Published in final edited form as:
Am J Ophthalmol. 2010 October ; 150(4): 534–542.e2. doi:10.1016/j.ajo.2010.04.031.

Incidence Rates and Risk Factors for Ocular Complications and Vision Loss in HLA-B27-Associated Uveitis

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Abstract

Purpose—To calculate the incidence rates of ocular complications and vision loss in HLA-B27-associated uveitis and to explore the effect of chronic inflammation on clinical outcomes.

Design—Retrospective longitudinal cohort study

Methods—The clinical records of 99 patients (148 uveitis-affected eyes) with HLA-B27-associated uveitis seen at a tertiary care center were included. The main outcome measures were ocular complications (posterior iris synechiae, band keratopathy, posterior subcapsular (PSC) cataracts, ocular hypertension, hypotony, cystoid macular edema and epiretinal membrane) and vision loss. Anterior chamber inflammation was defined as ≥1+ grade inflammation. Chronic uveitis was defined as persistent inflammation with relapse in <3 months after discontinuing treatment or requiring medications to suppress inflammation for >3 months after reviewing the patient's entire clinical course.

Results—The clinical course was most commonly acute/recurrent (75%) or chronic (20%). The most common complications to develop during follow-up were ocular hypertension (0.10/eye-year) and PSC cataracts (0.09/eye-year). In multivariate analysis, the presence of posterior synechiae at presentation, inflammation, corticosteroid-sparing therapy, corticosteroid injections, chronic disease

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c. *Contributions to Authors in each of these areas:*

Design and Conduct of the study (NA)

Collection and Management of data (AL, NA)

Analysis and Interpretation of data (AL, NA)

Preparation, review and approval of the manuscript (AL, NA)

d. Statement about Conformity with Author Information: This study was approved by expedited review by the University of California, San Francisco Committee on Human Research. Due to the retrospective nature of the research, the committee waived the need for informed consent. The study and data accumulation were in conformity with all country, federal and state laws. Additionally, the study was performed in accordance with HIPAA regulations and in adherence to the tenets of the Declaration of Helsinki.

b. *Financial Disclosures:* None.

e. *Other Acknowledgments:* None.

and male gender were associated with a statistically significant increased risk of developing vision loss (20/50 or worse). Chronic disease course was associated with a 7-fold increased risk of visual impairment (HR=6.8, $P<0.0001$). The presence of inflammation during follow-up was associated with an increased risk of developing visual impairment (HR=6.2, $P<0.0001$). In multivariate analysis, chronic disease course and topical corticosteroids were associated with an increased risk of developing any incident ocular complication (HR=2.2, $P=0.04$) and (HR=3.3, $P=0.01$), respectively.

Conclusions—Poorly controlled inflammation was associated with the development of ocular complications including vision loss. Patients with chronic inflammation were also at greater risk of complications.

Introduction

Human Leukocyte Antigen (HLA)-B27-associated uveitis is the most commonly diagnosed cause of acute anterior uveitis (AAU).[1–4] Within the general population in North America and Europe, the prevalence of HLA-B27 is approximately 8–10%5, but the prevalence of the HLA-B27 allele in patients with AAU is much higher, ranging from 15–60%.[2, 3, 5–10] The typical characteristics of HLA-B27-associated uveitis have been well-described in the literature: young age of onset, unilateral or unilateral alternating inflammation, presence of hypopyon or fibrin in the anterior chamber, development of posterior synechiae, and occurring frequently in the setting of systemic spondyloarthropathies like ankylosing spondylitis and reactive arthritis.[1, 3, 5, 11]

While most patients with HLA-B27-associated uveitis have acute or recurrent inflammation, some patients may develop chronic inflammation.[11–14] Approximately 5% to 19%[11–14] of patients with HLA-B27-associated uveitis develop chronic inflammation lasting longer than three months or requiring chronic therapy to suppress inflammation. This range may be explained by differences in recruitment methodology and potential differences in definitions of chronic disease; some studies only included patients with acute anterior uveitis at presentation and excluded those who presented with chronic HLA-B27-associated uveitis.[12, 13] Chronic HLA-B27-associated uveitis may represent a large proportion of chronic non-infectious uveitis cases; in one study, HLA-B27-associated uveitis was the largest known disease entity representing 37% of all chronic non-infectious uveitis.[14] However, little is known about how the degree of inflammation and chronic clinical course are associated with visual acuity loss and complications.

