Multiple Sclerosis Therapies in Pediatric Patients With Refractory Multiple Sclerosis

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Background: Currently available disease-modifying therapies (DMTs) are known to be only partially effective in adults with multiple sclerosis (MS). Little is known about pediatric patients with MS who experience refractory disease while receiving first-line DMTs.

Objective: To assess the occurrence and management of refractory disease in a group of pediatric patients with MS treated with first-line DMTs approved for adult patients within a network of pediatric MS centers in the United States.

Design, Setting, and Patients: A multicenter, retrospective, longitudinal, open-label study design involving record review of 258 patients with pediatric-onset MS (68.6% female; mean [SD] age at disease onset, 13.2 [3.5] years; range of age at onset, 2.0-17.9 years) who were seen at 6 pediatric MS centers in the United States.

Intervention: We evaluated medication changes owing to refractory disease in cases of pediatric-onset MS.

Main Outcome Measure: Disease stability as represented by lack of medication change for breakthrough disease.

Results: Records of 258 children with a confirmed diagnosis of MS and exposure to DMTs were reviewed. Interferon beta (prescribed to 200 of 258 children [77.5%]) and glatiramer acetate (prescribed to 53 of 258 children [20.5%]) were the 2 most frequently used first-line DMTs. Overall, 144 children (55.8%) continued receiving 1 therapy, while 65 (25.2%), 29 (11.2%), and 20 (7.8%) received 2, 3, or 4 or more sequential therapies, respectively, during a mean (SD) observation period of 3.9 (2.8) years. Second-line DMT use was restricted to interferon beta and glatiramer acetate in 203 children (78.7%), whereas other treatments such as broad-spectrum chemotherapies (cyclophosphamide, mitoxantrone hydrochloride), natalizumab, corticosteroids (monthly), and daclizumab were used at some point during the observation period for disease management in 55 children (21.3%). Hispanic children were more likely to experience breakthrough disease while receiving first-line DMTs than non-Hispanic children.

Conclusion: Although switching between first-line DMTs may be effective in pediatric patients with disease that is refractory to initial treatment, a subset of patients may require second-line therapeutic interventions.


Current available first-line DMTs for MS are reported to decrease the relapse rate by approximately 30% in adults with MS, although this number may be greater in present-day MS populations. Although definitions of partial therapeutic effectiveness and breakthrough disease may vary, in general these phrases imply clinical (ie, presence of recurrent relapses or progression of disability) and/or radiological (new
or enlarging magnetic resonance imaging [MRI] lesions) disease activity despite adherence to an appropriate therapeutic regimen. The biological mechanisms behind breakthrough disease on therapy have not been elucidated but may be due to genetic, immunological, or environmental disease heterogeneity.

In the pediatric MS population, multiple retrospective studies evaluating the safety and tolerability of first-line DMTs, including interferon beta and glatiramer acetate, suggest that they are well tolerated. Nevertheless, there are no data on the frequency of breakthrough disease on therapy have not been elucidated but may be due to genetic, immunological, or environmental disease heterogeneity.

In the pediatric MS population, multiple retrospective studies evaluating the safety and tolerability of first-line DMTs, including interferon beta and glatiramer acetate, suggest that they are well tolerated. Recent retrospective case series suggest that many children in this population may require therapeutic intervention beyond currently accepted first-line DMTs. However, there are no data on the frequency of breakthrough disease and its management in this population.

Our aim was to describe the frequency and management of disease refractory to first-line therapies in 258 pediatric patients with MS seen at 6 American Pediatric MS Centers of Excellence.

