Daclizumab Use in Patients With Pediatric Multiple Sclerosis

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Background: Daclizumab, a humanized monoclonal antibody specific for the interleukin 2 receptor α chain, reduces clinical and magnetic resonance imaging disease activity in patients with adult-onset multiple sclerosis (MS) as monotherapy or add-on therapy with interferon.

Objective: To report the use of daclizumab in pediatric-onset MS.

Design: Case series.

Setting: Two comprehensive pediatric MS centers.

Patients: Seven patients with pediatric-onset MS with clinical and magnetic resonance imaging disease activity despite first-line disease-modifying therapy.

Intervention: Intravenous daclizumab, 1 mg/kg monthly.

Main Outcome Measures: Annualized relapse rates, Expanded Disability Status Scale scores, contrast-enhancing lesions, and adverse effects.

Results: Treatment with daclizumab, primarily combined with interferon, was associated with reductions in annualized relapse rates and contrast-enhancing lesions and with reduction or stabilization of Expanded Disability Status Scale scores in each patient. However, 4 patients had relapses and new contrast-enhancing lesions during daclizumab treatment. No significant adverse effects occurred.

Conclusion: Daclizumab may be a safe and at least partially effective treatment option for patients with pediatric-onset MS with disease activity despite first-line disease-modifying therapy.

Arch Neurol. 2012;69(1):78-81

Although interferons and glatiramer acetate appear to be effective in patients with pediatric-onset (PO) multiple sclerosis (MS),¹ as many as 44% of patients with POMS undergo a change in their initial disease-modifying therapy (DMT) due to breakthrough disease activity, intolerance, or nonadherence.² There are limited data on treatment options for such patients.³⁴ Elevated levels of interleukin 2 (IL-2) can be detected in the serum, cerebrospinal fluid, and brain lesions of patients with MS, particularly those with active, relapsing disease.⁵ The IL-2 signals through the IL-2 receptor (IL-2R), which has low-, intermediate-, and high-affinity forms. The high-affinity receptor forms during T-cell activation when the α chain associates with the β and γ chains.

The monoclonal antibody daclizumab blocks the IL-2 binding site on the IL-2R α chain. In patients with adult-onset MS failing interferon treatment, intravenous and subcutaneous daclizumab monotherapy or add-on therapy decreased new contrast-enhancing lesions (CELs) and relapse rates in phase 2 studies.⁶⁻¹⁰ An ongoing phase 3 clinical trial is comparing the efficacy and safety of daclizumab, 150 mg subcutaneous monthly, with the efficacy and safety of interferon beta-1a in adults.¹¹ There have been no detailed reports on the safety and efficacy of daclizumab in POMS. We report the use of daclizumab in 7 patients with POMS with disease activity despite first-line DMT. Three patients were previously included in aggregate data in a study on DMT use in patients with POMS.²

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We extracted prespecified demographic, clinical, laboratory, and magnetic resonance imaging (MRI) data via retrospective review of electronic medical records of patients treated with...
daclizumab at Children’s Hospital Boston and Massachusetts General Hospital between March 1, 2006, and July 1, 2010. Inclusion criteria were (1) diagnosis of POMS and (2) daclizumab use prior to age 18. Patients were treated with intravenous daclizumab, 1 mg/kg every 2 weeks for 2 or 3 doses, followed by monthly doses based on prior studies. Annualized relapse rates (ARRs) were calculated, excluding the initial episode. Complete blood cell counts and liver function tests were performed every 3 to 6 months. Laboratory abnormalities were graded using National Cancer Institute Common Toxicity Criteria version 2.0 (http://ctep.cancer.gov/reporting/etc.html). Patients underwent MRI as clinically indicated. The number of CELs was recorded from the MRI immediately before initiation of daclizumab and the last available MRI while receiving daclizumab treatment.