Previous longitudinal studies on HLA-B27-associated uveitis have not reported the incidence rates of ocular complications. A few retrospective cohort studies have utilized long-term follow-up to characterize extraocular manifestations[12] and gender differences[13] in patients with HLA-B27-associated uveitis. It has also been reported that the prognosis of HLA-B27-associated uveitis is less favorable than HLA-B27-negative patients with idiopathic anterior uveitis.[15] Determining the incidence rates of ocular complications in HLA-B27-associated uveitis would be helpful in comparing the prognosis of this disease to other types of uveitis.

The purpose of our study was to calculate the incidence rates of ocular complications and vision loss in a cohort of 104 consecutive patients with HLAB27-associated uveitis and to explore the effect of inflammation and chronicity on clinical outcomes.

Methods

Study Population

In this retrospective longitudinal cohort study, the clinical records of 104 consecutive patients with HLA-B27-associated uveitis who were examined at the F.I. Proctor Foundation at the

University of California, San Francisco between April 1999 and November 2008 were reviewed. All patients with anterior uveitis in our practice undergo standard screening which routinely includes a complete blood count, serologic tests for syphilis, a purified protein derivative skin test, chest radiography and HLA-B27. In certain cases, additional tests are performed, including serum angiotensin-converting enzyme level, antinuclear antibody, and urine beta-2 microglobulin. The diagnosis of HLA-B27-associated uveitis required the presence of anterior uveitis and the HLA-B27 allele without any other known reason to have uveitis. Of the 104 HLA-B27 positive patients evaluated, five patients were excluded because their uveitis was linked to another disease not associated with HLA-B27 (2 sarcoidosis; 2 juvenile idiopathic arthritis; 1 HLA−A29+), and thus 99 patient records were analyzed.

Data Collection

Every clinic visit was entered into a database. Data included demographic characteristics, ophthalmologic examination results, associated systemic diseases, and medications. Only available data was analyzed. Uveitis was categorized as unilateral in the same eye, unilateral alternating or bilaterally concomitant. The characteristics of uveitis were analyzed according to definitions of the Standardization of Uveitis Nomenclature (SUN) criteria.[16] For exams prior to publication of the SUN criteria in 2005, the chart findings were translated into SUN terms for our analyses. Clinical course was described as acute, recurrent, chronic, or indeterminate. Chronic uveitis was defined as persistent inflammation with relapse in <3 months after discontinuing treatment or requiring medications to suppress inflammation for >3 months duration.16 The entire medical record was reviewed in order to determine chronicity; if a patient initially had recurrent disease and developed chronic disease over the course of follow-up, the patient's clinical course was recorded as chronic disease. If any medications were required to control inflammation for greater than three months, the uveitis was classified as chronic. The only circumstance in which the clinical course was defined as indeterminate was if patients were on corticosteroid-sparing medications at presentation for their systemic disease as well as ocular inflammation and it was not possible to determine whether or not the patients' inflammation would be controlled without medications. The visual acuity used was the best-spectacle corrected visual acuity from Snellen charts.

The spondyloarthropathies that were included as HLA-B27-associated systemic diseases were anklyosing spondylitis, reactive arthritis, inflammatory bowel disease, psoriatic arthritis and undifferentiated spondyloarthropathies. The systemic diagnoses were all verified by a rheumatologist. All patients were treated according to the degree of intraocular inflammation using a stepladder corticosteroid-sparing therapeutic algorithm.[17]

Statistical Analysis

For all analyses, including incidence rates of complications and proportional hazard models, only uveitis-affected eyes were included in the analyses. For analysis of vision loss, Snellen fractions were converted into the logarithm of minimum angle of resolution (logMAR). Incidence rates were calculated as the number of events in an affected eye per eye-years at risk. If a patient had a cataract at presentation in his only affected eye or had bilateral cataracts in both of his affected eyes, the patient was no longer at risk; however, if a patient had one cataract in only one of two affected eyes, he or she remained at risk. The Fisher exact and Mann-Whitney tests were used to compare baseline characteristics between groups.