### METHODS

#### STUDY POPULATION

This was a multicenter, retrospective, longitudinal, open-label study of 258 patients with pediatric-onset MS. These patients were seen at the Pediatric MS Centers of Excellence, a 6-center network supported by the National MS Society with centers located in San Francisco, California (University of California, San Francisco), Rochester, Minnesota (Mayo Clinic), Birmingham, Alabama (University of Alabama at Birmingham), Buffalo, New York (State University of New York, Buffalo), Stony Brook, New York (State University of New York, Stony Brook), and Boston, Massachusetts (Harvard University, Massachusetts General Hospital, and Partners HealthCare). The network prospectively collects data regarding children with demyelinating disorders, including clinically isolated syndromes, MS, acute disseminated encephalomyelitis, and neuromyelitis optica. Approval by the institutional review boards of each institution for data collection and sharing was granted.

Children younger than 18 years with a diagnosis of pediatric-relapsing-remitting MS who had been receiving first-line treatment with a DMT (IM or SC interferon beta-1a, SC interferon beta-1b, or glatiramer acetate) for a minimum of 6 months were included in the analysis. All patients who were diagnosed as having MS at each of the sites were offered therapy; the only children who did not receive therapy were those who went against these recommendations. Data from all children presenting between August 1997 and August 2009 who were treated were analyzed. Age at disease onset, clinical presentation, sex, ethnicity/race, time of initiation of DMT, time to change in therapy, and reason for change in therapy were recorded using a standardized data collection template. The distribution of patients according to center was as follows: 27 patients at the University of California, San Francisco; 58 at the University of Alabama at Birmingham; 90 at the State University of New York, Stony Brook; 25 at Mayo Clinic; 26 at Harvard University, Massachusetts General Hospital, and Partners HealthCare; and 32 at the State University of New York, Buffalo. Children whose diagnosis of MS could not be confirmed were excluded, as were patients with a diagnosis of MS who were not treated.

### CLINICAL DEFINITIONS

Pediatric-onset MS was diagnosed following operational definitions of pediatric demyelinating disorders published by the International Pediatric MS Study Group. According to these definitions, pediatric MS may be diagnosed after 2 clinical episodes of central nervous system demyelination that are separated by at least 30 days. No lower age limit is specified.

Refractory disease status was defined by individual health care practitioners and included the presence of clinical activity (MS relapses) and/or MRI activity (new lesions on T2-weighted imaging or gadolinium-enhancing lesions on repeated MRI scans of the brain or spine).

Race (American Indian or Native Alaskan, Asian, black or African American, Native Hawaiian or other Pacific Islander, white, and mixed) and ethnicity (Hispanic and non-Hispanic) were defined following National Institutes of Health guidelines.

In a small number of cases, children were treated with a lower dose of medication than that recommended for the adult population. When dose escalation owing to breakthrough disease occurred in that small subgroup of patients, the increased dose was not considered a change. Special note has been made of these cases as appropriate. Clinicians were asked to identify whether each medication change was owing to breakthrough disease or other issues, such as adverse effects or compliance issues. As only the primary reason for a change was elucidated from investigators, we did not note children who had a medication change owing to a combination of breakthrough disease and concomitant adverse effects.

### DATA ANALYSIS

We used SPSS version 15.0 statistical software (SPSS Inc, Chicago, Illinois) for all statistical analyses. Because of the multiple testing involved in the analysis of clinical data, we used a conservative \( \alpha = .01 \) to assess statistical significance. A statistical trend was assumed if \( P \leq .05 \).

One-way analysis of variance (ANOVA) followed by post hoc independent sample t tests were used for 2-group comparisons to test for differences in means of continuous demographic variables such as age, age at onset, and disease duration. The \( \chi^2 \) test was used for analysis of count variables for categorical data, and the Fisher exact test was used when appropriate. Logistic regression was used to analyze the use of second-line therapies (including chemotherapy, natalizumab, and combination therapies) as the dependent variable with age at symptom onset, sex, and Hispanic vs non-Hispanic ethnicity as predictor variables.
RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

The clinical and demographic features of the 258 children and adolescents are summarized in Table 1. During the observation period (mean [SD], 3.9 [2.8] years), 144 children (55.8%) were treated with only 1 therapy, 65 (25.2%) changed therapies once, 29 (11.2%) changed therapies 2 times, 10 (3.9%) changed therapies 3 times, and 10 (3.9%) children changed therapies 4 or more times (Figure, A). Therapy was limited to interferon beta and glatiramer acetate in 203 children (78.7%), whereas other treatments such as broad-spectrum chemotherapies (e.g., cyclophosphamide, mitoxantrone), natalizumab, monthly pulse corticosteroids, and daclizumab were used during the observation period for 55 children (21.3%) for disease management.

