Long-term Clinical and Anatomic Outcome of Birdshot Chorioretinopathy

Oren Tomkins-Netzer, MD, PhD; Simon R. J. Taylor, MA, PhD, FRCOphth; Sue Lightman, PhD, FRCP, FRCOphth, FMedSci

IMPORTANCE Birdshot chorioretinopathy is a chronic intraocular inflammatory disease with no uniform method to document long-term disease progression or response to treatment.

OBJECTIVE To examine the long-term visual, clinical, and anatomic outcomes of patients with birdshot chorioretinopathy.

DESIGN, SETTING, AND PARTICIPANTS A retrospective evaluation of 46 patients with birdshot chorioretinopathy treated at Moorfields Eye Hospital, London, England, was conducted. Medical records for a 19-year period (1993-2012) were reviewed.

EXPOSURES Patients received no treatment, short-term (<1 year) treatment including local or systemic corticosteroids, or long-term (>1 year) treatment including systemic corticosteroids and second-line immunosuppressive agents.

MAIN OUTCOMES AND MEASURES Details regarding clinical and anatomic outcome, including best-corrected visual acuity, and visual field indices were evaluated.

RESULTS Ninety-two eyes of 46 patients were monitored for a mean (SE) of 57.2 (5.8) months (445 eye-years, 17% follow-up of ≥10 years). Patients maintained a steady best-corrected visual acuity throughout the follow-up period. Some clinical indices correlated with transient worse best-corrected visual acuity, including presence of cataract (P = .05), foveal leakage on fluorescein angiography (P = .04), and increased central retinal thickness (P = .02). Serial visual field studies demonstrated that patients who received only short-term treatment had a worsening of their pattern standard deviation with time (Spearman correlation, 0.57; P = .003); for those who received long-term treatment, the pattern standard deviation remained stable (Spearman correlation, −0.24; P = .26).

CONCLUSIONS AND RELEVANCE Our results suggest that central visual acuity can be maintained long term in patients with birdshot chorioretinopathy. Those who receive long-term immunosuppression appear to maintain better peripheral visual fields compared with patients who receive short-term treatment.

Published online December 12, 2013.
Birdshot chorioretinopathy (BSCR) is a chronic intraocular inflammatory disease involving the retina, retinal pigment epithelium, and choriocapillaris. It is a relatively rare condition, accounting for approximately 2% of all uveitis cases\(^1\)-\(^2;\) affects both eyes; and has a strong association with HLA-A29 antigen, which is positive in more than 95% of affected patients.\(^3\) The condition has a long progressive course, and studies\(^4\)-\(^7\) have demonstrated a deterioration of both central and peripheral retinal function. However, other studies\(^8\)-\(^10\) indicate that visual acuity (VA) may not be as dramatically affected as was previously thought and that, for many patients, it remains stable for several years. Visual field (VF) and electoretinography (ERG) studies\(^6,11,12\) demonstrate variable changes, making it quite difficult to judge visually significant disease progression and response to immunosuppressive treatment.

Treatment regimens for BSCR depend on clinical findings, with some patients receiving no treatment if the disease is quiescent and others receiving combinations of oral corticosteroids and second-line immunosuppressive agents for active disease.\(^8,13,15\) With no uniform method to document disease progression, the most effective treatment regimen remains unclear. In this study, we examined the long-term clinical and functional outcome in our patients as well as any differences related to the use of short- or long-term immunosuppressive treatment.

**Methods**

**Patient Selection**

This retrospective study was conducted at the uveitis clinic (S.L.) at Moorfield’s Eye Hospital (ethical approval for data collection LIGS10201, visual loss in uveitis). All patients with BSCR evaluated between 1993 and 2012 were identified from the clinic database and included in the study. Evaluation of HLA-A29 antigen was performed routinely for all patients with clinical features compatible with BSCR, and only those with a positive result were included in the study. All patients received care managed by a single consultant (S.L.) based on a consistent treatment algorithm. Treatment decisions were based on vision, clinical evaluation of active inflammation, presence of cystoid macular edema, or progressive deterioration of retinal function as noted on VF and ERG testing.

