Retinal Thickening in HLA-B27–Associated Acute Anterior Uveitis: Evolution with Time and Association with Severity of Inflammatory Activity

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PURPOSE. To describe the evolution of retinal thickness in eyes affected with acute anterior uveitis (AAU) in the course of follow-up and to assess its correlation with severity of inflammatory activity in the anterior chamber.

METHODS. 72 eyes (affected and fellow eyes) of 36 patients presenting with HLA-B27related acute anterior uveitis were included in a prospective, institutional, cohort study. Patients were followed daily until beginning of resolution of inflammatory activity and weekly thereafter. Optical coherence tomography and laser flare photometry were performed at each visit. Treatment consisted of topical corticosteroids. Main outcome measures were retinal thickness of affected eyes, difference in retinal thickness between affected and fellow eyes and their evolution in time, association between maximal retinal thickness, and initial laser flare photometry.

RESULTS. Difference in retinal thickness between affected and fellow eyes became significant on average 7 days from baseline and remained so throughout follow-up (P < 0.001). There was a steep increase in retinal thickness of affected eyes, followed by a progressive decrease after reaching a peak value. Maximal difference in retinal thickness between affected and fellow eyes was observed between 17 and 25 days from baseline and exhibited a strong, positive correlation with initial laser flare photometry values (P = 0.015).

Conclusions. Retinal thickness in eyes affected with AAU presents a steep increase over 3 to 4 weeks and then gradually decreases. Severity of inflammation at baseline predicts the amount of retinal thickening in affected eyes. A characteristic pattern of temporal response of retinal anatomy to inflammatory stimuli seems to arise. (*Invest Ophthalmol Vis Sci.* 2012; 53:6171-6177) DOI:10.1167/iovs.12-10026

HLA-B27-associated acute anterior uveitis (AAU) is an important pathological entity in view of its high frequency and associated morbidity. Younger patients at the productive age range are more commonly affected; and, despite its overall favorable prognosis, HLA-B27-associated AAU remains a considerable public health concern, following a typically recurrent natural history and engendering potentially vision-

Investigative Ophthalmology & Visual Science, September 2012, Vol. 53, No. 10 Copyright 2012 The Association for Research in Vision and Ophthalmology, Inc. threatening ocular complications, such as cystoid macular edema (CME). $^{1\mathchar`-3}$

In contrast to the development of florid macular edema, subclinical retinal thickening in the context of AAU, although long suspected by clinicians, has yet to be verified in a prospective trial. The understanding of this phenomenon and its evolution over time could shed light into the mechanisms of other relevant clinical manifestations, such as the increased susceptibility of carriers of the HLA-B27 molecule to develop macular edema following ocular surgery.⁴

The purpose of this prospective study was to describe the response of retinal anatomy to inflammatory stimuli over time in the course of an episode of AAU. We particularly attempted to demonstrate the presence of subclinical retinal thickening in eyes of patients with HLA-B27-associated AAU when compared to their fellow eyes, as well as to investigate the association of this phenomenon with the severity of inflammatory activity in the anterior chamber and its evolution in the course of follow-up. A homogenous group of patients with AAU served as a model for assessing evolution of retinal thickness in time in the context of intraocular inflammation. Extrapolating from our findings, meaningful hypotheses can be made as regards retinal behavior over time in response to inflammatory stimulation of various origins.

METHODS

We conducted a prospective study, screening for inclusion all patients presenting to the emergency service of the Jules Gonin Eye Hospital with typical nongranulomatous unilateral AAU over a 2-year period. Initial evaluations included bilateral laser flare photometry and optical coherence tomography (OCT) to obtain a macular map. A blood sample was collected in search of HLA-B27 antigen, and patients were recruited for the study after a 24-hour reflection period. All carriers of the HLA-B27 antigen aged between 16 and 80 years were included in the study, and their follow-up was thereafter undertaken by the uveitis clinic. Exclusion criteria comprised: all other types of uveitis; suspicion of any underlying ocular or systemic disease that can cause macular thickening; cloudiness of refractive media interfering with accurate OCT measurements; pre-existing retinal lesions, such as epiretinal membrane; diabetic retinopathy; prior ocular surgery of any kind, including cataract surgery. Patients with severe, persistent inflammation necessitating systemic corticosteroid and/or immunomodulatory treatment or in whom accurate flare and OCT measurements could not be obtained as early as on the second follow-up visit (day 2 from baseline) were excluded from further study. Patients who missed more than one follow-up visit were also excluded from subsequent statistical analysis. As the study population was, by definition, made up of carriers of the HLA-B27 antigen, patients with HLA-B27-associated spondyloarthropathies were not excluded from the analysis.