There were no statistically significant differences between centers in numbers of therapies used, sex distribution, age at onset of symptoms, interval between start to stop of first agent or duration of disease, and Expanded Disability Status Scale score at initiation of therapy. There were modest differences in length of follow-up. This was greater at the State University of New York, Stony Brook, compared with the other centers. There were differences between center in the proportions of African American children (State University of New York, Stony Brook [17.8%], University of Alabama at Birmingham [46.6%], and Harvard University, Massachusetts General Hospital, and Partners HealthCare [19.2%] vs State University of New York, Buffalo [3.1%, University of California, San Francisco [7.4%], and Mayo Clinic [12.0%]) and Hispanic ethnicity (State University of New York, Stony Brook [24.4%], University of California, San Francisco [37.0%], and Harvard University, Massachusetts General Hospital, and Partners HealthCare [23.1%] vs State University of New York, Buffalo [0.0%, University of Alabama at Birmingham [1.7%], and Mayo Clinic [4.0%]) based on population demographic characteristics in the vicinity of the pediatric MS centers.

Figure. Therapies required and reasons for changing therapy. A, Distribution of the number of therapies required. For children using 1 therapy, 52.3% continued to receive the first therapy prescribed for the observation period and did not require changes in therapy (dark gray portion of bar), whereas 3.5% discontinued therapy (light gray portion of bar). B, Reasons for changing therapy. C, Distribution of the types of therapies required at each stage of therapy. IM indicates intramuscular; SC, subcutaneous.
Overall, baseline disability scores were low. The mean Expanded Disability Status Scale score at the first clinical visit was 2.1 (median, 2.0; interquartile range, 1.0-3.5). The mean Expanded Disability Status Scale score at the last visit was 1.7 (median, 1.5; interquartile range, 1.0-2.0). Using regression analysis, which corrected for sex, age at onset, and length of follow-up, change in Expanded Disability Status Scale score was significantly associated with the number of therapies used ($P = .004$).

**FIRST THERAPIES**

The mean (SD) interval between disease onset and initiation of the first DMT was 17.1 (20.4) months (range, 0.0-96.3 months). Interferon beta (200 of 258 patients [77.5%]) and glatiramer acetate (53 of 258 patients [20.5%]) were the most frequently used first therapies (Figure, C). Five patients (1.9%) received pulse cyclophosphamide (n=4) or azathioprine (n=1) as a first therapy ($P = .004$) owing to very active acute disease. These patients were later prescribed first-line DMTs.

**TOLERABILITY AND RESPONSE TO FIRST THERAPY**

The majority of children ($n=135$ [52.3%]) continued to receive the first therapy prescribed for the observation period and did not require changes in therapy (Table 3 and Figure, A). Nine children (3.3%) discontinued therapy. Medication was changed in 114 children (44.2%) on account of poor tolerance or noncompliance ($n=42$ [16.3%]) or refractory disease ($n=72$ [27.9%]). Overall, 11 children changed therapies owing to elevated liver function enzyme levels. All were receiving interferon beta products (IM interferon beta-1a, n=2; SC interferon beta-1a, n=8; SC interferon beta-1b, n=1). Medication changes after the first therapy occurred secondary to MRI changes alone in 10.7%, clinical relapses in 61.3%, and both MRI changes and clinical relapses in 28.0%; changes to a third therapy were owing to MRI changes alone in 6.0%, clinical relapses in 54.5%, and both MRI changes and clinical relapses in 39.3%.

