectomy
- Mature cataract with glaucoma (phacomorphic, phacolytic)

Dr. Amit Khosla

Surgery requirement in active uveitis can be required for glaucoma or retinal detachment, since it is a semi urgent situation, systemic steroids are required. Cataract surgery should be delayed for 3-6 months after control of inflammation

Dr. Soumyava Basu

I am not sure which surgical intervention would be required in the setting of acute B27 uveitis.

12. Do you find any role of lifestyle or dietary modifications in the management of HLAB27 related uveitis?

Dr. Kessara Pathanapitpon

- I find some patients relapse after stress, lack of rest, smoking or some food digestion (high fat diet) so I sometime convince the patient to modify lifestyle and dietary modifications

Dr. Amit Khosla

Patients of SpA and anterior uveitis have association with genes such as HLA B27, interleukin 23 receptor (IL-23R) and endoplasmic reticulum aminopeptidase (ERAP 1). Another attractive theory is the role of the microbiome in uveitis and SpA. SpA and other immune mediated conditions have been shown to have gut dysbiosis (altered gut microbial flora). In animal studies injection of microbial products and transfer of gut commensals has been associated with SpA. In murine models, it has been shown that there is traversing of labelled leukocytes from the intestine to the eye suggesting a correlation between the two organs. It has been shown that growing retina specific TCR transgenic mice under aseptic conditions reduces development of gut microbiome and consequently uveitis.

In another experiment, use of broad spectrum antibiotics in mice resulted in amelioration of uveitis. Observational studies in humans have suggested some visual improvement in refractory uveitis with broad spectrum antibiotics. Due to several risks with these drugs including resistance, removing beneficial gut organisms, this theory may not be viable in humans. Dietary supplement with short chain fatty acids that may regulate mucosal immunity has been demonstrated to reduce ocular inflammation in mice. At present it is still unclear whether gut microbiome and its modification can play a role in eye and SpA. Despite similarities in human and animal models in uveitis and SpA, including the possible role of HLA B27, uveitis has so many diverse causes that it is impossible to explain their coexistence by any simple or single mechanism.

Dr. Soumyava Basu

While there is no clear evidence of either, I enquire about possible triggers in patients with recurrent uveitis – e.g., change in diet, emotional stress etc, and advice patients to avoid those situations.
13. Do you see seasonal variations in the recurrences in HLA B27 related uveitis?

Dr. Kessara Pathanapitoon

Yes, in some patients, but haven’t seen many seasonal variations that I can identify the trend.

Dr. Amit Khosla

It is proposed that uveitis is precipitated by certain infections, which may be seasonal. Personally I don’t see a seasonal variation but post covid infection I have seen activation of uveitis.

Dr. Soumyava Basu

Yes, but those are patient specific. Some tend to recur in winters, others in the rains.

14. In a case of HLA B27 related uveitis with positive human immunodeficiency virus positive status, what do you do differently?

Dr. Kessara Pathanapitoon

- Depend on CD4 count, viral load and frequency of relapse.
- I will try to avoid using periocular, implant, intravitreal injection, immunosuppressive agents or biologic and prefer using topical and systemic steroids as needed. But if patients had high CD4 count, low viral load, multiple relapse and cannot be controlled with systemic steroid, I will consider antimetabolite and consult with the internist.

Dr. Amit Khosla

HIV positivity in HLA B27, likely to have anergy. Any active uveitis can be caused by HIV and associated infections. It is better to avoid IMT and Biologics and rely on short acting steroids.

Dr. Soumyava Basu

I treat the patient with topical corticosteroids.

15. Below is a 2*2 table of test positive results in an individual suspected to be HLA B27 uveitis:

<table>
<thead>
<tr>
<th>Investigation</th>
<th>HLA B 27 POSITIVE</th>
<th>HLA B 27 NEGATIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mantoux/Imaging Positive</td>
<td>CASE A</td>
<td>CASE B</td>
</tr>
<tr>
<td>Mantoux/Imaging Negative</td>
<td>CASE C</td>
<td>CASE D</td>
</tr>
</tbody>
</table>

How will you proceed differently in case A, B, C, D?