A Cox proportional hazards model was used to analyze risk factors for development of vision loss and complications while accounting for varying lengths of follow-up. The outcomes analyzed were time to development of any incident ocular complication that was not present at baseline or time to development of new vision loss (20/50 or worse and 20/200 or worse). For the analyses of any incident complication, the following were included: posterior iris

synechiae, band keratopathy, posterior subcapsular (PSC) cataracts (≥ trace opacity), ocular hypertension (> 21 mm Hg), hypotony (< 6 mm Hg), cystoid macular edema and epiretinal membrane. The outcomes of vision loss represented the first time a patient developed vision loss; patients who had vision loss at presentation were excluded. The presence of chronic disease at any time during follow-up, HLA-B27-associated systemic disease, race, and gender were used as binary predictors in the Cox model. We adjusted for duration of uveitis prior to presentation to our clinic because patients may present at varying stages of their disease. In addition, we conducted a sensitivity analysis using staggered entry.

Time-updated variables were used to reflect treatment and inflammation at each visit. The presence of any oral corticosteroid, corticosteroid injections, topical corticosteroid drops, corticosteroid-sparing therapy (including methotrexate, mycophenolate mofetil, cyclosporine, cyclophosphamide, infliximab, adalimumab, etanercept, and sulfasalazine) and grade of inflammation were recorded at each visit and analyzed in the Cox model as time-dependent covariates accounting for variation over the course of follow-up. Updating the variable in the analyses over time accounts for changing treatment. Therefore, overall treatment course is used as a predictor, not just one time-point (i.e. at presentation). Similarly, overall inflammation course was used, not just inflammation at presentation or average inflammation over the patient's course. The presence of inflammation ≥1+ anterior chamber cells was used as a dichotomous time-dependent covariate in the Cox proportional hazards model. The “robust feature” was used to account for multiple visits per patient. All analyses were performed using Intercooled Stata 9.0 statistical software (Stata Corp, College Station, Texas, USA).

Results

Study Population

Characteristics at presentation are summarized in Table 1. The patients were 57% male and the majority self-identified as Caucasian (75%) or Asian (15%). The median age of onset of uveitis was 31 years and the median presenting vision was 0.10 logMAR or approximately 20/25. The mean follow-up time was 2.1 years with 53% of patients having at least 6 months of follow-up. Among all 99 HLA-B27 patients, the course was most commonly acute or recurrent (75%), followed by chronic (20%). The clinical course was defined as indeterminate in 5 patients who were on corticosteroid-sparing medications at presentation for their systemic disease as well as ocular inflammation and it was not possible to determine whether or not the patients' inflammation would be controlled without medications. Nineteen out of twenty patients classified as having chronic uveitis fulfilled SUN criteria for chronic inflammation at the time of presentation to our clinic. Only one patient in the cohort had recurrent disease on presentation and later developed chronic disease. There were no patients who required greater than 3 months of treatment initially who were then able to taper off of all medications successfully.

The proportion of patients with recurrent and chronic inflammation were similar within the group of patients with greater than 6 months follow-up: recurrent (60%) and chronic (31%). The largest proportion of HLA-B27 patients had unilateral uveitis (52%) followed by unilateral alternating (39%) and bilateral concomitant (9%). The inflammation was non-granulomatous (98%) and anterior (96%). Nearly half of the patients had an HLA-B27-associated systemic disease (44%), and the most common systemic diseases were ankylosing spondylitis (30%) and reactive arthritis (7%).

Table 2 compares the characteristics of those HLA-B27 uveitis patients with chronic disease to those without chronic inflammation. The demographic characteristics and the HLA-B27 systemic disease breakdowns were not statistically different between the two groups. The

patients with chronic disease were more likely to have bilateral disease and there was a trend toward patients with chronic disease having worse baseline visual acuity.

Of the 148 total affected eyes, the most common ocular complications at presentation were vision loss of 20/50 or worse (26, 18%), posterior synechiae (25, 17%) and PSC cataract (20,14%). Only 12 eyes (8%) had a visual acuity that was 20/200 or worse at presentation. Nearly a third of patients had received oral corticosteroids (30%) or corticosteroid injections in either eye (26%) prior to presentation at our clinic. Twenty-six patients had been treated with at least one corticosteroid-sparing therapy prior to presentation. Ocular inflammation was the driving force for starting corticosteroid-sparing therapy in 23 of these patients. Prior to presentation, the most frequently used corticosteroid-sparing therapies were sulfasalazine (10%), methotrexate (9%) and etanercept (7%).