The mean (SD) time to change from first to second therapy for the group reporting poor tolerance or noncompliance was 1.1 (1.2) years. The mean (SD) time to change of first therapy in the refractory group was 1.3 (1.3) years. There was no evidence for differences in age at onset (1-way ANOVA, $P = .33$), length of follow-up from the first event to the last follow-up (1-way ANOVA, $P = .38$), or duration of treatment with the first agent (1-way ANOVA, $P = .46$) between the groups with no treatment change, poor tolerance or noncompliance, and refractory disease.

There was no evidence for sex differences in the frequency of changes owing to poor tolerance or noncompliance (11 of 81 boys [13.6%] vs 40 of 177 girls [22.6% of girls]) or in the frequency of changes owing to refractory disease (23 of 81 boys [28.4% of boys] vs 49 of 177 girls [27.7% of girls]).

<table>
<thead>
<tr>
<th>Drug</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
<th>Fourth</th>
<th>Fifth</th>
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<tr>
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<td>. . .</td>
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<td>2 (1.8)</td>
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<td>8 (7.0)</td>
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<td>MycopHENolate motefil</td>
<td>. . .</td>
<td>2 (1.8)</td>
<td>1 (2.0)</td>
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<td>. . .</td>
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<td>Daclizumab</td>
<td>. . .</td>
<td>3 (2.6)</td>
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<td>Monthly corticosteroids</td>
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<td>. . .</td>
<td>4 (8.2)</td>
<td>2 (10.0)</td>
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Abbreviation: ellipses, not applicable.

<table>
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<tr>
<th>Tolerability or Response</th>
<th>IM Interferon Beta-1a</th>
<th>SC Interferon Beta-1a</th>
<th>SC Interferon Beta-1b</th>
<th>Glatiramer Acetate</th>
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<td>(n=92)</td>
<td>(n=76)</td>
<td>(n=32)</td>
<td>(n=53)</td>
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<td>Continued receiving first therapy, %</td>
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<td>63.2</td>
<td>31.2</td>
<td>64.2</td>
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<td>Poor tolerance or noncompliance, %</td>
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<td>21.1</td>
<td>25.0</td>
<td>15.1</td>
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<td>Refractory disease, %</td>
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<td>15.8</td>
<td>43.8</td>
<td>20.8</td>
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<td>Time to second drug, mean (SD), y</td>
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<td>1.1 (0.7)</td>
<td>1.4 (1.5)</td>
<td>1.1 (0.7)</td>
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<tr>
<td>Total follow-up time, mean (SD), y</td>
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<td>2.9 (2.0)</td>
<td>3.9 (2.2)</td>
<td>3.6 (2.5)</td>
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<td>Second therapy</td>
<td>(n=12)</td>
<td>(n=31)</td>
<td>(n=8)</td>
<td>(n=33)</td>
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<tr>
<td>Continued receiving second therapy, %</td>
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<td>77.4</td>
<td>37.5</td>
<td>60.6</td>
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<tr>
<td>Poor tolerance or noncompliance, %</td>
<td>41.7</td>
<td>6.5</td>
<td>37.5</td>
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<tr>
<td>Refractory disease, %</td>
<td>25.0</td>
<td>16.1</td>
<td>25.0</td>
<td>21.2</td>
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Abbreviations: IM, intramuscular; SC, subcutaneous.
Table 4. Patient Characteristics According to Ethnicity, Race, and Age