### RESULTS

#### SUBJECTS

Seven patients met inclusion criteria. Demographic and clinical data are summarized in the Table. Patients presented with a first demyelinating event at a mean age of 13.4 years (range, 6.8-16.2 years). All patients had relapsing-remitting MS (RRMS) and were started on DMT after MS was diagnosed. Initial treatment consisted of weekly intramuscular interferon beta-1a (3 patients), thrice weekly subcutaneous interferon beta-1a (3), or glatiramer (1). One patient receiving weekly intramuscular interferon beta-1a and 2 patients receiving thrice weekly interferon beta-1a did not use other treatments prior to daclizumab. Two patients receiving weekly intramuscular interferon beta-1a and 1 patient receiving glatiramer switched to thrice weekly subcutaneous interferon beta-1a because of clinical and MRI disease activity. One patient switched from thrice weekly treatment with interferon beta-1a to glatiramer due to clinical and MRI disease activity and then to once weekly treatment with interferon beta-1a because of disease activity and nonadherence. The mean duration of DMT prior to daclizumab initiation was 1.3 years (range, 0.7-3.7 years). Although a predetermined definition of breakthrough disease activity was not used, 6 patients had ongoing clinical disease activity, and all patients had MRI disease activity while receiving the DMT they were prescribed prior to daclizumab initiation. Nonadherence to DMT contributed to the decision to initiate daclizumab in 2 patients, particularly patient 6.

Interferon-neutralizing antibodies were absent in the 5 patients who underwent testing before daclizumab initiation. Two patients were treated with daclizumab monotherapy and 5 in conjunction with interferon (4 with thrice weekly subcutaneous interferon beta-1a and 1 with weekly intramuscular interferon beta-1a). Patient 4 was also treated with monthly intravenous methylprednisolone. One patient switched from thrice weekly interferon beta-1a to glatiramer after developing interferon-neutralizing antibodies while receiving daclizumab.

#### ANNUALIZED RELAPSE RATES

Predaclizumab ARRs included relapses that occurred before and after initiation of DMT, excluding the initial episode, consistent with prior reports. During daclizumab treatment, ARRs decreased in all patients. The group mean ARRs decreased from 2.6 to 0.62.

#### MRI DISEASE ACTIVITY

Patient 4 was excluded from MRI analysis because of steroid treatment proximate to the MRIs. Patient 6 was nonadherent to DMT at the time of the MRI prior to daclizumab treatment but is included because nonadherence to self-injected DMT is a clinically relevant issue in this patient population. All other patients had been using the DMT at the time of the MRI prior to daclizumab initiation for a median of 8 months (range, 7-41 months). The median number of CELs decreased from 3 (range, 0-11) prior to daclizumab initiation to 0 (range, 0-2) on the last available MRI following a median of 10.5 months (range, 6-27 months) of daclizumab treatment. However, 4 of the 7 patients developed new CELs on MRI at some point during treatment with daclizumab.

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### Table. Demographic and Clinical Data

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age at MS Onset, y</th>
<th>Age at First DMT, y</th>
<th>Age at Start of Daclizumab Therapy, y</th>
<th>Daclizumab Duration, mo</th>
<th>Reasons for Treatment Change</th>
<th>Current Therapy</th>
<th>EDSS Score</th>
<th>ARR</th>
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<tr>
<td>1/F/15.7</td>
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<td>16.6</td>
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<td>Daclizumab, interferon</td>
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<td>17.3</td>
<td>26</td>
<td>Clinical, MRI</td>
<td>Daclizumab, interferon</td>
<td>1.5</td>
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<tr>
<td>3/M/16.8</td>
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<td>12.8</td>
<td>17</td>
<td>Clinical, MRI</td>
<td>Daclizumab, interferon</td>
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</tr>
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<td>16.1</td>
<td>17.2</td>
<td>33</td>
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<td>16.8</td>
<td>14</td>
<td>MRI, adherence interferon</td>
<td>Daclizumab</td>
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<td>Daclizumab</td>
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<td>Clinical, MRI</td>
<td>Daclizumab, glatiramer</td>
<td>2.5</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Abbreviations: ARR, annualized relapse rate; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis.
ADVERSE EFFECTS