All patients were initially managed with hourly topical corticosteroid drops (prednisolone acetate 1%) and scopolamine 1% three times a day over a short period and adaptation to inflammatory activity in

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FIGURE 1. OCT scan (patient 5) at 3 weeks from the beginning of the inflammatory episode. Retinal thickening of the affected eye (LE) is evident for all OCT subfields included in the analysis (A1-A5), compared to corresponding subfields from the contralateral, uninvolved eye. A particular ring pattern of retinal thickening involving the inner, perifoveal ring of OCT subfields can be identified.

subsequent daily follow-up visits. Patients were followed daily until manifest response to local treatment was observed (defined as a decrease of two crosses in anterior chamber cells or anterior chamber flare on slit-lamp examination or a decrease of more than 30% from baseline in laser flare photometry) and weekly thereafter until complete resolution of inflammatory activity. A further long-term follow-up visit at 3 months and beyond from the beginning of follow-up took place for all patients. At each visit a complete ophthalmic examination was performed, including best-corrected visual acuity, tonometry, biomicroscopy, and fundus examination. Bilateral laser flare photometry and macular OCT were also performed by the same observer (KB) at each follow-up visit.

OCT was performed using the Fast Macular Thickness Map protocol on the Stratus OCT (Software version 3.0; Zeiss-Meditec, Dublin, CA). The following retinal thickness values were obtained and recorded from the Stratus OCT Fast Macular Map of each eye at every visit: central 1-mm subfield, inner ring extending from 1 mm to 3 mm around the central subfield and comprising four quadrants, and outer ring extending from 3 mm to 6 mm around the inner ring and also comprising four quadrants (Fig. 1). The outer ring was excluded from the statistical analysis because frequent artifacts and insufficient resolution precluded credible thickness measurements. Subclinical retinal thickening was defined as a statistically significant difference in retinal thickness between inflamed and fellow eyes; that was, however, not clinically detectable on fundoscopy.

The effect of time on retinal thickness difference between the study eye and the contralateral eye (study minus contralateral) was assessed by random intercept mixed models with maximum likelihood estimation. These models account for the fact that a subject's data repeated over time are correlated. Random intercept models assume that individual specific regression lines are parallel, whereas the individual specific intercepts vary randomly. To take into account the nonlinear trajectory of retinal thickness over time, we used time (days) and log(time +1) as independent variables in the regressions. The same method was used to estimate the effect of time on retinal thickness of the affected eye. A different regression was run for each OCT subfield. For each OCT subfield, Pearson correlation coefficients were used to assess the correlation between initial OCT thickness and initial LogMAR and the correlation between final OCT thickness and final LogMAR. Spearman rank correlation coefficients were used to assess the correlation between initial flare value and the maximal retinal thickness of the affected eye measured over time, since the flare values did not follow normal distributions. Lowess regression (locally weighted scatterplot smoothing) was used to estimate the time when flare had decreased to 50% and 10% of the initial value. All analyses were performed using the statistical package Stata, version 11.1 (StataCorp, College Station, TX).

Described research adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all participants after explanation of the nature and possible consequences of the study. Research was approved by the Ethics Committee/Institutional Review Board of the University of Lausanne.