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<tr>
<th>Characteristic</th>
<th>Hispanic (n=40)</th>
<th>Non-Hispanic (n=219)</th>
<th>P Value</th>
<th>African American (n=54)</th>
<th>Non-African American (n=204)</th>
<th>P Value</th>
<th>Age at Symptom Onset, y</th>
<th>&lt;10 (n=41)</th>
<th>≥10 (n=210)</th>
<th>P Value</th>
</tr>
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<tr>
<td>Age at disease onset, mean (SD), y</td>
<td>12.8 (3.4)</td>
<td>13.2 (3.6)</td>
<td>.53</td>
<td>13.3 (3.1)</td>
<td>13.1 (3.7)</td>
<td>.73</td>
<td>6.4 (2.5)</td>
<td>14.5 (1.8)</td>
<td>&lt;.001</td>
<td></td>
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<tr>
<td>Disease duration at start of therapy, mean (SD), y</td>
<td>1.7 (2.1)</td>
<td>1.4 (1.6)</td>
<td>.37</td>
<td>1.3 (1.4)</td>
<td>1.5 (1.8)</td>
<td>.48</td>
<td>2.7 (2.6)</td>
<td>1.1 (1.3)</td>
<td>.001</td>
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</tr>
<tr>
<td>Time to second drug, mean (SD), y</td>
<td>1.2 (1.1)</td>
<td>1.2 (1.3)</td>
<td>.89</td>
<td>1.4 (1.1)</td>
<td>1.2 (1.3)</td>
<td>.33</td>
<td>2.1 (2.2)</td>
<td>1.1 (1.0)</td>
<td>.17</td>
<td></td>
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<tr>
<td>Total follow-up time, mean (SD), y</td>
<td>3.9 (2.2)</td>
<td>3.9 (2.9)</td>
<td>.87</td>
<td>4.4 (2.8)</td>
<td>3.8 (2.8)</td>
<td>.17</td>
<td>5.7 (4.0)</td>
<td>3.5 (2.4)</td>
<td>.002</td>
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<td>First therapy, No. (%)</td>
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<td></td>
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<tr>
<td>Interferon beta</td>
<td>28 (70.0)</td>
<td>172 (78.9)</td>
<td>$\chi^2 = 8.0; P = .02$</td>
<td>49 (90.7)</td>
<td>151 (74.0)</td>
<td>$\chi^2 = 7.3; P = .003$</td>
<td>36 (87.8)</td>
<td>158 (75.2)</td>
<td>.001</td>
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<tr>
<td>Glatiramer acetate</td>
<td>9 (22.5)</td>
<td>44 (20.2)</td>
<td>$\chi^2 = 4.7; P = .05$</td>
<td>4 (7.4)</td>
<td>49 (24.0)</td>
<td>$\chi^2 = 4.9; P = .02$</td>
<td>4 (8.8)</td>
<td>48 (22.9)</td>
<td>.017</td>
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<tr>
<td>Chemotherapy</td>
<td>3 (7.5)</td>
<td>2 (0.9)</td>
<td></td>
<td>1 (1.9)</td>
<td>4 (2.0)</td>
<td></td>
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<td>Reason for change</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>No change</td>
<td>9 (22.5)</td>
<td>126 (57.8)</td>
<td>$\chi^2 = 17.8; P &lt; .001$</td>
<td>27 (50.0)</td>
<td>108 (52.9)</td>
<td>$\chi^2 = 0.3; P = .87$</td>
<td>28 (68.3)</td>
<td>106 (50.5)</td>
<td>.17</td>
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<tr>
<td>Poor tolerance or noncompliance</td>
<td>11 (27.5)</td>
<td>40 (18.3)</td>
<td></td>
<td>12 (22.2)</td>
<td>39 (19.1)</td>
<td></td>
<td>3 (7.3)</td>
<td>45 (21.4)</td>
<td>.002</td>
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<tr>
<td>Breakthrough disease</td>
<td>20 (50.0)</td>
<td>52 (23.9)</td>
<td></td>
<td>15 (27.8)</td>
<td>57 (27.9)</td>
<td></td>
<td>10 (24.4)</td>
<td>59 (28.1)</td>
<td>.017</td>
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</table>

* The categories with the largest-fold differences in proportions are in bold for the $\chi^2$ test involving 3 categories.