Dr. Kessara Pathanapitoon

Case A, B (no different approach): if patient required systemic steroid/IMT, I will treat him with ATT drugs prior to start systemic steroid/IMT. Case C, D (no different approach): Route and aggressiveness of treatment will depend on severity of uveitis, relapse, posterior involvement, presence of cystoid macular edema.

Dr. Amit Khosla

In the Indian context, tuberculosis can coexist with SpA, especially in patients on TNF inhibitors. In contrast to SpA, tubercular uveitis is granulomatous and may involve all layers of the uvea. We should suspect tuberculosis in bilateral cases, granulomatous anterior uveitis and pan uveitis. Ocular TB is associated with systemic paucibacillary TB. CT Chest with contrast helps us in finding systemic tuberculosis. (Flowchart 3). It is important to stop TNF for 3 months, and then restart if needed, and avoided if other drugs can control the uveitis.

Dr. Soumyava Basu

There are several other factors to be considered since both B27 and Mantoux can be positive in normal individuals. What is the pattern of uveitis – granulomatous or non-granulomatous, disease course – acute, recurrent or chronic, other ocular signs, systemic symptoms etc? Tests alone cannot guide the etiological diagnosis. It is possible that the patient may have a third etiology – say, syphilis – despite both being positive.
1. HLA B27 is strongly associated with all of the following except
   a. Ankylosing Spondylitis (AS)
   b. Reactive arthritis (ReA)
   c. Seropositive spondyloarthropathies
   d. Alternating acute fibrinous anterior uveitis

2. The subtype of HLA B27 not associated with ankylosing spondylitis
   a. HLAB27 05
   b. HLAB27 04
   c. HLAB27 06
   d. HLAB27 02

3. Factors associated with increased prevalence of acute anterior uveitis in HLA B27 positivity
   i. Male gender
   ii. Presence and duration of axial spondyloarthropathy
   iii. Age >60 years
   iv. Female gender
   Choose the true statements
   a. Only i
   b. iii and iv
   c. ii and iv
   d. i and ii

4. Pick the mismatched condition
   a. HLAB27- Enteropathic arthritis
   b. HLAB5/B51-Adamantiades-Behcet’s disease
   c. HLA A27-Bird shot retino-choroidopathy
   d. HLAB27-Tubulointestinal nephritis and uveitis syndrome

5. HLA B27 AAU is characterised by
   i. Non-granulomatous fibrinous anterior uveitis
   ii. Unilateral episodes of anterior uveitis and alternating between eye
   iii. Hypopyon and posterior synechiae may occur
   iv. There can be prominent intermediate uveitis and posterior segment involvement.
   v. Strong association with MHC type 2 allele.
   The incorrect statements are
   a. i and ii
   b. i, ii, and iii
   c. v only
   d. iv and v

6. Refractory cases of HLAB27 uveitis is associated with
   a. Glaucoma
   b. Complicated cataract
   c. Cystoid macular edema
   d. All the above

7. Of the following TNF-alpha inhibitors, which drug is FDA approved for uveitis associated with seronegative spondyloarthropathy
   a. Infliximab
   b. Adalimumab
   c. Certolizumab
   d. Golimumab

8. Pick the incorrect one
   a. Marie Strumpell disease- Bamboo spine
   b. Paradoxical occurrence of uveitis- Infliximab
   c. Reactive arthritis -Keratoderma blenorrhagica
   d. Inflammatory bowel disease-Keratitis

9. Extraintestinal manifestations of patients with inflammatory bowel disease includes
   a. Non-granulomatous anterior uveitis
   b. Scleritis
   c. Episcleritis
   d. All the above

