Daclizumab for Treatment of Birdshot Chorioretinopathy

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**Objective:** To report the outcomes for daclizumab in the treatment of birdshot chorioretinopathy (BSCR) refractory to traditional immunomodulatory therapy (IMT).

**Methods:** We retrospectively reviewed medical records of 8 patients with BSCR whose disease was refractory to or who were intolerant of traditional IMT. All patients received 1 mg/kg of daclizumab intravenously at 2-week intervals initially at 1 referral uveitis practice. Main outcome measures were changes in visual acuity, vitreous inflammation, fluorescein angiographic pathologic features, electroretinography (ERG) parameters, concomitant IMT requirements, and adverse events.

**Results:** Over a mean follow-up of 25.6 months, 7 patients had either stabilization or improvement in visual acuity of both eyes and complete resolution of vitreous inflammation. Six patients had resolution of vasculitis on fluorescein angiography. The ERG 30-Hz implicit times and the bright scotopic amplitudes worsened in some patients despite abolition of clinically evident inflammation. Four patients were able to discontinue all other IMT and remain inflammation free while receiving only daclizumab treatment. Two patients developed adverse effects that led to daclizumab treatment discontinuation.

**Conclusions:** Daclizumab therapy was effective in stabilizing vision and decreasing inflammation in most patients with BSCR. The ERG parameters continued to decline in some patients despite adequate inflammatory control. Regular serologic monitoring is critical to detect adverse events.

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METHODS

The Human Studies Committee of the Massachusetts Eye and Ear Infirmary approved the retrospective review of data with waiver of informed consent. Cases were consecutive patients with BSCR refractory to traditional IMT who received daclizumab (Zenapax; Hoffman-LaRoche, Inc, Nutley, NJ) between January 1, 2001, and December 31, 2006, administered by one of the us (C.S.F.) at a tertiary referral center. All patients met the diagnostic criteria for BSCR determined at an international consensus conference.23 In our practice, a step ladder approach to IMT is used with patients with BSCR. Initially, either an antimetabolite alone or in combination with a signal transduction inhibitor, such as cyclosporine or sirolimus, is used. If patients are refractory to or intolerant of this therapy, other antimetabolites and signal transduction inhibitors are used until an effective, tolerable combination is found. Patients with BSCR were considered refractory to IMT if the clinical examination and ancillary test results demonstrated persistent inflammation while taking maximum doses of at least 2 immunosuppressive agents for at least 2 years of continuous therapy. Intolerance to medical therapy included any of the following adverse effects: significant gastrointestinal symptoms; pronounced fatigue, leukopenia, and clinically significant changes in liver function test (LFT) results, creatinine level, or blood pressure.

Daclizumab (1 mg/kg) was infused over 1 hour every 2 weeks initially. After suppression of inflammation was sustained over 3 infusions, the interval was increased by 1 week. This process was repeated until the longest effective interval was achieved. Before each infusion, a complete blood cell count and LFTs were done. At each follow-up visit, a thorough history was taken and examination performed. Vitreous cells were graded by means of previously described standardized grading criteria.24 Every 6 months, full-field electroretinography (ERG) was performed in accordance with a standard protocol.25 Fluorescein angiograms (FAs) were also obtained every 6 months. Retinal vasculitis was defined as retinovascular leakage on FA. Therapy failure occurred if subjective symptoms, visual acuity (VA), and/or signs of inflammation (vitreous cell, retinal vasculitis on FA) did not improve after 3 infusions. Intolerance of daclizumab requiring cessation of treatment was defined as stated earlier for other IMT.

The outcome measures were changes in Snellen VA, degree of vitreous cells, vascular leakage on FA, ERG parameters, and concomitant immunosuppressive requirements. Adverse events were also assessed. A Snellen VA change of 2 lines or more in either eye was considered a clinically significant change. Standardization of Uveitis Nomenclature Working Group criteria for improvement and worsening of inflammation were applied to our grading scale for vitreous cells.26 The 30-Hz flicker implicit times and bright scotopic amplitudes were 2 ERG indicators chosen because of their correlation with clinically relevant parameters such as VA and the ability to taper IMT.27-33 A change in the implicit time by 2 milliseconds or more and a change in the amplitude by 25% or more were considered clinically significant.32 Results of FA were graded according to a previously described scale: 0 = no retinovascular leakage, 1 = large vessel leakage, 2 = small vessel leakage, 3 = cystoid macular edema, and 4 = retinal pigment epithelium atrophy in the posterior pole.32 A 1-step change on this scale was considered a clinically significant change. Concomitant IMT was tapered if the patient achieved control of inflammation. Any decrease in the number or dosage of IMT medications was recorded. Unexpected complaints and complications were recorded as adverse events.