*a Age at symptom onset was missing for 7 patients.

Table 4 provides details on age, ethnicity, and race. In general, children younger than 10 years compared with those aged 10 years or older were less likely to change therapy owing to noncompliance or poor medication tolerability (7.3% vs 21.4%, respectively). The proportion of children with refractory disease requiring a change in therapy was similar in the 2 groups (24.4% vs 28.1%, respectively). The time between the first demyelinating episode and initiation of the first DMT was longer in children younger than 10 years.

Despite similar disease duration, age at onset, and time to the first medication change, Hispanic children were significantly more likely than non-Hispanic children to require medication changes. Medication changes owing to poor tolerance and noncompliance were higher in Hispanic children than in non-Hispanic children. There was no evidence for differences between African American and non–African American children in the frequency of medication changes owing to poor tolerance or noncompliance or to refractory disease (Table 4).

Of the 42 children who changed medications owing to poor tolerability or noncompliance, 4 (9.5%) went on to experience refractory disease while receiving the second agent tried and 13 (31.0%) changed therapies owing to poor tolerability or noncompliance again. The majority of children (42 of 72 children [58.3%]) who experienced refractory disease while receiving the first agent responded to treatment with the second agent.

**INTERFERON BETA THERAPY**

Table 3 provides information on the interferon beta therapies used as the first treatment. Four of the children requiring a medication change while receiving IM interferon beta-1a were initially prescribed a low dose (7.5 µg). Three experienced refractory disease requiring dose escalation, and 1 required change to SC interferon beta-1a after dose escalation owing to refractory disease. The frequency of poor tolerability or noncompliance was similar across all 3 interferon beta products. Duration of therapy was similar in all groups. There was no evidence for differences in the time to change to second therapies among the different first therapies (ANOVA, $P = .79$) (Table 3).

We also compared the frequency of changes owing to refractory disease in Hispanic patients with that in non-Hispanic patients for each of the interferon beta products used as a first therapy. The frequency of changes owing to refractory disease in Hispanic patients treated with IM interferon beta-1a was higher than that in non-Hispanic patients. The frequencies of refractory disease in Hispanic and non-Hispanic patients treated with SC interferon beta-1a were similar ($\chi^2 = 0.9; P = .64$). Hispanic patients treated with SC interferon beta-1b were more likely than non-Hispanic patients to have poor tolerance or noncompliance; the frequency of refractory disease in Hispanic patients treated with SC interferon beta-1b was not significantly different from that in non-Hispanic patients treated with SC interferon beta-1b. Duration of therapy was similar in the groups (Table 4).

Nineteen children were tested for anti-interferon beta neutralizing antibodies. Two of the children (10.5%) had positive results (one was receiving SC interferon beta-1a and the other was receiving SC interferon beta-1b). Of those with negative results, 9 were receiving IM interferon beta-1a, 7 were receiving SC interferon beta-1a, and 1 was receiving interferon beta-1b.

**GLATIRAMER ACETATE THERAPY**

Of the 53 children (20.5%) who were prescribed glatiramer acetate as a first agent, 8 (15.1%) changed medication owing to poor tolerability or noncompliance and 11 (20.8%) changed medication owing to refractory disease. Children receiving glatiramer acetate compared with those receiving any interferon beta products as group showed no differences in the overall frequencies of changes.
Pairwise comparisons of therapy changes owing to refractory disease while receiving glatiramer acetate vs individual interferon beta products showed a trend toward a lower frequency of medication changes owing to breakthrough disease with glatiramer acetate compared with SC interferon beta-1b (20.8% vs 43.8%, respectively; \( \chi^2 = 8.8; P = .01 \)). The frequency of medication changes for breakthrough disease with glatiramer acetate was similar to that with SC interferon beta-1a (20.8% vs 15.8%, respectively; \( \chi^2 = 1.0; P = .60 \)) and to that with IM interferon beta-1a (20.8% vs 35.9%, respectively; \( \chi^2 = 5.4; P = .07 \)). Hispanic children were more likely to change therapy owing to refractory disease while receiving glatiramer acetate (5 of 9 children [55.6%]) than non-Hispanic children (6 of 44 children [13.6%]) (\( \chi^2 = 13.5; P = .001 \)).

