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.


PEDiATRIC-ONSET MULTIPLE sclerosis (MS) composes approximately 3% to 5% of cases of MS in North America.1-4 Six disease-modifying therapies (DMTs) have been approved for treatment of relapsing-remitting MS in the adult population. The 4 first-line DMTs are glatiramer acetate, intramuscular (IM) interferon beta-1a, subcutaneous (SC) interferon beta-1a, and SC interferon beta-1b; the 2 second-line DMTs are mitoxantrone hydrochloride and natalizumab. In addition, therapies such as rituximab, daclizumab, and cyclophosphamide have been evaluated in phase 2 trials in adults with breakthrough disease, as have add-on therapies such as monthly steroids and intravenous immunoglobulin.5-10 Currently available first-line DMTs for MS are reported to decrease the relapse rate by approximately 30% in adults with MS,11 although this number may be greater in present-day MS populations.12 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

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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. 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.

### 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 board 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 α = .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 χ² 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.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>177 (68.6)</td>
</tr>
<tr>
<td>Male</td>
<td>81 (31.4)</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>54 (20.9)</td>
</tr>
<tr>
<td>White</td>
<td>169 (65.5)</td>
</tr>
<tr>
<td>Asian</td>
<td>6 (2.3)</td>
</tr>
<tr>
<td>Native American</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Mixed race</td>
<td>6 (2.3)</td>
</tr>
<tr>
<td>Not available</td>
<td>20 (7.8)</td>
</tr>
<tr>
<td>Hispanic ethnicity, No. (%)</td>
<td>40 (15.5)</td>
</tr>
<tr>
<td>Age at disease onset, mean (SD), y</td>
<td>13.2 (3.5)</td>
</tr>
<tr>
<td>Follow-up duration, mean (SD), y</td>
<td>3.9 (2.8)</td>
</tr>
</tbody>
</table>
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 (eg, 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.
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%] of boys 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).

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**Table 2. Frequency of Use of Chemotherapies and Other Second-Line Drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
<th>Fourth</th>
<th>Fifth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natalizumab</td>
<td></td>
<td>7 (6.1)</td>
<td>10 (20.4)</td>
<td>5 (25.0)</td>
<td>5 (50.0)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>4 (1.6)</td>
<td>3 (2.6)</td>
<td>7 (14.3)</td>
<td>2 (10.0)</td>
<td>2 (20.0)</td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td>1 (0.4)</td>
<td>5 (4.4)</td>
<td>3 (6.1)</td>
<td>1 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>1 (0.4)</td>
<td>2 (1.8)</td>
<td>1 (2.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitoxantrone hydrochloride</td>
<td></td>
<td>8 (7.0)</td>
<td>1 (2.0)</td>
<td>3 (15.0)</td>
<td>1 (10.0)</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td></td>
<td>2 (1.8)</td>
<td>1 (2.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daclizumab</td>
<td></td>
<td>3 (2.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly corticosteroids</td>
<td></td>
<td></td>
<td>4 (8.2)</td>
<td>2 (10.0)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ellipses, not applicable.

**Table 3. Tolerability and Response to Different Disease-Modifying Therapies**

<table>
<thead>
<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>
</tr>
</thead>
<tbody>
<tr>
<td>First therapy</td>
<td>(n=92)</td>
<td>(n=76)</td>
<td>(n=32)</td>
<td>(n=53)</td>
</tr>
<tr>
<td>Continued receiving first therapy, %</td>
<td>45.6</td>
<td>63.2</td>
<td>31.2</td>
<td>64.2</td>
</tr>
<tr>
<td>Poor tolerance or noncompliance, %</td>
<td>19.6</td>
<td>21.1</td>
<td>25.0</td>
<td>15.1</td>
</tr>
<tr>
<td>Refractory disease, %</td>
<td>35.9</td>
<td>15.8</td>
<td>43.8</td>
<td>20.8</td>
</tr>
<tr>
<td>Time to second drug, mean (SD), y</td>
<td>1.3 (1.5)</td>
<td>1.1 (0.7)</td>
<td>1.4 (1.5)</td>
<td>1.1 (0.7)</td>
</tr>
<tr>
<td>Total follow-up time, mean (SD), y</td>
<td>4.8 (3.4)</td>
<td>2.9 (2.0)</td>
<td>3.9 (2.2)</td>
<td>3.6 (2.5)</td>
</tr>
<tr>
<td>Second therapy</td>
<td>(n=12)</td>
<td>(n=31)</td>
<td>(n=8)</td>
<td>(n=33)</td>
</tr>
<tr>
<td>Continued receiving second therapy, %</td>
<td>33.3</td>
<td>77.4</td>
<td>37.5</td>
<td>60.6</td>
</tr>
<tr>
<td>Poor tolerance or noncompliance, %</td>
<td>41.7</td>
<td>6.5</td>
<td>37.5</td>
<td>18.2</td>
</tr>
<tr>
<td>Refractory disease, %</td>
<td>25.0</td>
<td>16.1</td>
<td>25.0</td>
<td>21.2</td>
</tr>
</tbody>
</table>

Abbreviations: IM, intramuscular; SC, subcutaneous.
after dose escalation owing to refractory disease. The fre-

Table 3 provides information on the interferon beta ther-

Table 4. Patient Characteristics According to Ethnicity, Race, and Agea

INTERFERON BETA THERAPY

Table 3 provides information on the interferon beta ther-

GLATIRAMER ACETATE THERAPY

Of the 53 children (20.5%) who were prescribed glat-

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owing to poor medication tolerability or breakthrough disease ($\chi^2 = 3.6; P = .17$) (Figure).

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.

**COMMENT**

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%). It is unclear whether the different definitions of breakthrough disease used in this study and adult studies may explain these different outcomes or whether there are underlying biological processes resulting in a differential rate of refractory disease.

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.

Children whose families self-categorized as Hispanic (n=40) were more likely to have refractory disease requiring a change in first-line therapy and to need second-line therapies than non-Hispanic children. It is unclear whether referral bias may in part explain this finding as we could not adjust our analysis for pre-DMT relapse rate or socioeconomic status. Complex socioeconomic, psychological, and biological factors outside the scope of this study may have influenced this outcome.

Even 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 discontinuing 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.

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Author Contributions: Dr Yeh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Yeh, Waubant, Kuntz, Belman, Chabas, Rodriguez, and Weinstock-Guttman. Acquisition of data: Yeh, Waubant, Krupp, Ness, Chitnis, Kuntz, Belman, Chabas, Gorman, Rinker, and Weinstock-Guttman. Analysis and interpretation of data: Yeh, Waubant, Ness, Kuntz, Ramanathan, Belman, Rodriguez, and Rinker. Drafting of the manuscript: Yeh, Waubant, Chitnis, Kuntz, Ramanathan, Belman, Chabas, and Rodriguez. Critical revision of the manuscript for important intellectual content: Yeh, Waubant, Krupp, Ness, Chitnis, Kuntz, Ramanathan, Gorman, Rinker, and Weinstock-Guttman. Statistical analysis: Yeh and Ramanathan. Obtained funding: Yeh, Ness, Chitnis, and Chabas. Administrative, technical, and material support: Waubant and Rodriguez. Study supervision: Waubant, Krupp, Rodriguez, and Weinstock-Guttman.

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**REFERENCES**