10. False statement among the following
    a. HLAb27 gene shows a high degree of polymorphism
    b. Retinal vasculitis can occur secondary to immune complex vasculitis in enteropathic arthritis.
    c. Immunomodulatory therapy is indicated in refractory anterior uveitis associated with HLA B27.
    d. The presence of anterior uveitis correlates with the severity of the ankylosing spondylitis.
Role of Microbiome in HLA-B27 associated Uveitis

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Introduction
Evolution of the knowledge about the gut microbiome has been rapidly evolving in the recent era. Its role in various immune related disorders has been increasingly apparent. It has been widely studied in various rheumatological conditions like ankylosing spondylitis, reactive arthritis and inflammatory bowel diseases. Many a times these systemic conditions are associated with various HLA alleles. We shall discuss about the role of microbiome in HLAB27 associated uveitis in detail in subsequent section.

HLA allele and microbiome
Genes of the major histocompatibility complex (MHC) are otherwise known as human leukocyte antigens (HLA). Several hypotheses are being proposed to understand the pathophysiology of HLA alleles in causation of these immune related disorders. Alteration of the gut microbiome by HLAB27 has been reported by various authors. There is also sequence homology between a nitrogenase from Klebsiella and HLA-B27. Penttinen et al. showed that HLA-B27 transfected monocytes had enhanced inflammatory responses to lipopolysaccharide found on bacterial cell walls. Bacteria including Shigella, Salmonella, Yersinia, and Campylobacter are well-characterized triggers for HLA-B27 associated reactive arthritis. Experimental studies from transgenic rats demonstrated that HLAB27 modulates the gut microbiome. Transgenic rats have the ability to express human HLA B27 and beta 2 microglobulin. Data from transgenic mice which express HLA DR0401 and data from infants who are HLA DQ2 + are at risk for celiac disease also support the concept that HLA molecules shape the microbiome.

HLAB27 associated uveitis and microbiome
HLAB27 causes loss of ocular tolerance leading to uveitis through various proposed mechanisms. Intestinal microbiome forms a key element in the pathogenesis of HLAB27 associated anterior uveitis. We shall discuss the common hypotheses being proposed over the decades.

First, the microbiome could induce a loss of gastrointestinal tolerance that ultimately leads to inflammatory responses to ocular self-antigen. Gut microbiota regulates the induction of FoxP3+ cells, T cells secreting IL-10 (interleukin) and Th17 cells. A reduction in the FoxP3+ cells and or IL10 or an increase in the Th17 cells could predispose to immune mediated disorders. Lymphoid cells like NK cells and other innate lymphoid cells, intraepithelial lymphocytes, gamma delta T cells and mucosal associated invariant T cells (MAIT cells) are also being affected by the gut microbiome.

Molecular mimicry has been the most widely accepted pathway of dysbiosis causing autoimmune disorders. Various bacterial or viral antigens have been found to have a similar shape or amino acid sequence that could mimic an endogenous autoantigen. They can be presented by a shared epitope as well. This could lead to a cross reaction with the self antigen. Various reports discuss about this mimicry between HLAB27 and bacterial antigen as well. Caspi et al. demonstrated the role of antigenic mimicry in activating T cells from the intestine in response to exposure to a bacterial antigen. They recognised IRBP (inter-photorceptor binding protein) in this transgenic mouse model of posterior uveitis having phenotypic similarity with the bacterial antigen, in the causation of the posterior uveitis.

Another proposed mechanism for involvement of gut microbiome in autoimmune disorders is increased intestinal permeability leading to translocation of the triggering stimulus to the local secluded ocular microenvironment. It is usually the byproducts of the bacterial or viral infection that could dislodge from the affected site like synovial fluid and permeate through the ocular barriers. Any bacterial product which is non commensal to a particular organ, should therefore be considered as potential trigger for any immune mediated process in that particular organ.