OTHER THERAPY

The second therapy to which children were changed consisted of interferon beta or glatiramer acetate in 62.5% of children experiencing refractory disease. Generally, the frequency of the low-dose IM interferon beta-1a regimen declined and the frequency of other therapies increased (Figure, C). Other therapies including broad-spectrum chemotherapy (cyclophosphamide, mitoxantrone [10 of 72 children]), natalizumab (7 of 72 children), or others (intravenous immunoglobulin, daclizumab, azathioprine, mycophenolate mofetil [10 of 72 children]) were used in more than one-third of patients experiencing refractory disease (27 of 72 children [37.5%]). Combination therapies were used in 22 instances; most of these were the addition of intravenous immunoglobulin or steroids to first-line DMTs (intravenous immunoglobulin and first-line DMT, 9 of 22 children; monthly steroids and first-line DMT, 3 of 22 children), but combination therapies also included chemotherapy plus first-line DMTs (9 of 22 children) and glatiramer acetate plus interferon beta-1a (1 of 22 children).

Seven children were tested for natalizumab-neutralizing antibodies. Two patients receiving natalizumab developed breakthrough disease and were found to have antinatalizumab antibodies. One patient developed a hypersensitive reaction after reintroduction of natalizumab and was found to have developed neutralizing antibodies.

The use of other therapies was analyzed as a dependent variable in logistic regression with age at symptom onset, sex, and Hispanic ethnicity as predictor variables. The overall model for use of other therapies was strongly associated with Hispanic ethnicity (B [SE], 1.7 [0.38]; \( P < .001 \)). In contrast, age at symptom onset (\( P = .19 \)) and sex (\( P = .98 \)) were not significant predictors of breakthrough disease. It is remarkable that approximately half of the children included in this study had their therapy changed to a second agent owing to refractory disease (27.9%) or poor tolerability of a first-line DMT (16.3%) or quit therapy (3.5%). These figures stand in contrast to some adult MS studies, where, depending on the criteria used, up to 49% of patients may be considered nonresponders to first-line therapy, although other more recent data from adult MS studies suggest a similar rate of changing therapy owing to refractory disease (30%).

Although African American patients with adult-onset MS have more aggressive disease and possibly poorer response to interferon beta than white patients, we did not confirm a higher rate of poor response in pediatric patients with MS who were African American compared with white patients. This may be owing in part to the relatively small sample size, although the proportion of African American children in our cohort (20.9%) is greater than that in adult MS cohorts. Although another explanation for this might be that poor outcomes in Hispanic white children worsened overall outcomes in the group of white children, analysis comparing non-Hispanic, non–African American children with African American children showed no significant differences between the 2 groups in the rate of refractory disease requiring medication change (22.9% in non–African American, non-Hispanic children vs 26.9% in African American children). Earlier intervention after disease onset, differences in time receiving DMT, and fewer comorbidities than those encountered in the adult population of African American patients with MS may also contribute to this difference.

As in adult MS, a widely accepted consensus definition of treatment failure, a phrase often interchangeable with breakthrough disease, does not exist. Some have suggested that the presence of more than 1 relapse per year, no decrease in the relapse rate, incomplete recovery from relapses or accumulation of disability, new brainstem or spinal cord lesions on MRI, or worsening of motor or cognitive status may support the need for a therapy change. In general, these criteria are reserved for those who have been receiving therapy for at least 6 months.