**Data Collection**

Information for each patient was collected according to the length of follow-up at the time of presentation and at months 1, 2, 6, and 12 as well as at years 5 and 10 and the final follow-up visit. Information from each visit was recorded, including best-corrected VA (BCVA), Ishihara color testing, anterior chamber cells and flare, presence of cataract, vitreous cells and haze, retinal lesion distribution, foveal thickening, and presence of vasculitis as well as treatment decisions. Further information was collected from any testing that was performed based on the clinical judgment at the time. These included fluorescein angiography, spectral-domain optical coherence tomography, VF (Humphrey Field Analyzer; Carl Zeiss Meditec, Inc), and ERG studies.

The BCVA results were converted to logMAR values. The outcome of permanent visual loss (\(<20/50\)) and severe visual loss (\(<20/200\)) was determined according to the criteria set by the Standardization of Uveitis Nomenclature working group.\(^16\)

All VF tests were performed using the 24-2 Swedish Interactive Threshold Algorithm standard protocol, stimulus III; foveal threshold, mean deviation (MD), and pattern standard deviation (PSD) were recorded.

**Statistical Analysis**

Univariate analyses were performed using the Mann-Whitney ranking test, and, for multivariate analysis, we used the Friedman analysis of variance (ANOVA). Changes in correlation between continuous variables were calculated using the Spearman correlation. The Kaplan-Meier estimator was used to examine survival from visual loss. All analyses were conducted using SPSS, version 13, statistical software (SPSS Inc). The accepted level of significance for all tests was \(\alpha = .05\). Results are presented as mean (SE). For BCVA, results are presented as \(\Delta\) change compared with BCVA at 6 months after the first visit.

**Results**

Forty-eight patients had a diagnosis of BSCR (29 women [60%], 19 men [40%]); 2 patients (4%) had a negative HLA-A29 antigen result and were excluded from further analysis. Ninety-two eyes from the remaining 46 patients were included in this study. Thirty-six patients (78%) were tertiary referrals, and the other 10 patients (22%) were either referred by primary medical practitioners or were seen through our own accident and emergency department. The mean age at beginning of follow-up was 55.4 (1.6) years. Eyes were monitored for a mean of 57.2 (5.8) months (range, 1-209 months, 445 eye-years), and for 16 of the 92 eyes (17%), follow-up was at least 10 years (215 eye-years).

**Long-term Clinical Outcome**

To explore changes in BCVA and visual outcome during follow-up, we used the 6-month visit as a baseline, separating early fluctuations secondary to active disease at presentation from longer-term disease changes. For the entire patient population, BCVA was stable with a change of 0.01 (0.08) logMAR at 10 years (Figure 1A). Using the Kaplan-Meier estimator, we examined long-term visual outcome and found that 88% (\(n = 81\)) and 97% (\(n = 89\)) of eyes maintained BCVA and did not progress to permanent visual loss or severe visual loss, respectively (Figure 1B). Table 1 lists the causes of vision loss.

To examine the outcome of midperipheral retinal function, we analyzed automated 24-2 VF properties for 25 eyes that had serial studies. These eyes differed from the rest of the cohort only by having a longer follow-up period (83.45 [18.92] months vs 49.49 [8.74] months; \(P = .02\)). The MD remained unchanged throughout the follow-up period (Spearman correla-
We used multivariate analysis to explore other correlations between BCVA and clinical findings, including anterior chamber cells and flare, vitreous cells or haze, retinal lesion distribution, and presence of cataract, foveal leakage on fluorescein angiography, as well as optical coherence tomographic findings, including central retinal thickness, the third highly reflective band, or an epiretinal membrane. As expected, during clinical follow-up, lower transient BCVA correlated with cataract (0.27 [0.03] logMAR vs 0.20 [0.03] logMAR; \( P = .05 \)) and increased central retinal thickness of more than 300 μm (0.20 [0.03] logMAR vs 0.35 [0.05] logMAR; \( P = .02 \))\(^{17,18} \) No other correlations were found. Intraocular pressure did not change significantly throughout follow-up (15.24 [0.16] mm Hg).

Color testing using Ishihara plates demonstrated a correlation between abnormal testing and BCVA (0.47 [0.11] logMAR vs 0.12 [0.03] logMAR; \( P = .01 \)). However, abnormally prolonged ERG findings, including the 30-Hz flicker implicit time, did not correlate with BCVA in our cohort.