The fourth proposed mechanism is the extension of the above mentioned pathway of translocation. The authors propose that it is the translocation of the lymphocytes or other inflammatory cells from the gut to the ocular tissue that leads to autoimmune ocular disorders or even flare up of the inflammatory process. Various EAU models have expressed the migration of the the lymphocytes from gut to eye through a photoactivating pigment, kaede.

Microbiome and management of uveitis
Experimental autoimmune uveitis (EAU) models for posterior uveitis has shown the effects of broad spectrum systemic antibiotics on elevating the levels of FoxP3 + cells in the mesenteric lymph nodes as well as in the retina. However, most antibiotics does not have a long term or sustainable effect to prevent recurrences of uveitis. Also, this might lead to antibiotic resistance as well, in long term usage. Probiotics are live microorganisms that help improve and/ or restore the healthy gut microenvironment. However, it is difficult for the available probiotics to evade the effects of gastric pH and colonize the gut. Dietary modification including oral supplementation of short chain fatty acids (SCFAs), has been
found to reduce the inflammatory cytokines like IL1, IL-17 and interferon gamma.\(^{(23)}\) Another option is fecal transplantation. This procedure involves transplantation of the gut microbiota from a healthy donor to a patient to restore normal diversity and function. This surgical option is mainly reserved for recalcitrant cases of immune mediated disorders. It has shown dramatic response in the treatment of ulcerative colitis and recalcitrant Clostridia difficile infection.\(^{[24-26]}\) Though oral route of administration options are available, its role in HLA b27 uveitis is not known. However, this surgical approach is not devoid of safety issues, risks of transmission of viral infection and transplant failure as well.

**Conclusion**

Microbiome plays a vital role in modulation of the immune system of the human being. The knowledge regarding the effects of gut microbiome over the uveitis is very limited and is evolving in recent decade. HLAB27 allele has been widely studied to have modulatory effects on the gut microbiota. Though oral route of administration options are available, its role in HLA b27 uveitis is not known. However, this surgical approach is not devoid of safety issues, risks of transmission of viral infection and transplant failure as well.

**References**

Across
6. Most common systemic association seen with HLA-B27 anterior uveitis.
7. Major diagnostic criteria in reactive arthritis
10. FDA approved monoclonal antibody for HLA- B27 anterior uveitis.
11. Extra articular involvement in psoriatic arthritis.
12. Complication seen with HLA-B27 anterior uveitis.

Down
1. Commonly seen ocular manifestation with ulcerative colitis
2. Uveitis in HLA-B27 is_____________
3. Ocular sign seen in HLA-B27
4. Seronegative disease associated with HLA- B27 and skin manifestations.
5. Bacterial association seen in HLA-B27.
8. Gene mutation increasing the risk of ankylosing spondylitis in HLA-B27.
9. Most accurate testing for HLA-B27

The HLA B-27 Challenge

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Vittal Institute of Ophthalmology, Bengaluru
HLA B-27 associated Uveitis: Literature Review

Dr. Gazal Patnaik
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Outcomes of early and late immunomodulatory treatment in patients with HLA-B27-associated chronic uveitis

Androudi et al.

To evaluate the outcomes of early versus late immunomodulatory treatment (IMT) in patients with HLA-B27-associated chronic uveitis

- The median time between diagnosis and start of IMT was 3.05 years.
- The mean follow-up for the group A was 2.14 years and for the group B was 3.46 years.
- Control of inflammation was achieved in 29 patients (80.5%) of the group A and in 33 patients (91.6%) of the group B.
- A steroid-sparing effect was achieved for 13 (81.25%) of the 16 patients and for 11 (73.33%) of the 15 patients who were on systemic steroid in the group A and group B respectively.