The lack of a consensus definition of breakthrough disease in adults, the relative rarity of pediatric MS, and the unknown magnitude of effect of DMT in the pediatric population have prevented the development of both a consensus definition for breakthrough disease and recommended therapeutic management strategies in pediatric MS. Most health care practitioners participating in this study made changes after patients experienced more than 1 clinical relapse or MRI change per year. Second-line agents and combination therapies were used with relative frequency for severe or refractory dis-
ease in our patients. This suggests that pediatric MS may not be a benign disease. The long-term safety of these second-line therapies or combination strategies in children is unknown. Vigilance should be maintained while using these agents in this population.

Our study has several limitations. First, its retrospective nature limits the availability of information such as pre-DMT relapse rate and socioeconomic status, which would help to adjust some of our analyses and verify the robustness of the finding of a higher rate of breakthrough disease in Hispanic children. Second, the relapse rate while the patients are receiving treatment is not available, thus limiting our ability to better describe the treatment benefit in our cohort. Third, our ability to comment on the benign or aggressive nature of pediatric MS is limited by the potential bias that children not receiving therapy were not included in the analysis. However, we emphasize that all children seen at the centers who were diagnosed as having MS received the recommendation to initiate therapy, and only a small number (3.5%) of children discontinued therapy altogether and were therefore untreated. Finally, as this was a retrospective analysis, initial treatment choices may have been influenced by individual practice patterns and perceived disease severity, thus potentially skewing the results.

Further studies evaluating the short- and long-term safety and efficacy of these agents are needed, as are studies examining the socioeconomic, psychological, and biological mechanisms behind differences in breakthrough disease in pediatric-onset MS. Finally, collaborative work clarifying the definition of breakthrough disease and identifying optimal treatment strategies in pediatric MS is necessary to improve patient care in the future.

Accepted for Publication: September 21, 2010.
Published Online: December 13, 2010. doi:10.1001/archneurol.2010.325

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Financial Disclosure: Dr Yeh has received financial support for research activities from the National Institutes of Health, the Jog for the Jake Foundation, and the Children’s Guild Foundation. Dr Waubant has received free medication for clinical trials from Biogen Idec and Sanofi-aventis. Dr Krupp has received personal compensation for activities with Bayer HealthCare Pharmaceuticals, Biogen Idec, EMD Serono, GlaxoSmithKline, and Teva Neuroscience; has received royalty payments from Demos Medical Publishing, Eli Lilly and Co, MedImmune, Vertex Pharmaceuticals, Wyeth Pharmaceuticals, and ZymoGenetics; and has received research support from Acorda Therapeutics and Biogen Idec. Dr Ness has received funding from the National Institutes of Health and serves as an unpaid consultant for Merck. Dr Chitnis has been a consultant for Teva Neuroscience, Biogen Idec, EMD Serono, and Bayer HealthCare Pharmaceuticals. Dr Ramanathan has received research funding from EMD Serono, Pfizer, Novartis, the National Multiple Sclerosis Society, the National Institutes of Health, and the National Science Foundation and has received compensation for serving as an editor for the American Association of Pharmaceutical Scientists (which are unrelated to the research presented in this article). Dr Chabas has received personal compensation for activities with Teva Neuroscience. Dr Rinker has received speaking honoraria from Biogen Idec, EMD Serono, Pfizer, and Teva Neuroscience and has received research funding from Biogen Idec, Novartis, and EMD Serono. Dr Weinstock-Guttman has received compensation for speaking from Teva Neuroscience, Biogen...
Idec, and EMD Serono and has received financial support for research activities from the National Institutes of Health, the National Multiple Sclerosis Society, the National Science Foundation, EMD Serono, Biogen Idec, Teva Neuroscience, Cyberonics, and the Jog for the Jake Foundation.

**Funding/Support:** The National Multiple Sclerosis Society provided financial support for the Pediatric Multiple Sclerosis Center of Excellence of the Jacobs Neurological Institute.

**Additional Contributions:** We acknowledge the National Multiple Sclerosis Society for providing clinical funding for the US National Network of Pediatric MS Centers of Excellence.

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**REFERENCES**