During follow-up, 41 patients (41%) were treated with oral corticosteroids. Additionally, 42 patients (42%) received at least one corticosteroid-sparing therapy. The most common corticosteroid-sparing therapies were methotrexate (18%), sulfasalazine (17%), adalimumab (7%) and etanercept (7%). Twenty-six eyes out of the 148 total affected eyes received at least one corticosteroid injection during follow-up.

Incidence of Ocular Complications and Vision Loss

Incidence rates of ocular complications and vision loss are given in Table 3. The most common complications to develop during follow-up were ocular hypertension and PSC cataracts: the incidence rate of high intraocular pressure was 0.10/eye-year (EY) and the rate of development of PSC cataract was 0.09/EY. Development of posterior synechiae (0.05/EY) and vision loss 20/50 or worse during at least one visit (0.06/EY) was relatively common in this population. Of the 148 affected eyes, there were 92 eyes at risk for developing vision loss after excluding those patients with 20/50 or worse vision at presentation as well as patients without necessary follow-up time, and 15 of those 92 eyes developed vision loss. 73% of those eyes that developed vision loss to 20/50 or worse improved to better than 20/50 by last visit. Median time to first improvement was 3 months, although 50% of those eyes that improved had multiple episodes of vision loss, and 20% required cataract surgery.

Other complications such as hypotony, CME, and blindness (20/200 or worse) were more rare. Of the 100 eyes at risk to develop blindness, there were seven who developed a visual acuity of 20/200 or worse over the course of follow-up. 67% of eyes that developed 20/200 or worse vision improved to better than 20/200 by last visit. Median time to first improvement was 5 months, although 75% of the eyes that improved required cataract surgery.

Risk Factors of Visual Acuity Loss and Incident Complications Among Eyes Affected with HLA-B27-associated Uveitis

Risk factors for vision loss (20/50 or worse) are presented in Table 4. During the follow-up period, 15 of 92 eyes developed vision loss to 20/50 or worse. In a univariate analysis of risk factors for vision loss, the predictors included duration of uveitis prior to presentation, gender, ethnicity (Caucasian vs other), presence of HLA-B27 systemic disease, posterior synechiae, ocular hypertension, chronic disease course, oral corticosteroids, topical corticosteroids, corticosteroid injections, corticosteroid-sparing therapy and inflammation. The presence of posterior synechiae at presentation, inflammation during follow-up, oral corticosteroids, corticosteroid injections and topical corticosteroids were statistically significant risk factors for vision loss. Inflammation during the course of follow-up was associated with an increased risk of developing visual impairment (20/50 or worse) (HR=10.2, $P < 0.0001$). Chronic disease course and corticosteroid-sparing therapy were each associated with a nearly 3-fold increased

risk of vision loss, but did not meet statistical significance (CI=0.93 to 7.7, *P*=0.07) and (CI=0.93 to 7.8, *P*=0.07), respectively.

After backward step-wise multivariate regression predicting visual acuity loss (20/50 or worse), the presence of posterior synechiae at presentation, inflammation, chronic disease, corticosteroid-sparing therapy, corticosteroid injections and male gender were associated with a statistically significant increased risk of developing vision loss. Chronic disease course was associated with a 7-fold increased risk of visual impairment (CI=3.2 to 37, *P*=<0.0001). Development of blindness during follow-up was rare: there were only 7 eyes that developed 20/200 or worse vision and analysis of risk factors was not conducted because of the small number of events.

Risk factors for developing incident complications are shown in Table 5. Of the 53 eyes without complications at presentation, 21 developed new complications. In the univariate analysis, chronic disease course was associated with a 3-fold increase in incident complications (CI= 1.3 to 5.0, *P*=0.006). Time-updated topical corticosteroid use and corticosteroid injections were each associated with a 3-fold increase in the risk of incident complications (CI=1.4 to 7.4, *P*=0.007) and (CI=1.6 to 16, *P*=0.005), respectively. After backward stepwise regression of all covariates, chronic disease and topical corticosteroids remained significant risk factors for the development of incident complications.

In addition to adjusting for duration of uveitis in our multivariate Cox proportional hazards model, we conducted a Cox proportional hazards sensitivity analysis using staggered entry. In this model, date of diagnosis was taken as the origination time but entry into the risk set occurred at date of presentation to our clinic. With this method, hazard ratio estimates are adjusted for the duration of time of uveitis before entry into our clinic for all analyses. Univariate and multivariate estimates for both vision loss and incident complications were not meaningfully different from the model in which staggered entry was ignored (data not shown).