Purpose

Study Participants

Result

- Seventy-two patients (114 eyes) with HLA27-associated chronic uveitis received IMT at the Ocular Immunology & Uveitis Service of the Massachusetts Eye and Ear Infirmary

Methodolog

- Retrospective study
- Patients were divided into two groups:
  - Group A - those in whom initiation of IMT was within the first 3 years (36 patients).
  - Group B - initiation of IMT was more than 3 years from the initial diagnosis (36 patients).
- Main outcome measures were visual acuity, control of inflammation, number of flare-ups and steroid-sparing effect

Conclusion

- IMT is an effective treatment for severe HLAB27 uveitis that fails to respond to conventional steroid treatment, regardless of the timing of its initiation.
- However, introduction of IMT within 3 years of the disease onset prevents the adverse effects of steroids (cataract, glaucoma) and reduces the likelihood of repeated recurrences of the uveitis.
Ocular Immunology and Inflammation, DOI: 10.1080/09273948.2021.1873396

Mesorazone Suppresses Proinflammatory Cytokines in Patients with Acute Anterior Uveitis Independently of HLA-B27

Smatlik et al.

To unravel the mechanism of mesorazone (5-ASA) on proinflammatory cytokines in PBMCs of patients with HLA-B27 + and HLA-B27 - acute anterior uveitis (AAU)

- Mesorazone (5-ASA) suppressed IL-6 mRNA in healthy donors and in HLA-B27+ and HLA-B27- patients
- 5-ASA did not lead to induction and secretion of IL-1β.
- In HLA-B27 + or – patients the stress associated markers CHOP (DDIT3) and ATF6 were suppressed.

Study Participants

- HLA-B27 positive (+) and HLA-B27 negative (-) associated AAU patients were included

Methodology

- PBMCs from 12 HLA-B27+ and 4 HLA-B27- AAU patients were preincubated with 5-ASA and stimulated with LPS.
- Proinflammatory cytokines and markers were measured

Result

Conclusion

- Mesorazone (5-ASA) inhibits the transcription of proinflammatory and stress associated cytokines and markers, independently of the HLA-B27 status.
**Study confirms seasonal variation in HBU patients by documenting the least incidence from March to June**

- 56% of patients can have a maximum number of recurrences in a specific season of the year.
- Of the 44 patients with HLA-B27 associated uveitis, 22 patients (50%) were noted to demonstrate posterior segment involvement.
- Disc leakage and peripheral vasculitis were the most common findings of posterior involvement.
- Those with anterior chamber inflammation were found to have a significantly increased risk of posterior involvement.
- Those with posterior involvement were also noted to have a statistically significant decreased visual acuity.
- No significant association was found between documented duration of disease and posterior segment involvement.

- HLA-B27-associated uveitis from a tertiary uveitis clinic.
- Patients with significant systemic and ocular comorbidities were excluded.

- Medical records of patients were retrospectively reviewed, including posterior segment involvements and various imaging modalities including wide field fluorescein angiography and optical coherence tomography.
- Demographic characteristics, accompanied with systemic diseases as well as duration and chronicity of uveitis, were also evaluated.
- Statistical analyses including chi-squared tests and paired t-tests were employed.

- The prevalence of posterior segment involvement in HLA-B27 associated uveitis is higher compared to previous reports when evaluated with wide angle imaging modalities.
Choroidal change in acute anterior uveitis associated with human leukocyte antigen-B27

Ahn et al.

To evaluate choroidal changes in eyes with acute anterior uveitis associated with human leukocyte antigen (HLA)-B27.

**Purpose**

- Compared to the fellow eyes, eyes with acute anterior uveitis showed significant choroidal thickening on the subfoveal and parafoveal areas at baseline (all P <0.05)
- En face choroidal imaging showed dilation of large choroidal vessels on the macula
- Relative choroidal thickening significantly correlated with the degree of anterior chamber inflammation at baseline (correlation coefficient = 0.341, P = 0.023).
- After treating inflammation, the choroid on the macula thinned significantly (from 262.1 ± 66.5 to 239.5 ± 61.0 μm in the subfoveal choroid, P<0.001)

**Methodology**

- Choroidal thickness was measured by automated segmentation (using wide-field three-dimensional volumetric raster scan using swept-source optical coherence tomography) and thickness mapping and compared between uveitic eyes and the normal fellow eyes at baseline
- Choroidal thickness was compared before and after topical and/or systemic corticosteroid therapy.
- Relative choroidal thickening was defined as the choroidal thickness of the uveitic eye minus that of the corresponding eye and correlated with the degree of intraocular inflammation.