There were no allergic reactions or serious infections. One patient developed mild headaches on the day of infusions. Two patients developed leukopenia (one developed grade 1 and the other developed grade 2) during treatment with daclizumab, both of whom were treated concurrently with thrice weekly subcutaneous interferon beta-1a. In the patient with grade 2 leukopenia (lowest white blood cell count, 2800/μL), the white blood cell count normalized after halving the interferon dose. Three patients had grade 1 anemia. Another patient developed grade 2 elevation in the aspartate aminotransferase level (169 U/L; upper reference value, 40 U/L) that improved to grade 1 after halving the thrice weekly subcutaneous interferon beta-1a dose. Patient 4 was switched to natalizumab treatment due to relapses and MRI disease activity despite treatment with daclizumab, thrice weekly subcutaneous interferon beta-1a, and monthly methylprednisolone.

In summary, we describe 7 patients with POMS who had relapses (6 patients), new MRI lesions (7), and/or difficulty with adherence (2) during treatment with interferon beta-1a and/or glatiramer. Treatment with daclizumab, largely in combination with interferon beta-1a, was associated with reductions in ARRs in all patients, reduction in the group's median number of CELs, and stabilization or improvement in Expanded Disability Status Scale scores. However, 4 patients had relapses and new CELs during daclizumab treatment. Daclizumab was well tolerated, with no significant adverse effects.

There are limitations to our report. First, patients received open-label treatment and were evaluated clinically and radiographically at nonuniform times, using nonuniform MRI protocols, reflecting clinical practice. Regression to the mean may account for decreased numbers of MRI lesions on follow up, which could not be accounted for in our single-arm, open-label study. Second, 5 patients used daclizumab in addition to a first-line DMT and 1 used monthly methylprednisolone. Third, we did not use a predetermined definition of treatment failure. However, 6 of the patients met inclusion criteria (other than the age requirement) for each of the prior daclizumab studies in adult patients on the basis of clinical relapses in the 12 months prior to daclizumab treatment while receiving DMT for at least 6 months.

In patient 6, nonadherence to first-line DMT played a major role in breakthrough disease activity and the decision to initiate daclizumab. Nonadherence and/or intolerance to self-injected DMT is an important issue in patients with POMS and contributes to treatment changes in at least 16% of patients with POMS. Furthermore, there is no widely accepted definition of treatment failure in patients with POMS or adult-onset MS. Lastly, the youngest patient at daclizumab initiation was aged 12 years, and the data cannot necessarily be generalized to younger children. Nonetheless, our report adds to the very limited published data on treatment options in pediatric patients with treatment-refractory RRMS.

In prior studies, the beneficial effects of daclizumab in patients with adult-onset MS developed gradually during the first 2 months of treatment. We observed a similar delay in 2 patients who had relapses and new CELs within the first 3 months of daclizumab treatment.

Several studies in patients with adult-onset MS have suggested that daclizumab is beneficial in reducing MS disease activity, likely through the increased number and activity of regulatory CD56bright natural killer cells with secondary effects on T-cells. In an open-label study of 11 patients with RRMS or secondary progressive MS and disease activity despite interferon-beta treatment, the addition of daclizumab, 1 mg/kg intravenously every 4 weeks, was associated with an 81% reduction in ARRs and a 70% reduction in CELs. In an open-label study of 19 patients with RRMS or secondary progressive MS, the use of daclizumab, mainly as monotherapy, improved ARRs, the appearance of CELs, and Expanded Disability Status Scale scores. Daclizumab was started at 1 mg/kg intravenously every 4 weeks and adjusted based on patient response, to a final dose ranging between 0.8 and 1.9 mg/kg. An overall 77% reduction in CELs was observed in a study of 15 patients with RRMS or secondary progressive MS initially added to treatment with interferon-beta at 1 mg/kg intravenously every 4 weeks for 5.5 months, and then used as monotherapy in 11 patients. In another study of 9 patients with adult-onset MS failing interferon treatment, daclizumab, at a dose of 1 mg/kg intravenously, was initially combined with interferon for 5.5 months, followed by daclizumab monotherapy. In 3 patients, CELs returned; therefore, interferon was restarted and daclizumab was increased to 1.5 mg/kg per dose. Finally, a randomized, placebo-controlled trial compared the addition of low-dose (1 mg/kg every 4 weeks) or high-dose (2 mg/kg every 2 weeks) subcutaneous daclizumab with placebo in 230 patients failing interferon beta treatment. The mean number of new or enlarged CELs decreased by 72% (P = .004) in the high-dose group and decreased by 25% (P = .51) in the low-dose group. In both daclizumab groups, the ARRs decreased (43% in the high-dose group and 32% in the low-dose group). Overall, these studies suggest that daclizumab may be beneficial in reducing ARRs and CELs in patients with MS. Its effects may be dose dependent, and some patients may require combination therapy with interferon for optimal results.