In the univariate analysis, presence of HLA-B27-associated systemic disease was associated with an increased risk of developing PSC cataracts (HR=3.6, *P*=0.01) and elevated IOP (HR=2.3, *P*=0.05). Presence of HLA-B27-associated systemic disease was not associated with vision loss.

Discussion

Our study confirms a good visual prognosis overall for patients with HLA-B27-associated uveitis: the rate of blindness is low (0.02/EY) and many of those who develop visual impairment improve. The incidence rate of any ocular complication was 0.22/EY. This rate is lower than those reported for other common uveitis populations: juvenile idiopathic arthritis (0.33/EY)18 and Behcet's disease (0.45/EY)19. The most common ocular complication to develop in our cohort was elevated intraocular pressure (0.10/EY). Although the incidence rate of elevated intraocular pressure in our cohort was lower than the rates of elevated intraocular pressure reported for Behcet's (0.17/EY)19 and juvenile idiopathic arthritis (0.18/EY)18, elevated IOP was the most common ocular complication to develop in all three of these studies.

A recently published paper on HLA-B27-associated uveitis focused on differences in clinical characteristics and outcomes based on gender, demonstrating that HLA-B27-associated systemic disease was more frequent in men than women but that there was no difference in vision loss between males and females.[13] Similarly, in our study, HLA-B27-associated systemic diseases were slightly more common in men (46%) than women (41%), but the difference was not statistically significant. In contrast to the prior study, our study demonstrated that male gender was a risk factor for vision loss (20/50 or worse). Men with ankylosing spondylitis have been shown to have worse systemic disease than women,[20] so it is plausible

that a difference could occur in HLA-B27-associated uveitis. It is possible that variation in the definition of vision loss as well as differences in inclusion criteria explain this difference in results. Rothova et al included only acute anterior uveitis and excluded any patients with chronic uveitis. They defined vision loss as 20/50 or worse at the end of a given time interval, so patients may have had intervening visits when their vision was worse. By our definition of vision loss, commonly used in other studies,[16, 18, 21] any patient who developed 20/50 vision or worse on a single visit qualified, even if the vision loss was not permanent. Unlike previous studies, we describe the subsequent visual acuity changes after their initial vision loss, demonstrating that most recover better than 20/50.

We observed high numbers of patients with chronic disease (20%) for a disorder that has been commonly characterized by short recurrent attacks[1, 10, 15]. In another series examining gender differences in HLA-B27-associated uveitis, Braakenburg and associates found a similarly high number of patients with chronic disease13 but did not explore chronicity as a risk factor for outcomes. Because our institution is a tertiary care center, it is likely that severe cases of HLA-B27-associated uveitis were more often referred to our center as suggested by the high frequency of previous corticosteroid-sparing therapy and long duration of uveitis prior to presentation. Most of our patients with chronic uveitis were able to eventually control their inflammation with medication, but the duration of active inflammation was longer than three months and all patients required chronic medication to suppress inflammation on an ongoing basis. Our relatively high number of patients with chronic disease allowed us to look at outcomes in a population previously not studied.

Our study documents an increased risk of ocular complications and vision loss for patients with chronic inflammation compared to those with acute or recurrent disease. In our multivariate models we accounted for disease severity by adjusting for inflammation and treatment as time-dependent covariates. Chronic inflammation remained a risk factor after adjusting for time-updated topical, oral, and regional corticosteroid use, corticosteroid-sparing therapy, and disease severity. We considered attempting to account for disease severity by adjusting for the number of flare-ups in our analysis, but decided that defining flare-ups would be difficult since there is no consensus on the definition. By recording inflammation and treatment at each visit we would be sufficiently accounting for disease severity while introducing less bias.