**Result**

**Conclusion**

- Eyes with HLA-B27-associated anterior uveitis showed significant choroidal thickening at acute phase that subsequently decreased after treatment, indicating subclinical choroidal inflammation in the eyes.
- Choroidal thickness might indicate disease activity in acute anterior uveitis associated with HLA-B27
To investigate the vision-related quality of life (VR-QOL) in patients with HLA-B27 associated anterior uveitis (AU)

- NEI VFQ-25 mean overall composite score was 88.9±8.8, which is relatively high, but lower than that found in a normal working population.
- The mean general health score was 47.4±20.8, which is lower than in patients with other ocular diseases.
- Patients with a systemic disease scored significantly lower on general health and VR-QOL, compared to patients without a systemic disease.
- Patients with a depression (6/59 (10%)) frequently had ankylosing spondylitis (5/6 patients) and they scored significantly worse on VR-QOL

AU patients who were HLA-B27 positive and/or were diagnosed by a rheumatologist with an HLA-B27 associated systemic disease

- All patients filled-out the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25), Beck Depression Inventory (BDI-II), social support lists and an additional questionnaire for gathering general information.
- Medical records were reviewed for clinical characteristics.
- Analyses were conducted on various patient and ocular characteristics.
- NEI VFQ25 scores were compared with those previously found in the literature.
- Main outcome measures were VR-QOL scores and their associations with various general patient and ocular characteristics

Patients with HLA-B27 associated AU have a relatively high VR-QOL.
- The presence of a systemic disease is associated with lower VR-QOL and general health scores.
- Depression is associated with a lower VR-QOL.
To evaluate basal serum prolactin levels in patients with HLA-B27-associated uveitis

- Fourteen out of 23 patients with arthritic disease had ankylosing spondylitis.
- Prolactinemia was significantly higher (mean=15.84 ng/mL) in patients vs controls (mean=11.50 ng/mL) (p=0.026).
- Subgroup analysis revealed prolactinemia in arthritic disease patients (mean=17.21 ng/mL) significantly higher than controls (mean=11.50 ng/mL) (p=0.009) and in ankylosing spondylitis (mean=17.65 ng/mL) vs controls (mean=11.50 ng/mL) (p=0.006).
- No correlation was found between prolactinemia and systemic treatment.
- Prolactinemia did not correlate with disease activity.
- Autoimmunity features also correlated with higher prolactinemia (mean=17.26 ng/mL) vs controls (mean=11.50 ng/mL) (p=0.015)

- Patients HLAB27-associated uveitis and age- and sex-matched healthy control subjects

- Prospective, nonrandomized comparative trial.
- Age, systemic disease, treatment, and uveitis activity were recorded for comparative analysis between groups.
- Basal serum prolactin levels were determined by electrochemiluminescence immunoassay on a Modular Analytics E170 analyzer.

- Serum prolactin levels has a role in HLA-B27-associated uveitis pathogenesis and its subgroups.
- There was no correlation with disease activity.
To assess the incidence of, risk for, and visual outcomes of acute anterior uveitis (AAU) in human leukocyte antigen (HLA)-B27 positive patients who had laser in situ keratomileusis (LASIK).