RESULTS

Fifty-two patients were diagnosed with HLA-B27-associated AAU over a 2-year period and were enrolled in the study. Out of these, 2 patients were excluded due to media opacities interfering with OCT measurements, 1 patient because of persistent, severe inflammation necessitating administration of systemic corticosteroids, and 13 patients because of more than one missed follow-up assessment. Three patients out of 36 (8.33%) had concomitant HLA-B27-related spondyloarthropathies. There were 36 patients included in the statistical analysis. The effect of time on retinal thickness difference between affected and fellow eyes is presented in Table 1. Analyses were repeated after exclusion of one patient whose outlying values influenced the models (patient 32 presenting florid CME), though emerging patterns of evolution in retinal

 TABLE 1. Effect of Time on Difference in Retinal Thickness between

 Study and Fellow Eyes for Corresponding Areas on OCT

OCT		All Subjects			
Subfield	Predictors	Parameter	95% CI	P *	
A1	Time	-0.26	-0.39 to -0.14	< 0.001	
	Log(time+1)	6.83	3.99 to 9.66	< 0.001	
	Intercept	0.62	-10.46 to 11.69	0.913	
A2	Time	-0.31	-0.40 to -0.24	< 0.001	
	Log(time+1)	6.35	4.70 to 8.00	< 0.001	
	Intercept	5.79	-0.75 to 12.32	0.083	
A3	Time	-0.36	-0.44 to -0.28	< 0.001	
	Log(time+1)	6.66	4.90 to 8.42	< 0.001	
	Intercept	6.03	-0.97 to 13.02	0.092	
A4	Time	-0.30	-0.38 to -0.22	< 0.001	
	Log(time+1)	6.41	4.68 to 8.13	< 0.001	
	Intercept	4.24	-1.96 to 10.44	0.18	
A5	Time	-0.32	-0.38 to -0.25	< 0.001	
	Log(time+1)	6.11	4.59 to 7.63	< 0.001	
	Intercept	5.19	-1.97 to 12.36	0.156	
A2 to A5	Time	-1.29	-1.52 to -1.05	< 0.001	
	Log(time+1)	25.47	20.23 to 30.70	< 0.001	
	Intercept	21.38	-3.74 to 46.50	0.095	
A1 to A5	Time	-1.49	-1.83 to -1.14	< 0.001	
	Log(time+1)	30.99	23.24 to 38.74	< 0.001	
	Intercept	21.87	-13.57 to 57.31	0.226	
	-				

A1, central subfield; A2, superior inner ring subfield; A3, temporal inner ring subfield; A4, inferior inner ring subfield; A5, nasal inner ring subfield.

* Difference in retinal thickness is not statistically significant at time 0 (intercept) for any OCT subfield, though it becomes so in the course of follow-up in relation with time.



FIGURE 2. Evolution of observed values (*irregular line*) and values estimated by the statistical model (*regular line*) of retinal thickness difference (in μm) (with and without patient 32, presenting florid CME) for all OCT subfields in the course of follow-up.

thickness were not affected. For all OCT subfields, difference in retinal thickness between affected and fellow eyes is not statistically significantly different from zero at day 0 (see intercepts in Table 1) but becomes significantly different in the course of follow-up. Difference in retinal thickness evolves in a statistically significant way in the course of follow-up (P <0.001). Figure 2 depicts the evolution of observed values (irregular line) and values estimated by the statistical model (regular line) of retinal thickness difference for all OCT subfields in the course of follow-up. As can be inferred, the statistical model offers an adequate estimate of the actual evolution of retinal thickness difference in time for the first 70 to 80 days from the beginning of follow-up. A characteristic pattern of evolution of difference in retinal thickness between affected and fellow eyes in the course of follow-up emerges for all OCT subfields. Difference in retinal thickness presents a steep increase over a period of 17 to 25 days (depending on the OCT subfield) before reaching a peak value, followed by a progressive decrease. The model allows for identifying the exact value of retinal thickness difference between fellow eyes for each individual day of follow-up. Starting from the seventh day of follow-up, difference in retinal thickness steadily exceeds 10 µm for all OCT subfields. As is obvious from presented curves, there is a discrepancy between observed and estimated values later than 70 to 80 days from the beginning of the episode, with actual difference values stabilizing, whereas

those estimated by the statistical model present a continuous diminishing trend.

The day from the beginning of follow-up at which the difference in retinal thickness obtains a maximum value for every OCT subfield is presented in Table 2 (highest point of curves of estimated values). For the A1 subfield, the greatest difference in retinal thickness between affected and fellow eyes is observed on day 25 from the beginning of the follow-up, whereas it ranges between days 17 and 21 for the other OCT subfields. The same statistical model as above was applied for describing the evolution in retinal thickness of the affected

 TABLE 2. Day of Maximal Difference in Retinal Thickening between

 Affected and Fellow Eyes from the Beginning of the Inflammatory

 Episode

OCT Subfield	All Subjects, d	Subject 32 Excluded, d*	
A1	25	25	
A2	19	19	
A3	18	17	
A4	18	21	
A5	18	18	
A2 to A5	19	19	
A1 to A5	20	20	

* Patient presenting florid CME.