### Short- vs Long-term Treatment

We examined differences in functional outcome between patients who did not require treatment or received only short-term (≤1 year per episode) treatment with local or systemic corticosteroids and those receiving long-term (>1 year) treatment including systemic corticosteroids and second-line immunosuppressive agents. Forty-two eyes received short-term treatment and 50 eyes received long-term treatment. During the follow-up period, patients received various second-line immunosuppressive agents, including mycophenolate mofetil (86% [43]), methotrexate sodium (20% [10]), cyclosporine (12% [6]), and azathioprine (4% [2]). Baseline characteristics were similar between the groups; BCVA was the only significant difference (Table 2).

Change in BCVA over time was referenced to the first 6-month time point (as described in the Methods section). We used this visit to separate early fluctuations secondary to active disease at presentation from longer-term disease changes. We noted that for eyes in the short-term treatment group, vision at baseline (−0.03 [0.04] logMAR) remained stable at 2 years’ follow-up (−0.03 [0.04] logMAR; Friedman ANOVA, \( P = .08 \)). For eyes in the long-term treatment group, baseline BCVA (0.1 [0.04] logMAR) improved at 2 years (−0.11 [0.04] logMAR; Friedman ANOVA, \( P < .001 \)). For both groups, BCVA continued to remain stable for the duration of follow-up (Figure 2 and Table 2).

To explore midperipheral retinal function, we analyzed serial VF results. Eyes in the short-term treatment group had no progression in MD (Spearman correlation, −0.19; \( P < .001 \)) (Figure 2A) but a worsening of PSD (Spearman correlation, 0.57; \( P = .003 \)) (Figure 2B). Eyes in the long-term treatment group had MD improvement (Spearman correlation, 0.55; \( P < .001 \)) (Figure 3A) with PSD remaining stable (Spearman correlation, −0.24; \( P = .26 \)) (Figure 3B), suggesting VF stabilization.
Discussion

In this study, we compared the long-term outcome of patients with BSCR. We found that (1) patients had stable BCVA extending over 10 years of follow-up; (2) although some transient clinical indices, including cataract, foveal leakage, increased central retinal thickness, transient abnormal color vision, reduced foveal threshold, and MD, correlated with a worse BCVA, others were unrelated; (3) after the acute period, BCVA remained stable for all patients; and (4) subsequent VF test results suggest that patients receiving long-term treatment have more stable VF indices compared with patients receiving short-term treatment.

In some studies, BSCR is described as a progressive disease with advancing choroidal lesions resulting in loss of central and peripheral vision in a substantial percentage of patients. However, our 10-year results as well as the results of others suggest a more steady course with long-term stable BCVA, and few patients experience permanent visual loss. This discrepancy among studies may reflect a difference in disease control as well as the results bias resulting from nonhomogeneous patient cohorts. Our group of patients comprised those referred from other secondary centers and primary referrals, including patients with refractory disease and those with a more favorable prognosis. The improvement in baseline BCVA for some of our patients during the first few months of follow-up supports the role of an acute, “wet” phase of the inflammation as a cause of reduced VA, resulting from active anterior-chamber inflammation, vitritis, macular edema, or optic nerve involvement. Once this phase resolved and the condition entered the “dry” stage, VA remained stable and changed little throughout the remainder of the follow-up period. Transient changes in BCVA correlated with various clinical factors, including presence of cataract, vitreous haze, foveal leakage on fluorescein angiography, central retinal thickness, and color vision; severe visual loss was mainly related to macular scarring secondary to atrophy or choroidal neovascularization. These correlations support a complex relationship between VA and clinical or anatomic properties, challenging our ability to identify the exact contribution of each factor.

Visual acuity can remain stable for many years in patients with BSCR; however, retinal disease may continue uninterrupted, resulting in progressive peripheral retinal dysfunction, as reflected in abnormal retinal function studies. To attempt documenting changes in these peripheral areas, we used testing, including ERG and VF. Different patterns of VF defects are found in these patients with a variety of protocols, but no uniform approach has yet emerged. Although Goldman VF tests are increasingly unavailable in the clinical setting, automated VF studies are readily available and may be used to monitor disease progression and response to treatment. In our cohort, patients who received short-term treatment had a progressive increase in PSD; for patients who received long-term treatment, PSD was stable and MD improved, suggesting a change in lesion size. Although other studies have demonstrated Goldman VF test improvement for patients receiving long-term immunosuppressive therapy, our findings in the midperiphery possibly reflect changes with a larger effect on daily function. The combined changes in VA and VF support an approach toward long-term immunosuppression for the prolonged stability of retinal function—first, central vision, and later, the continued resolution of peripheral retinal disease. Second-line agents with or without corticosteroids are regularly used for the control of BSCR with the aim of preventing long-term retinal