- Twenty eyes (10 patients) had LASIK a mean of 36 months (SD) after the diagnosis of HLA-B27.
- In the HLA-B27 positive patients, the incidence rates of uveitis between eyes that had and eyes that did not have LASIK were not significantly different.
- The incidence rates of uveitis after LASIK did not differ significantly between eyes with and eyes without episodes of uveitis before LASIK (PZ .135).
- The probability of an eye having no episode of uveitis in the fourth and fifth year of follow-up was not significantly different between eyes that had LASIK and those that did not (PZ .668).

- HLA-B27 positive patients with a 5-year follow-up

- University-based center
- 46 eyes of 23 HLA-B27 positive patients with a 5-year follow-up were reviewed retrospectively
- Incidence rates of episodes of uveitis was calculated for LASIK and non-LASIK eyes.
- Kaplan-Meier survival probabilities were calculated for uveitis occurring during the final 36 to 60 months of the study.
- Survival probabilities between LASIK and non-LASIK eyes were compared

- The occurrence rate of post-LASIK AAU in the HLA-B27 positive population was not higher than the general incidence in a similar HLA-B27 population without previous LASIK.
- A previous episode of uveitis did not appear to increase the risk for uveitis after LASIK in HLA-B27 positive patients
To determine the efficacy and safety of infliximab therapy in patients with HLA B-27-associated ocular inflammation resistant or intolerant to conventional immunomodulatory therapy.

- Twenty-four patients (38 eyes) were included.
- All patients were followed for 24 months.
- Sixteen (66.7%) patients had active uveitis at the beginning of therapy.
- Thirteen (87.5%) out of sixteen active patients were in steroid-free remission.
- The mean duration of treatment to induce remission was 16.5 months (range 6–24 months).
- Corticosteroid was stopped in 19 (90.5%) patients.
- 14 (58.3%) patients were in remission on infliximab therapy and 6 (25%) patients were in remission off infliximab therapy.
- Of the 38 eyes, 8 (21.05%) showed improvement in BCVA (three eyes had successful cataract extraction with intraocular lens implantation during infliximab therapy with no subsequent inflammation), while 26 eyes (68.4%) had stable BCVA over the 24-month study period.

- Uveitic patients with positive HLA-B27, resistant or intolerant to conventional immunomodulatory therapy.

- Retrospective observational case series.
- The primary outcome of the study was to identify the efficacy of infliximab determined by the control of inflammation, duration of remission, and the ability to reduce conventional immunomodulatory therapy.
- The secondary outcome was an improvement of two or more lines of best-corrected visual acuity (BCVA) on the Snellen visual acuity chart

- Infliximab might induce and maintain the steroid-free remission in HLAB27-associated ocular inflammation in patients resistant or intolerant to conventional immunomodulatory therapy.
Bilateral macular thickening (MT) in mild unilateral anterior uveitis (AU): is HLA-B27 involved?

To study the rate and extent of MT in both AU-affected and quiescent fellow-eyes of phakic AU patients with good visual acuity (VA).

- Subclinical MT is present in both quiet fellow-eyes and AU-affected eyes of patients.
- MT was found in most cases of AU, even in phakic eyes with good VA.
- There was a larger increase in MT in HLA-B27-positive than in HLA-B27-negative patients.
- No differences in MT were found between patients with their first AU episode and patients with recurrent episodes.

Purpose

Study Participants

- Patients with AU were prospectively included.
- MT was measured with OCT initially and on follow up.
- MT in affected eyes (n = 30) as well as in their quiet fellow-eyes (n = 28) was compared with eyes of age- and gender matched controls.
- Inter-ocular differences in MT between AU affected eyes and their fellow-eyes were assessed with visual acuity ≥ 0.8 (n = 23) by one-sample Student’s t-tests.
- Inter-ocular differences were also assessed related to HLA-B27 presence and related to the status of current AU episode (initial or relapse).