FIGURE 3. Evolution of observed values (*irregular line*) and values estimated by the statistical model (*regular line*) of retinal thickness of the affected eye (in μm) (with and without patient 32, presenting florid CME) for all OCT subfields in the course of follow-up.

eye for all OCT subfields included in the analysis. Figure 3 depicts the evolution of observed values (irregular line) and values estimated by the statistical model (regular line) of retinal thickness of the affected eye for all OCT subfields in the course of follow-up. The retinal thickness of the affected eyes presents a characteristic pattern of evolution in the course of follow-up, with a steep increase over the first 20 to 25 days (depending on the OCT subfield) and a subsequent progressive decrease.

At baseline, retinal thickness was higher in the affected than in the contralateral eye in 85.25% to 94.12% of subjects depending on the OCT subfield, though this difference did not reach statistical significance for any of the OCT areas. Zone A3 corresponding to the temporal subfield was less affected (increased in 85.25% of cases at baseline), whereas the nasal subfield was the most frequently affected in the inflamed eye (increased in 94.12% of cases). The difference in retinal thickness increased progressively during follow-up and became universal between 17 and 25 days, when thickness difference reached its maximum in the various OCT subfields.

Correlations between initial mean visual acuity (LogMAR) and initial mean retinal thickness for all OCT subfields are presented in Table 3. As is evident, patient 26 alone, suffering from amblyopia in the affected eye, has an important effect on obtained correlations, which lose any statistical significance once the patient is excluded from the analysis. Correlations between mean final visual acuity at 3 months and beyond from the beginning of follow-up and mean final retinal thickness for all OCT subfields are presented in Table 4. Once again, any statistical significance fades once patient 26 is excluded from the analysis.

Correlations between initial laser flare values and maximal retinal thickness of the affected and fellow eyes are presented in Table 5. Correlations are positive, statistically significant, and quite strong (rho around 0.5) between initial flare value and maximal retinal thickness of affected eyes for all OCT subfields.

Figure 4 portrays the evolution of mean laser flare values in the course of follow-up. Mean initial laser flare estimated by

 TABLE 3.
 Correlation between Initial Visual Acuity and Initial Mean

 Retinal Thickness in the Affected Eye (with and without Patient 26)

	All Subjects		Subject 26 Excluded*		
OCT Subfield	Rho	Р	Rho	Р	
A1	0.41	0.027	0.09	0.667	
A2	0.41	0.027	0.22	0.264	
A3	0.41	0.027	0.14	0.483	
A4	0.38	0.041	0.18	0.350	
A5	0.40	0.030	0.11	0.562	
A2 to A5	0.42	0.023	0.18	0.363	
A1 to A5	0.44	0.015	0.17	0.373	

* Patient suffering from amblyopia (outlier).

TABLE 4. Correlation between Final Visual Acuity and Final Mean Retinal Thickness in the Affected Eye (with and without Patient 26)

OCT Subfield	All Patients		Subject 26 Excluded*		
	Rho	Р	Rho	Р	
A1	0.53	0.002	0.19	0.324	
A2	0.23	0.222	-0.04	0.832	
A3	0.26	0.164	-0.28	0.147	
A4	0.15	0.415	-0.23	0.226	
A5	0.34	0.060	0.002	0.991	
A2 to A5	0.26	0.154	-0.19	0.362	
A1 to A5	0.37	0.038	-0.02	0.901	

* Outlier.

Lowess regression is 118.16 photon units/ms. This value is reduced by 50% after 14 days (59.18 photon units/ms) and by 90% after 57 days (11.83 photon units/ms).