Our study does not allow us to investigate why patients develop chronic disease because 19 out of 20 of our patients with chronic inflammation met criteria at the time of presentation to our clinic. It is possible that patients with chronic disease may have had previous episodes of more severe disease and poorly controlled uveitis in the past which may account for some of the difference in outcomes, although patients with chronic disease as well as those with recurrent disease often had a long duration of uveitis prior to coming to our clinic. By demonstrating that patients with chronic disease have a worse prognosis, we highlight that patients with inflammation that is difficult to control require extra care. This raises the question as to whether or not earlier and more aggressive intervention could prevent development of chronic disease and change outcomes.[22]

Our study demonstrated that time-updated inflammation was a risk factor for vision loss. Although inflammation is thought to increase the risk of vision loss, this association has not been demonstrated in the literature consistently.[19, 23, 24] In our study, inflammation greater than or equal to 1+ anterior chamber cell during follow-up was associated with a 10-fold increased risk of vision loss. This provides further evidence supporting the principle that control of inflammation is necessary to minimize vision loss.

Although it is important to account for inflammation in any analysis that looks at vision loss or the development of complications, there are some potential limitations with using inflammation as a predictor. The subjectivity of measuring anterior chamber cells as well as the possibility of a ceiling effect due to the inability to have “worse inflammation” once a patient has 4+ anterior chamber cells contributes to the difficulty in using inflammation as a predictor. The patients in our study were predominantly evaluated by trained uveitis specialists who after the publication of SUN criteria in 2005 followed the guidelines to grade inflammation. However, it is important to note that the chart findings of patients examined prior to 2005 were translated into SUN terms for the purposes of this study. This limitation is impossible to overcome and is present in all retrospective studies with long-term outcomes. In Kempen et al's study of interobserver agreement of grading ocular inflammation, uveitis specialists agreed on the grade of anterior chamber inflammation nearly perfectly (93–100%) although there was variation in the exact number of cells counted.[25] We used 1+ or greater anterior chamber cells as our definition of inflammation which is considered as an acceptable threshold by many uveitis specialists.

Additionally, it is difficult to determine causality in a retrospective study describing associations between risk factors and outcomes. There are multiple factors which may contribute to vision loss and complications, including disease-related factors as well as treatments. While we can not directly attribute the occurrence of poor outcomes to a specific predictor, we are able to understand their relative contribution by adjusting for multiple predictors in a multivariate analysis. In our univariate analyses, topical, oral and regional corticosteroids were each statistically significant risk factors for developing vision loss. However, we do not believe that corticosteroids were solely responsible for vision loss and complications because after adjusting for their time-updated use in a multivariate model, other predictors such as inflammation and chronicity remain significant. The treatment by indication bias also makes it difficult to assess the effect of treatment on outcomes. For example, even after multivariate adjustment, corticosteroid-sparing therapy was associated with an increased risk of vision loss, but we do not believe that corticosteroid-sparing therapy causes vision loss. Rather, we believe that patients with more severe disease received more aggressive treatment. We included all corticosteroid-sparing therapies that modulate ocular inflammation. Etanercept is not thought to be as effective as other tumor necrosis factor alpha inhibitors for uveitis, but there is evidence that it reduces uveitis flare-ups in ankylosing spondylitis patients.[26]

Other limitations of this study include those that affect retrospective studies, including non-standardized data collection, assessment at irregular intervals, and differential follow-up. Although our study did not have standardized appointment intervals, our patients generally receive all of their uveitis care in our clinic and were typically seen at least once every three months and were seen if there was any change in status. There was no statistical difference in the follow-up time between patients with chronic disease and those with acute/recurrent disease, but we acknowledge that standardized appointment intervals would eliminate the possibility that patients with chronic disease were seen more frequently and their complications detected earlier. In order to take into account differential follow-up, survival analyses were used. A strength of the study is the fact that every visit from every patient was recorded in the database which allowed for time-dependent analysis of inflammation and treatment. Finally, we cannot exclude the possibility that the chronic inflammation was related to disease entities other than HLA-B27. However, other known associations (e.g. juvenile idiopathic arthritis, sarcoidosis, syphilis) were considered during our comprehensive work-up. Ultimately, we interpret our results cautiously and acknowledge that confirmation in further studies is required.

In summary, the results of this study provide evidence that patients with HLA-B27-associated uveitis typically have a good visual prognosis and a very low incidence rate of blindness. The most common complications to develop are elevated intraocular pressure and PSC cataract.

Although the disease course is most commonly manifested as short recurrent episodes, poorly controlled inflammation was associated with vision loss. Patients with chronic inflammation were also at greater risk for complications. More aggressive and early control of inflammation may be warranted to prevent poor clinical outcomes.