We did not use doses higher than 1 mg/kg intravenously, which may have contributed to breakthrough disease activity; however, optimal dosing regimens of daclizumab have yet to be established. Beside the possible ineffectiveness of daclizumab, the finding of relapses and new CELs in 3 of our patients, even after the first 3 months of daclizumab and interferon combination therapy, may reflect high relapse rates in patients with POMS. It is also possible that these patients developed neutralizing antibodies to daclizumab that were not measured in our patients.

Although other second-line treatments exist, daclizumab is an attractive option in pediatric patients. Compared with chemotherapy, daclizumab is not known to cause infertility or secondary malignancies, both of which are major concerns in young patients requiring long-term treatment. As opposed to natalizumab and ritux-
imab, progressive multifocal leukoencephalopathy has not been associated with daclizumab. Finally, daclizumab has been used safely and successfully in pediatric patients with solid-organ transplants \(^{16}\) and autoimmune uveitis.\(^ {17}\) However, adverse effects reportedly associated with daclizumab therapy, including elevated liver function test results, infections, psoriasis, and oral ulcers, highlight the need for close monitoring.\(^ {8,18}\)

Although the manufacturer has stopped production of the intravenous form of daclizumab, there are ongoing trials of the subcutaneous form in adult-onset MS.\(^ {10}\) Efficacy of daclizumab in patients with POMS cannot be confirmed from this report because of the heterogeneity of our patient population and lack of predetermined definitions of treatment response. However, our report, in conjunction with prior studies of daclizumab in other pediatric disorders, suggests an acceptable safety profile and provides a reasonable basis for conducting trials with subcutaneous daclizumab in children and adolescents with MS. Given the paucity of second-line treatment options for pediatric patients with MS, our observations highlight the need for formal trials to study safety and dosing as well as mechanistic studies to assess the role of daclizumab as monotherapy or with interferon in children and adolescents with MS.

Accepted for Publication: April 4, 2011.
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Author Contributions: Study concept and design: Gorman and Chitnis. Acquisition of data: Gorman, Tillema, Ciliax, and Chitnis. Analysis and interpretation of data: Gorman, Tillema, Ciliax, Guttmann, and Chitnis. Drafting of the manuscript: Gorman, Tillema, and Chitnis. Critical revision of the manuscript for important intellectual content: Gorman, Tillema, Ciliax, Guttmann, and Chitnis. Obtained funding: Chitnis. Administrative, technical, and material support: Ciliax. Study supervision: Gorman, Guttmann, and Chitnis.

Financial Disclosure: Dr Guttman has served as a consultant for Tibotec Therapeutics/Johnsen & Johnson and has received research support from Teva Neuroscience. Dr Chitnis has served as a consultant for Biogen-Idec, EMD-Serono, Teva Neuroscience, and Novartis and has received salary support from Merck-Serono and EMD-Serono.

Funding/Support: This work was supported by the Pediatric Multiple Sclerosis Centers of Excellence Grant from the National Multiple Sclerosis Society.

REFERENCES