Table 2. Baseline Characteristics of Patients With Birdshot Chorioretinopathy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Short-term Treatment</th>
<th>Long-term Treatment</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>21</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Age at baseline, mean (SE), y</td>
<td>57 (2.53)</td>
<td>54 (1.75)</td>
<td>.26</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>9 (43)</td>
<td>8 (32)</td>
<td>.52</td>
</tr>
<tr>
<td>Mean visual acuity, logMAR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.14</td>
<td>0.40</td>
<td>.001</td>
</tr>
<tr>
<td>6 mo</td>
<td>0.22</td>
<td>0.29</td>
<td>.36</td>
</tr>
<tr>
<td>12 y</td>
<td>0.18</td>
<td>0.25</td>
<td>.26</td>
</tr>
</tbody>
</table>

* Visual acuity was the only significant difference noted between the groups.
deterioration.\textsuperscript{8,13,14} It remains a challenge to convince patients to begin treatment with such agents when VA remains good or there is no objective evidence of active inflammation, such as vitritis, disc swelling, or cystoid macular edema. The use of such objective measures to demonstrate disease progression may be helpful in this.

Recording peripheral VF and optical coherence tomographic changes are used to assist in demonstrating disease activity in patients with otherwise good VA. However, it remains to be determined whether these retinal changes have any effect on patients’ day-to-day function. Studies\textsuperscript{21-22} examining correlations between VF deterioration and quality of life among patients with glaucoma have demonstrated that progression of VF loss among these individuals has functional consequences that are reflected in quality-of-life questionnaires. Although the changes seen in patients with BSCR are without a doubt milder and of a slower rate of progression, these patients are generally much younger than those with glaucoma when the condition is diagnosed and have many years for continued disease progression and accumulated damage. Thus, early detection and aggressive disease control at any signs of retinal dysfunction may be paramount in achieving lasting visual function stability.

Whereas the use of cyclosporine and low-dose methotrexate for treatment in BSCR has been documented in previous studies,\textsuperscript{8,13,14} in our cohort, 86% of the patients were given mycophenolate mofetil (average dose, 1 g twice daily). This anti-metabolite has a good safety profile and is reported to reach full potency more quickly, be better tolerated, and cause fewer adverse reactions related to cellular toxic effects than methotrexate.\textsuperscript{23-25} Furthermore, cyclosporine is not ideal for long-term use in this group of patients because of its renal toxic effects, especially in a population such as those with BSCR because they are typically older at the time of diagnosis compared with other patients with uveitis.\textsuperscript{26} Mycophenolate mofetil may therefore be a good first choice of second-line immunosuppressive agent in this group of patients and may result in better adherence, less need for discontinuation due to drug toxicity or adverse effects, and better disease control in the long term.\textsuperscript{27}

Conclusions

This study examined the long-term outcome, including vision, of patients with BSCR, demonstrating overall disease stability. The use of second-line agents, specifically mycophenolate mofetil, is well tolerated and may stabilize the disease during the acute phase, as reflected in VA changes, as well as during longer follow-up, which may be reflected only in peripheral retina function. Because this condition is relatively uncommon and has slow progression, all data recorded are limited to small series of mainly retrospective studies and limited follow-up. In the present study, we evaluated a comparatively large cohort of patients treated with uniform regimens, with some patients monitored for 10 years or more. Because of its retrospective design, the study inherently contains biases resulting from patient selection, varied follow-up time, and nonuniform ancillary testing. Therefore, the results we presented are limited to the treatments we use and cannot be generalized to all second-line treatment agents. Therefore, in the future it may be interesting to examine the collected data gathered from all second-line studies and examine whether any single agent is superior for control of this disease.
Drafting of the manuscript: Tomkins-Netzer, Lightman.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Tomkins-Netzer, Taylor.
Administrative, technical, and material support: Lightman.
Study supervision: Taylor, Lightman.

Conflict of Interest Disclosures: Dr Lightman has received consultancy fees from Allergan, GSK, Alcon, 4Sight, and Paraxel; is on the advisory boards of Allergan and GSK; and has received consultancy fees from Allergan. No other disclosures were reported.

Funding/Support: Dr Taylor was supported by the UK National Institute of Health Research.

Role of the Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication.

REFERENCES