RESULTS

Of the 34 patients with BSCR who received conventional IMT during the period of this study, 26 responded favorably while 8 patients were refractory to IMT and given daclizumab. The clinical data and outcomes for each patient are summarized in the Table. The mean patient age was 50 years with a range of 42 to 61 years. All patients were HLA-A29–positive women. The indications for switching to daclizumab treatment were ongoing inflammation despite maximal medical therapy in 6 patients and IMT intolerance in 2 patients. Patient 2 had pronounced fatigue with 2 different signal transduction inhibitors and previous monotherapy with antimetabolites had failed. Patient 5 had persistent leukopenia with conventional IMT regimens. All patients had retinal vasculitis on FA at daclizumab treatment initiation, and all patients except patient 2 had vitreous cells at the onset. The mean number of daclizumab infusions was 27.6, with a range of 16 to 49, and the mean follow-up time from the first infusion was 25.6 months, with a range of 12 to 55 months. The medications listed in the Table reflect the IMT regimen immediately prior to the initiation of daclizumab treatment.

All 8 patients achieved initial control of vitreous inflammation with the addition of daclizumab treatment, and 7 patients had control of vitreous inflammation over the entire follow-up period. After achieving suppression of ocular inflammation, we were able to reduce either the dosage of a particular IMT or the number of IMTs for 2 patients (patients 2 and 3). Four patients (patients 1, 5, 6, and 8) were able to discontinue all other IMT while receiving only daclizumab treatment.

One patient (patient 4) had recurrent vitreous inflammation and unilateral vision loss. After 11 months of inflammation suppression while taking daclizumab, she had an increase in vitreous inflammation requiring concurrent intravenous methylprednisolone infusions for 2 cycles. Her VA decreased from 20/50 OS to 20/200 OS within 9 months of starting daclizumab treatment, secondary to progression of preexisting subfoveal choroidal neovascularization treated with various modalities, including photodynamic therapy, intravitreal bevacizumab administration, and intravitreal triamcinolone acetonide administration. In addition, patient 7 lost vision in her right eye within 3 months of starting daclizumab treatment because of progression of a preexisting posterior subcapsular cataract. She underwent cataract surgery, and 1 month postoperatively, she recovered vision back to the level she had at daclizumab treatment initiation. The cataract progression was not thought to be related to daclizumab treatment as it was unilateral and occurred early in the daclizumab treatment; in addition, no other patient had cataract progression during the follow-up period.

When compared with pre–daclizumab treatment values, 30-Hz flicker implicit times at 6 months after therapy initiation were prolonged by 2 milliseconds or more in 5 eyes (right eye of patient 1, left eyes of patients 3 and 7, and both eyes of patient 4). At 6 months, only the 2 eyes from patient 8 showed a shortening of their implicit times. When comparing the pre–daclizumab treatment ERG with the last available ERG for each patient, the 30-Hz implicit times were more prolonged in 4 eyes. This prolongation was found not only in the patient who had uncontrolled vitreous inflammation (patient 4) but also in 1 eye of each of 2 patients who had inflammation control.
After 6 months of daclizumab treatment, the bright scotopic amplitudes decreased by at least 25% in 3 eyes, increased by at least 25% in 3 eyes, and remained stable in the rest. Over the follow-up period, 2 eyes demonstrated a decrease in the bright scotopic amplitude by 25% or more. This included the 1 eye of patient 4, who had clinical control of inflammation. Six eyes of 4 patients (patients 1 and 6-8) showed an increase in bright scotopic amplitudes by 25% or more. Changes in dim scotopic (isolated rod) b-wave amplitudes mirrored the changes of the bright scotopic amplitudes.