Result

Methodology

Conclusion

- MT probably reflects systemic immune-mediated response to the inflammatory disorder in AU.
- It is possible that HLA-B27-related factors are involved in the pathogenesis of AU.
**Awards and Recognitions**

**Dr. Jyotirmay Biswas**
Delivered the oration dedicated to Dr. K S Ratnakar at the 15th Oration of Indian College of Pathologists at Bengaluru

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**Prof. Amod Gupta**
Hearty congratulations for receiving the Life time achievement award from VRSI

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**Dr. Aditya Patil**
Best Physical Poster
Exploring Tear Cytokine Profile in Fuch’s Uveitis Syndrome versus controls at AIOC 2023, Kochi

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**Dr. Abhilasha Baharani**
Best Poster Podium Presentation
Epidemic Retinitis: Doxycycline or Steroids First? An OCT Angiography Based Study AIOC 2023, Kochi

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**Dr. Mayur R Moreker**
Best Scientific Paper Award
Demystifying the role of Mantoux Test in Ocular Tuberculosis at Annual conference of the Bombay Ophthalmologists’ Association at Mumbai in March 2023

**Best E-Poster Award for**
Uveitis Pe Charcha, 26th February, 2023 - Manipal,
Organised by Department of Ophthalmology, Kasturba Medical College and Hospital

Uveitis Simplified, 9th April, 2023 - Pune
Organised by Poona Ophthalmological Society at Ruby Hall Clinic, Pune

Matching Trends With Basic Principles, 9th July, 2023, Tirunelveli
Organised by Aravid Eye Hospital, Tirunelveli

Uveitis Decoded, 12th & 13th August, 2023, Ludhiana
Organised by Ludhiana Ophthalmological Society at Dhami Eye Care Hospital, Ludhiana
USI Session in IOIS 2023, 6th - 9th September 2023, Berlin

The Uveitis society of India had an intriguing session at the International Ocular Inflammation Society-2023 held at Berlin, Germany entitled "Twists in the tale: late diagnostic revisions in uveitis". It was a case based discussion with the challenging scenarios neatly highlighted by the speakers. It was highly enlightening and well appreciated by the attending members.
1. HLA B27 is strongly associated with all of the following except:
   C. Seropositive spondyloarthropathies

2. The subtype of HLA B27 not associated with ankylosing spondylitis.
   C. HLAB27 06

3. Factors associated with increased prevalence of acute anterior uveitis in HLA B27 positivity.
   D. i and ii

4. Pick the mismatched condition
   C. HLA A27-Bird shot retino-choroidopathy

5. HLA B27 AAU is characterised by
   C. v only

6. Refractory cases of HLAB27 uveitis is associated with
   D. All the above

7. Of the following TNF-alpha inhibitors, which drug is FDA approved for uveitis associated with seronegative spondyloarthropathy
   B. Adalimumab

8. Pick the incorrect one
   B. Paradoxical occurrence of uveitis- Infliximab (Etanercept is associated with paradoxical occurrence of uveitis)

9. Extraintestinal manifestations of patients with inflammatory bowel disease includes
   D. All the above

10. False statement among the following
    D. The presence of anterior uveitis correlates with the severity of the ankylosing spondylitis.
Thank you

With due perseverance and hard work of the editorial and scientific committee members, we have been able to publish this edition of the USI Newsletter for the readers. I sincerely wish to convey my heartfelt special thanks to Dr. Kalpana Babu, Dr. Sudharshan S, Dr. Parthopratim Dutta Majumder Dr. Gazal Patnaik, Dr. Mayur R Moreker, Dr. Anup Kelgaonkar, Dr. Vinaya Kumar Konana, Dr. Dipankar Das Dr. Somasheila Murthy, Dr. Anjana Somanath, Dr. Reema Bansal, Dr. Amit Khosla, Dr. Soumyavu Basu Dr. Ankush Kawali, Dr. Navneet Mehrotra, Mrs. Veidhehi J and design team of Hallmark Events for sparing their precious time to co-edit the contents of this issue. Thanks to all the fraternity members who have contributed their manuscript.

The incessant encouragement from all my dear friends and seniors is highly appreciated!

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