DISCUSSION

Posterior segment involvement in the context of HLA-B27associated AAU has been well established, although the prevalence of posterior segment manifestations varies considerably in relevant literature, ranging from 0% to 62%.⁴⁻¹⁰ The most common findings reported include vitritis, retinal vasculitis, papillitis, epiretinal membrane formation, and CME. As regards the latter manifestation, Uy et al. found its frequency in HLA-B27-associated AAU to be 13.7%.⁹ In the present study, there was only one case of florid CME (1:36 patients, 2.8%), in a patient suffering from ankylosing spondylitis (patient 32). The proportion of patients in our series with concomitant HLA-B27-related spondyloarthropathies is similar to that reported in a previous analysis by Rosenbaum.¹¹

Few studies have tackled the issue of subclinical retinal thickening in AAU. These include a retrospective study by Castellano, which demonstrates a statistically significant difference in retinal thickness between the study and fellow eyes for all OCT subfields,¹² and the study by Traill, which shows significant thickness asymmetry between eyes of patients with typical unilateral AAU, as opposed to the control group.¹³ Nevertheless, none of these studies incorporates in their design a scheduled follow-up that would allow study of the evolution of retinal thickness in the course of the disease and its response to treatment. A difference in retinal thickness between affected and fellow eyes was used to demonstrate that retinal thickening of affected eyes was statistically significant, thus not accounted for by physiologic variation, bearing in

TABLE 5. Correlation between Initial Flare Values and Maximal Retinal Thickness of the Affected Eye, Fellow Eye, and Maximal Difference in Retinal Thickness between Eyes (Spearman's Correlation Coefficient)

OCT Subfield	Affected Eye		Contralateral Eye		Difference between Eyes	
	Rho	Р	Rho	Р	Rho	Р
A1	0.50	0.003	0.05	0.796	-0.21	0.268
A2	0.47	0.005	-0.01	0.972	0.14	0.466
A3	0.55	< 0.001	-0.04	0.816	0.16	0.400
A4	0.47	0.005	-0.05	0.797	0.06	0.748
A5	0.41	0.017	0.02	0.918	0.05	0.748
A2 to A5	0.49	0.003	-0.02	0.896	0.17	0.385
A1 to A5	0.54	0.001	-0.05	0.789	0.04	0.815



FIGURE 4. Evolution of flare values in the course of follow-up. (Lines pointing to time of 50% and 90% decrease in initial flare values.)

mind that retinal thickness of fellow eyes is strongly correlated under normal circumstances.^{14,15}

An individualized statistical approach was employed in this study, based on random intercept mixed models to approximate the clinical evolution of retinal thickness of the affected eye and its difference between affected and fellow eyes. The obtained curves show a striking homogeneity in the response of all macular subfields to inflammatory stimuli, with thickness asymmetry between affected and fellow eyes becoming clinically significant with a time lag of 1 week on average from baseline, presenting a steep increase over a period of 17 to 25 days, depending on the OCT subfield, and subsequently decreasing more gradually after reaching a maximal value. Although all OCT subfields included in the statistical analysis presented statistically significant retinal thickening, the phenomenon was more pronounced in the inner retinal ring surrounding the foveal zone, especially on its nasal side. This ring-like pattern of retinal thickening was also observed in the studies by Castellano and DeLahitte,^{12,16} signifying a potential increased susceptibility of this anatomical region to thickening in response to inflammatory stimuli.

An important finding of the present study is the identification of a time lag between the onset of inflammatory activity and the point of maximal retinal thickening in the affected eye. This phenomenon was suggested in the study by Castellano, although a prospective study design was needed to confirm it.¹² This gradual, accumulative response of the retina to inflammatory stimuli may also account for the established presentation of CME in patients undergoing cataract surgery, with an onset several weeks following the procedure. It seems indeed that retinal response to inflammatory agents is not an all or none phenomenon; rather, retinal thickening progressively ensues in the course of an inflammatory episode, once the compensatory activity of the retinal pigment epithelium pump has been overwhelmed.¹⁷

As the graphical representation of our findings eloquently demonstrates, there is a long-term persistence of minimal subretinal thickening of the affected eye at 3 months and beyond from baseline. This finding may suggest a chronic alteration of retinal anatomy following an episode of inflammation-related retinal thickening. Repeated inflammatory episodes may have a cumulative effect, increasing the susceptibility of the retina to thickening in response to inflammatory stimuli, though this hypothesis cannot be verified in the context of the present study design.