The Figure shows a representative patient with large-vessel retinal vasculitis that resolved with daclizumab treatment. Over the full follow-up period, the grade of FA pathologic features was improved or stable in all but 2 eyes. One was patient 4 who developed scarring secondary to her choroidal neovascular membrane. The other was patient 8 who had persistent perifoveal small-vessel leakage in her right eye despite resolution of vitritis and vision stability.

Two patients developed adverse events that prompted discontinuation of daclizumab treatment. Patient 4 had a rise in alanine aminotransferase (ALT) level to 27 U/L and an AST level of 25 U/L; no other cause of liver toxic reaction was discovered. Daclizumab treatment was restarted at two-thirds of her usual dose to control recurrent inflammation. The ALT levels rose once again (ALT, 112 U/L and ALT, 57 U/L) after 1 infusion and the medication was stopped. This patient also had transient ALT elevation while taking a sirolimus and mycophenolate mofetil combination. Patient 7’s white blood cell count decreased to 2000 cells/µL (to convert to ×10^9/L, multiply by 0.001) during her third year of daclizumab treatment (lower limit of normal in our laboratory is 3800 cells/µL). After the medication was stopped, her white blood cell count recovered slowly over 7 months to 3500 cells/µL. She did not have any infections during the period of leukopenia. She has remained inflammation free not taking any medication during this interval. This patient also had transient leukopenia while taking mycophenolate mofetil once. One patient developed a less serious adverse event, transient diarrhea, after 1 infusion, which did not recur.

We report the successful use of daclizumab treatment in patients with BSCR resistant to traditional IMT with ini-

### Table. Clinical Data of Patients With Birdshot Chorioretinopathy Treated With Daclizumab

<table>
<thead>
<tr>
<th>Patient/ Age, y</th>
<th>Therapy Before Daclizumab</th>
<th>Current Therapy</th>
<th>No. of Infusions</th>
<th>Follow-up, mo</th>
<th>VA</th>
<th>Inflammation&lt;sup&gt;a&lt;/sup&gt;</th>
<th>30-Hz IT, ms</th>
<th>Bright Scotopic Amplitude, µV</th>
<th>FA Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/43</td>
<td>MMF 2 g/d; CSA 200 mg/d</td>
<td>DAC every 4 wk</td>
<td>25</td>
<td>18</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>2/42</td>
<td>MMF 2.5 g/d; CSA 200 mg/d</td>
<td>DAC every 2 wk</td>
<td>18</td>
<td>12</td>
<td>Pre</td>
<td>Post</td>
<td>Quiet</td>
<td>Quiet</td>
<td>38</td>
</tr>
<tr>
<td>3/49</td>
<td>MMF 3 g/d; sirolimus 2 mg/d</td>
<td>DAC every 3 wk</td>
<td>24</td>
<td>14</td>
<td>Pre</td>
<td>Post</td>
<td>2 + OD</td>
<td>1 + OD</td>
<td>Quiet</td>
</tr>
<tr>
<td>4/45</td>
<td>MMF 2 g/d; sirolimus 2 mg/d</td>
<td>None&lt;sup&gt;b&lt;/sup&gt;</td>
<td>29</td>
<td>20</td>
<td>Pre</td>
<td>Post</td>
<td>1 + OD</td>
<td>0.5 + OD</td>
<td>1 + OD</td>
</tr>
<tr>
<td>5/50</td>
<td>MMF 1 g/d; CSA 200 mg/d</td>
<td>DAC every 6 wk</td>
<td>49</td>
<td>55</td>
<td>Pre</td>
<td>Post</td>
<td>0.5 + OD</td>
<td>2 + OD</td>
<td>Quiet</td>
</tr>
<tr>
<td>6/49</td>
<td>MMF 2.5 g/d; CSA 300 mg/d</td>
<td>DAC every 8 wk</td>
<td>28</td>
<td>32</td>
<td>Pre</td>
<td>Post</td>
<td>3 + OD</td>
<td>2 + OD</td>
<td>Quiet</td>
</tr>
<tr>
<td>7/59</td>
<td>MMF 500 mg/d; CSA 300 mg/d</td>
<td>None&lt;sup&gt;c&lt;/sup&gt;</td>
<td>32</td>
<td>42</td>
<td>Pre</td>
<td>Post</td>
<td>2 + OD</td>
<td>Quiet</td>
<td>29</td>
</tr>
<tr>
<td>8/61</td>
<td>MMF 1 g/d; CS 100 mg/d</td>
<td>DAC every 3 wk</td>
<td>16</td>
<td>12</td>
<td>Pre</td>
<td>Post</td>
<td>0.5 + OD</td>
<td>Quiet</td>
<td>36</td>
</tr>
</tbody>
</table>