Acknowledgments

a. *Funding/Support:* The Department of Ophthalmology at UCSF is supported by a core grant from the National Eye Institute, EY02162. Dr. Acharya is supported by a National Eye Institute K23EY017897 grant and a Research to Prevent Blindness Career Development Award. This work was supported in part by a grant from the Doris Duke Charitable Foundation to UCSF to fund Allison Loh.

Allison R. Loh BIOSKETCH

Allison R. Loh, BA, obtained a BA in Human Biology at Stanford University in 2004. She is currently a medical student at University of Pennsylvania. She also completed a Doris Duke Clinical Research Fellowship at the University of California, San Francisco in 2009. Allison Loh will begin her residency in ophthalmology at UCSF in 2011.

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TABLE 1

General Characteristics of 99 Patients with HLA-B27-associated Uveitis

Demographics	**n/N[a]**	**%**
Male	56/99	57
Caucasian	73/97	75
East Asian	15/97	15
South Asian	5/97	5
Hispanic	3/97	3
African-American	3/97	3
Native American	3/97	3
Non-granulomatous	97/99	98
Median age of uveitis onset (range)	31 years (4 to 84)	
Median presenting logMAR vision[b]	0.1 (−.12 to 2.0)	

Clinical Course[c]		
Acute	13/94	14
Recurrent	61/94	65
Chronic	20/94	21

Laterality of Uveitis[d]		
Unilateral	50/96	52
Unilateral alternating	37/96	39
Bilateral concomitant	9/96	9

HLA-B27 Systemic Disease		
Any HLA-B27 disease[e]	44/99	44
Ankylosing spondylitis	30/99	30
Reactive arthritis	7/99	7
Inflammatory Bowel Disease	2/99	2
Psoriatic arthritis	1/99	1
Other spondylarthropathy	6/99	6

[a] number/total number of patients assessed

[b] Best spectacle-corrected visual acuity at presentation is expressed in logarithm of the minimum angle of resolution (logMAR) in uveitis-effected eyes only.

[c] Clinical course could not be determined in five patients

[d] Laterality could not be determined in 3 patients for whom unilateral alternating and bilateral could not be distinguished.

[e] Two patients had two HLA-B27-associated diseases. One patient had ankylosing spondylitis and inflammatory bowel disease; one patient had ankylosing spondylitis and reactive arthritis.

TABLE 2

Comparison of Chronic to Acute/Recurrent HLA-B27-Associated Uveitis

	Acute/Recurrent Patients[b] (n=74) % (no)	Chronic HLA-B27 Patients (n=20) % (no)	*P* value[c]
HLA-B27 Systemic Disease			
Any HLA-B27 disease	41 (30)	50 (10)	0.450
Ankylosing spondylitis	26 (19)	30 (6)	0.700
Reactive arthritis	4 (3)	15 (3)	0.110
Psoriatic arthritis	1 (1)	0 (0)	1.000
Inflammatory bowel disease	1 (1)	5 (1)	0.381
Other spondylarthropathy	6 (5)	5 (1)	1.000
Demographics			
Male	57 (42)	50 (10)	0.592
Caucasian	78 (56)	70 (14)	0.717
Asian	18 (13)	5 (1)	0.289
Non-granulomatous	0 (0)	10 (2)	0.045
Median age of uveitis onset,(range)	33 years (11–58)	28 years (5–85)	0.203
Median presenting vision (range)	0.1 (0–1.0)	0.18 (0–1.9)	0.094
Laterality of Uveitis			
Unilateral	51 (38)	45 (9)	0.501
Unilateral alternating	42 (30)	30 (6)	0.324
Bilateral concomitant	4 (3)	25 (5)	0.012

[a] The 20 patients with chronic inflammation include 19 patients who had chronic disease from their first presentation to our clinic and the one patient who initially had recurrent disease but developed chronic disease during follow up.

[b] Acute/Recurrent includes 13 patients with acute inflammation and 61 patients with recurrent disease. The five patients whose clinical course could not be determined were excluded.

[c] Fisher's exact test and Mann-Whitney test

TABLE 3

Incidence of Structural Ocular Complications and of Visual Acuity Loss in HLA-B27-Associated Uveitis

Event	n/N[a]	Rate/EY (95% CI)[b]
Any ocular complication	21/53	0.224 (0.146–0.344)
Elevated intraocular pressure (> 21 mm Hg)	25/102	0.102 (0.069–0.151)
Posterior Subcapsular Cataracts (≥ trace opacity)	20/99	0.091 (0.059–0.143)
Posterior Synechaie	12/89	0.053 (0.030–0.094)
Epiretinal Membrane	7/109	0.022 (0.011–0.047)
Cystoid Macular Edema	5/109	0.016 (0.007–0.039)
Band Keratopathy	3/109	0.010 (0.003–0.030)
Hypotony (< 6 mm Hg)	2/110	0.006 (0.001–0.025)
Vision Loss 20/50 or worse	15/92	0.062 (0.037–0.102)
Vision Loss 20/200 or worse	7/100	0.023 (0.011–0.049)

[a] Number of events/Number of eyes at risk

[b] Incidence rate is number of events in an affected eye per eye-years at risk

TABLE 4

Risk Factors for Loss of Visual Acuity (20/50 or worse) in 92 Eyes with HLA-B27-associated Uveitis

	20/50 or worse	
Predictors	**Crude Hazard Ratio (95% CI, *P*)[a]**	**Adjusted Hazard Ratio (95% CI, *P*)[b]**
Duration of uveitis prior to presentation (years)	0.98 (0.92–1.0, 0.43)	
Male	1.9 (0.68–5.2, 0.22)	6.0 (2.3–34, 0.001)
Caucasian vs other	2.0 (0.35–11, 0.44)	
Chronic disease	2.6 (0.93–7.7, 0.07)	6.8 (3.2–37, <0.0001))
HLA-B27 systemic disease	0.91 (0.33–2.5, 0.87)	
Presenting complications		
Posterior Synechiae	6.2 (2.0–18, 0.001)	4.0 (2.5–21, <0.0001)
Elevated intraocular pressure	2.4 (0.52–11, 0.25)	
Oral corticosteroids[c]	3.4 (1.2–10, 0.03)	
Inflammation[c]	10 (1.4–2.6, <0.0001)	6.2 (3.3–33, <0.0001)
Corticosteroid-sparing therapy[c]	2.7 (0.93–7.8, 0.07)	2.6 (1.2–14, 0.021)
Topical corticosteroids[c]	3.9 (1.0–15, 0.04)	
Corticosteroid injections[c]	6.5 (2.7–35.7, 0.001)	5.1 (5.4–27, <0.0001)

[a] Crude HR = hazard ratio (95% CI = 95% confidence interval, *P* value) for univariate Cox proportional hazard model using robust feature.

[b] Adjusted HR = hazard ratio (95% CI = 95% confidence interval, *P* value) for multivariate analyses in which all exposure variables were included and stepwise regression was utilized to eliminate all variables with P values ≥0.10

[c] Time-updated variables

TABLE 5

Risk Factors for Incident Complications in 53 Eyes with HLA-B27-associated Uveitis

Predictors	Crude Hazard Ratio (95% CI, *P*)[a]	Adjusted Hazard Ratio (95% CI, *P*)[b]
Duration of uveitis prior to presentation (years)	1.0 (0.97–1.0, 0.62)	
Male	0.91 (0.42–2.0, 0.80)	
Caucasian vs other	1.0 (0.45–2.4, 0.93)	
Chronic disease	2.8 (1.3–5.0, 0.006)	2.2 (1.0–4.6, 0.04)
HLA-B27 systemic disease	1.1 (0.51–2.5, 0.76)	
Inflammation[c]	0.88 (0.30–2.6, 0.82)	
Corticosteroid-sparing therapy[c]	1.3 (0.56–2.9, 0.56)	
Oral corticosteroids[c]	1.0 (0.27–3.8, 0.97)	
Topical corticosteroids[c]	3.2 (1.4–7.4, 0.007)	3.3 (1.3–8.4, 0.01)
Corticosteroid injections[c]	3.0 (1.6–16, 0.005)	

[a] Crude HR = hazard ratio (95% CI = 95% confidence interval, *P* value) for univariate Cox proportional hazard model using robust feature.

[b] Adjusted HR = hazard ratio (95% CI = 95% confidence interval, *P* value) for multivariate analyses in which all exposure variables were included and stepwise regression utilized to eliminate all variables with P values ≥0.30.

[c] Time-updated variables