The use of laser flare photometry for the quantification of anterior chamber inflammation is well established and devoid of the subjectivity in measurements of anterior chamber flare and inflammatory cells by slit-lamp biomicroscopy.^{18–20} In the study by de Ancos et al., peak flare values in HLA-B27-associated AAU occurred at baseline, with mean initial values of 160+22 photon units/ms, whereas a 50% reduction of flare was noted by day 2 of follow-up and a 90% reduction after day 8.²¹ In the present study, a different pattern of evolution in flare values was observed, with a mean initial flare value of 118.16 photon units/ms and a reduction by 50% and 90% of the initial value after 14 and 57 days, respectively.

The association between severity of inflammation in the anterior chamber, as measured by anterior chamber cells, and retinal thickening identified in the study by Castellano is modest and limited to the outer ring of the OCT map.12 On the other hand, in the study by De Lahitte et al. in patients with juvenile idiopathic arthritis-associated chronic anterior uveitis, the association between the degree of inflammation, as measured by laser flare photometry, and retinal thickening is not confirmed. That study, however, only examines mean foveal thickness and does not consider perifoveal areas of the OCT separately.¹⁶ Gonzales et al. identify a positive correlation between increased flare values obtained by laser flare photometry and presence of CME in patients with uveitis of various origins,²² whereas in the study by Magone et al. a significant correlation between extent of peripheral retinitis and laser flare photometry readings in patients with CMV retinitis is identified.²³ In our study, the association between laser flare photometry values and maximal retinal thickness of the affected eye was confirmed for all OCT subfields included in the statistical analysis.

A negative correlation between retinal thickness and visual acuity has been identified in patients with uveitic macular edema.²⁴ In the study by Castellano et al., a moderate correlation between visual acuity and retinal thickness of subfields outside the foveal center is reported.¹² In the present study no statistically significant association could be identified between visual acuity and retinal thickness either at baseline or at the end of follow-up, following the exclusion of a single patient suffering from amblyopia whose low visual acuity disproportionately affected statistical associations. Given that visual function in AAU is generally preserved and retinal thickness subclinical, we believe this study sample is unsuitable for investigating the association between retinal thickness and visual acuity.

Previous attempts to evaluate the effect of anterior chamber inflammation on retinal thickness were not focused on any particular cause of anterior uveitis. In the present study, only patients bearing the HLA-B27 antigen were included, as an increased susceptibility to the development of CME has been attributed to this group of patients.⁴ Moreover, patients with HLA-B27-associated AAU constitute a homogenous group with distinct characteristics, suitable for assessing the effect of intraocular inflammatory activity on retinal thickness. This cohort of patients sharing a common inflammatory pattern served as a model for studying the response of retinal anatomy to inflammatory stimuli over time.

This study has certain limitations. The statistical model employed is complex, aiming at accommodating both anatomical and temporal evolution of retinal thickening in HLA-B27associated AAU. While obtained estimates are in good agreement with observed values for the first 70 to 80 days of follow-up, the model fails to describe the long-term evolution of the observed phenomenon at 3 months and beyond. Curves for observed values were obtained by locally weighted scatterplot smoothing of individual values. Such curves are less accurate in graphical regions where there are fewer data points. Since our data were becoming scarcer with the length of follow-up, the right ends of the observed curves are likely to be inaccurate. This may partly explain the difference between observed and model-estimated values at times longer than 80 days from baseline. Moreover, although observed and estimated curves show considerable overlap, predicted values are marginally overestimated by the model. There was one patient with florid macular edema included in the study, though statistical analyses performed with and without this patient did not yield significantly different results.

In conclusion, our study demonstrated statistically significant, yet subclinical, retinal thickening of eyes affected by HLA-B27-associated AAU for all OCT subfields included in the statistical analysis. Retinal thickening of affected eyes, as well as difference in retinal thickness between affected and fellow eyes, remained significant throughout the follow-up period and presented a characteristic pattern of evolution of steep increase and then slower decrease until stabilization. Maximal retinal thickness of affected eyes correlated significantly with initial flare values, measured by automated flare photometry. The temporal evolution of retinal thickening in the course of an acute episode of HLA-B27-associated AUU may shed exciting new light into the response of retinal structures to inflammatory stimuli over time.

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