Abbreviations: CSA, cyclosporin A; DAC, daclizumab; FA, fluorescein angiogram; IT, implicit time; MMF, mycophenolate mofetil; OD, right eye; OS, left eye; OU, both eyes; Pre, before daclizumab treatment (refers to the visit immediately prior to starting daclizumab treatment); Post, after daclizumab treatment (refers to the last follow-up visit); VA, visual acuity.

<sup>a</sup>Grading of inflammation refers to vitreous cell score.

<sup>b</sup>Daclizumab treatment discontinued because of elevated liver function test levels.

<sup>c</sup>Daclizumab treatment discontinued because of leukopenia.
tial inflammation control in all 8 patients. To our best knowledge, this is the first series exclusively examining daclizumab treatment in BSCR. There are 2 prior reports that include daclizumab-treated patients with BSCR. One study of subcutaneous daclizumab treatment for uveitis included 1 patient with BSCR, and 1 series on long-term outcomes of IMT for BSCR by our group included 2 patients who are also included in this series. The current report describes patients who have tolerated up to 49 infusions (to our knowledge, the largest number reported to date for BSCR) with adequate inflammatory control. This suggests that daclizumab treatment may be efficacious for inflammation control in patients who need such therapy over a protracted period.

Six patients in this study had inflammation that was refractory to mycophenolate mofetil treatment combined with either cyclosporine or sirolimus but then responded to daclizumab treatment. The reasons for response to daclizumab treatment following nonresponse to traditional IMT are unclear. Mycophenolate mofetil inhibits T- and B-lymphocyte proliferation by blocking production of nucleotides required for DNA synthesis but has no effect on cytokine production associated with early T-cell signaling transduction. Thus, it may be less effective for preexisting, ongoing inflammation than daclizumab. Cyclosporine inhibits IL-2 production and T-cell stimulation by blocking calcineurin, a phosphatase-required IL-2 gene transcriptional activation. Again, previously activated T cells may not be suppressed as well with cyclosporine as with daclizumab. Sirolimus binds intracellular protein kinases, thereby interrupting IL-2 receptor signal and blocking T-cell proliferation in response to IL-2. It works downstream from daclizumab and should inhibit ongoing inflammation to a similar degree. Intravenous delivery of daclizumab and superior ocular penetration may be partly responsible for its increased effectiveness.

Despite the positive effects on visual stabilization, intraocular inflammation, and vasculitis, some patients experienced deterioration in ERG 30-Hz implicit times and bright scotopic amplitudes. This is troubling because it indicates continued retinal function loss in a subset of patients despite other indicators of controlled inflammation. Many patients’ implicit times were prolonged beyond the normal range (25–32 milliseconds) prior to starting daclizumab treatment. While ERG values decline with age, this effect alone is insufficient to explain the worsening seen over the follow-up period. There are no re-

Figure. Fluorescein angiography before and after daclizumab treatment for patient 6. A and B, Late-phase fluorescein angiography frames of right and left eyes while patient is taking mycophenolate mofetil and cyclosporin A and immediately before starting daclizumab treatment. Note the temporal arcade vasculitis. C and D, After 2 years of daclizumab treatment, there is no vasculitis in the late frames of the angiogram.
ports examining retinal toxic reaction caused by daclizumab treatment and no reports in the rheumatologic or transplantation literature to suggest ocular toxic reaction caused by daclizumab treatment. This divergence between traditional outcome measures of success (preservation of vision and inflammation control) and ERG parameters in some patients suggests that the traditional measures may not be the best ones for monitoring this disease process with its tendency for subclinical, insidious progression in many patients.

Daclizumab treatment was associated with stability or improvement of both ERG parameters in 3 eyes that had treatment for more than 2 years (patient 6, both eyes and patient 7, left eye). To our knowledge, there is no documentation of sustained stability or improvement of ERG parameters for longer than 2 years with traditional IMT. There are some reports of ERG parameter improvement over approximately 1-year periods in patients treated with steroid-sparing IMT, including cyclosporine.29,31 Patients treated with steroids alone show progressive ERG decline.10 Serial visual field tests are another potentially useful ancillary test for following up BSCR.45 However, we did not perform serial visual field tests as part of this study.

Six patients in this study continue to receive daclizumab treatment on a regular basis. The appropriate length of treatment is unclear and may be indefinite. We have found that most patients begin to complain of symptoms of floaters and blurred vision prior to their next infusion once the infusions are extended beyond every 6 weeks, and we have been able to prolong the interval successfully to greater than 6 weeks in only 1 patient. The stable VA and sustained vitreous inflammation control in patient 7, who stopped treatment, indicates therapy could be finite in some cases; we do not yet know how to identify which patients this will be true for. Thus, we have not established any criteria for stopping daclizumab treatment for patients who are responding well to the medication. Currently, our only criteria for withdrawing daclizumab are intolerance and/or lack of response.

In the United States, where daclizumab is used off-label for uveitis, it is challenging to convince third-party payers to cover the expense of daclizumab treatment. The cost can vary but is approximately $1000 per infusion. Payment approval invariably involves hours of telephone conversations and written correspondence explaining the need for treatment. Despite these obstacles, we were able to obtain third-party payer coverage of daclizumab treatment for all the patients who were considered for the drug.

Elevated LFT levels and leukopenia were the 2 adverse events necessitating therapy discontinuation. Because both patients had experienced the same adverse effects with previous IMT, it may be that their liver and bone marrow, respectively, were particularly susceptible. Regardless, these findings underscore the need for regular monitoring during therapy.

The number of patients in this study is too small to form conclusions about daclizumab safety in patients with BSCR. The daclizumab adverse effect profile in patients with renal allograft has been widely studied and does not differ from that of placebo except for an increased risk of cellulitis and wound infections.10,35-37 There have been no reports of increased malignancy risk or mortality in long-term studies.37 In the field of cardiac transplantation, 1 randomized, placebo-controlled study for rejection prophylaxis showed increased mortality in patients receiving daclizumab at 6 and 12 months.38 Some of the increase in mortality appeared related to a higher incidence of severe infections and concomitant use of anti-lymphocyte antibody therapy. Other cardiac transplantation studies have failed to show an increased risk of mortality or infection.39,40 In uveitis studies, daclizumab treatment has not been associated with serious infection or death.19-21,41 The most common adverse effects reported are skin rashes, mild peripheral edema, and lymphadenopathy. There is 1 report of a patient with uveitis treated with daclizumab for 4 years who developed a malignancy that was curatively resected; the cancer was not clearly related to therapy.41

All of the patients in this study were women. While BSCR has been found by some to be more common in women,4 our sample appears unusual and may indicate that BSCR in women is more resistant to conventional IMT. Alternatively, there may be a selection bias for women in our study that was not readily apparent to us. We recently began to treat our ninth patient with BSCR, a man, with daclizumab.

Dacizumab treatment was efficacious in controlling inflammation and stabilizing vision for the majority of patients with BSCR in this study. However, some patients' ERG parameters continued to worsen despite these positive indicators. Patients' blood cell counts and LFT levels must be monitored closely to detect leukopenia or toxic hepatitis and discontinue therapy promptly, even if the patient has tolerated the therapy well for a year or more. This study's results must be interpreted in the context of the retrospective design, lack of a control group, relatively small number of patients, and limited follow-up for some patients. Larger studies are needed to definitively answer questions of safety and efficacy. In particular, prospective, controlled, long-term trials to explore continued ERG decline in some patients despite inflammation suppression are necessary in the ongoing search for treatments that can halt progressive retinal dysfunction in BSCR.

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Author Contributions: Dr Foster had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES


