Advances in Immunomodulatory Therapy for Multiple Sclerosis

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Abstract Significant research has been directed toward the development of more convenient and effective immunomodulatory therapy for relapsing-remitting multiple sclerosis (RRMS). During the 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis in Copenhagen, Denmark, investigators presented information on emerging immunomodulatory therapies, including alemtuzumab, peginterferon beta-1a, and daclizumab high-yield process. With the number of treatment options rapidly expanding, the need to fully understand the potential risks and benefits of these novel therapies and how to safely transition between them is of utmost importance. While many new immunomodulatory therapies have been shown to be effective in decreasing the frequency of clinical relapse and reducing MRI lesion burden in patients with RRMS, identifying the patient subgroup that would most benefit from these therapies and the optimal time for their introduction have yet to be determined.

Over the past several years, the number of therapies developed to treat multiple sclerosis (MS) has increased significantly. It is critically important that physicians understand the potential adverse effects, drug interactions, and immunologic effects of these agents before they recommend particular treatments for individual patients.

Many of the posters exhibited at the 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) in Copenhagen, Denmark, presented current data on immunomodulatory therapies that are either newly approved or in phase 3 clinical trials; these data also identified some of the risks related to the use of these treatments. Other key posters described the potential risks and benefits of switching between these medications and proposed algorithms for doing so. Results of these studies likely will impact clinical practice and standards for MS therapy in the near future.

**ALEMTUZUMAB**

Alemtuzumab is a humanized monoclonal antibody recently approved in the European Union to treat active relapsing-remitting MS (RRMS). In the United States, it is approved only for use in the treatment of B-cell chronic lymphocytic leukemia.

Alemtuzumab selectively targets the CD52 antigen on mature lymphocytes to effectively deplete circulating T and B lymphocytes. Use of this drug reduced the annualized relapse rate in one phase 2 study (CAMMS223) and two phase 3 studies (CARE-MS I and CARE-MS II) when compared with subcutaneous (SC) administration of interferon beta-1a.

A number of posters at ECTRIMS 2013 described the potential adverse effects, immunogenicity, and pattern of lymphocyte depletion and repopulation associated with alemtuzumab therapy of RRMS. The two CARE-MS studies were randomized, rater-blinded, active-controlled phase 3 trials of 24 months’ duration that enrolled patients between September 2007 and April 2009.

CARE-MS I enrolled treatment-naive patients with RRMS who were believed to have active disease (as determined by the occurrence of at least two relapses over the past 2 years and at least one relapse within the past year) and who were between 18 and 50 years of age. Participants in this study needed to have a baseline Expanded Disability Status Scale (EDSS) score ≤ 3 and MS symptom onset within the past 5 years. They could not have been previously treated with MS disease-modifying therapy, immunosuppressants, investigational agents, or monoclonal antibodies.

CARE-MS II enrolled patients who relapsed despite therapy for RRMS. Study participants had to be 18–55 years of age and have a baseline EDSS score ≤ 5, MS symptom onset within 10 years, and currently active disease (at least two relapses over the past 2 years and at least one relapse within the past year) with disease activity despite treatment (one or more relapses during treatment with interferon beta-1a or glatiramer acetate for at least 6 months).

In both studies, patients were randomized to receive intravenous (IV) infusions of alemtuzumab (12 mg/d on 5 consecutive days at study entry and on 3 consecutive days 12 months later) or interferon beta-1a (44 μg SC 3 times weekly). Primary endpoints were annualized relapse...
rate and time to accumulation of disability sustained over 6 months.

In both CARE-MS studies, alemtuzumab demonstrated superior efficacy over interferon beta-1a in patients with active RRMS over a span of 2 years. In CARE-MS I, the relapse rate was reduced by 55% with no significant reduction in sustained disability. In CARE-MS II, alemtuzumab therapy was associated with a 49% reduction in relapse rate and a 42% reduction in the risk of 6-month sustained disability, when compared with interferon beta-1a. Adverse events associated with alemtuzumab treatment in both trials included infusion-associated reactions, infections of mild-to-moderate severity, and subsequent autoimmune disorders (eg, immune thrombocytopenia, thyroid disorders).

Lymphocyte Counts and Efficacy Outcomes with Alemtuzumab

Based on a presentation by Per Soelberg Sørensen, MD, University of Copenhagen and Department of Neurology, Rigshospitalet, Copenhagen, Denmark.

Alemtuzumab selectively depletes B and T lymphocytes after each treatment course, with the cell counts reaching a nadir about 1 month after treatment.4,5 Within weeks after depletion, B cells start to repopulate, with mean values approaching the normal range about 3 months after a treatment course.5 T-cell reconstitution usually is slower, with mean CD4 and CD8 cell counts reaching the lower limit of normal within about 12 and 9 months, respectively, after treatment.7 Whether the rate and degree of lymphocyte repopulation after treatment with alemtuzumab was associated with a change in clinical disease activity was unknown. Therefore, Sørensen and colleagues6 performed an analysis to detect whether patterns of lymphocyte depletion or reconstitution were associated with disease activity in patients enrolled in the CARE-MS studies. Lymphocyte counts at months 1 and 13 (after initial treatment) and lymphocyte repopulation rates were compared with subsequent relapse rates and risk for 6-month sustained disability in all subjects. There was no significant difference between lymphocyte counts at months 1 and 13 among study participants who did or did not experience a subsequent relapse or accrual of sustained disability. There also was no significant difference in the calculated lymphocyte repopulation rates among patients who experienced a relapse or showed sustained disability as compared with those who did not. Thus, the rate of lymphocyte repopulation after alemtuzumab administration cannot be used to predict the return of clinical disease activity.

Evaluating the Immunogenicity of Alemtuzumab

Based on a presentation by Tjalf Ziemssen, MD, University Clinic Carl Gustav Carus, Dresden, Germany.

Anti-drug antibodies may reduce treatment efficacy in some patients with MS.

In both CARE-MS studies, alemtuzumab demonstrated superior efficacy over interferon beta-1a in patients with active RRMS over a span of 2 years.

Anti-alemtuzumab antibodies develop after treatment; therefore, Ziemssen and others7 investigated the effect of these antibodies on the efficacy and safety of alemtuzumab in patients enrolled in the CARE-MS I trial.

Screening for anti-alemtuzumab antibodies was accomplished in these treatment-naïve patients via enzyme-linked immunosorbent assay (ELISA) just prior to infusion and at 1, 3, and 12 months after each treatment course. If anti-alemtuzumab antibodies were detected, an assay was performed to assess for inhibitory antibodies, and a titer was determined. These values were then correlated with safety and efficacy data and total lymphocyte counts to determine an association.

In the course of this 2-year study, 87% of patients had detectable anti-alemtuzumab antibodies at least once, and 81% of patients also had at least one positive inhibitory antibody test. The highest proportion of patients with positive anti-alemtuzumab antibodies following the initial infusion was observed soon after treatment (months 1 and 3) and slowly declined until the second treatment was administered 1 year later. Identification of both binding and inhibitory antibodies was further increased (with higher peak titers) after the second treatment course of alemtuzumab, with the highest proportion of patients having a positive antibody test at month 13.

Although they were commonly detected, neither anti-alemtuzumab nor inhibitory antibodies were associated with significant changes in the annualized relapse rate, magnetic resonance imaging (MRI) outcome measures, or accrual of sustained disability over the 2-year study period. Further, antibody status did not affect the overall incidence of adverse effects or infusion-associated reactions during the study.

Infection Risk with Alemtuzumab in Patients with RRMS

Based on a presentation by Eva Havrdova, MD, Charles University in Prague, First Medical Faculty, Prague, Czech Republic.

Havrdova and colleagues8 studied infection risk in patients treated with alemtuzumab versus interferon beta-1a in the CARE-MS studies. Throughout both CARE-MS studies, safety assessments for infections, including the incidence, grade, relationship to study drug, and outcome, were recorded. Additionally, lymphocyte and neutrophil counts before and after treatment with alemtuzumab were investigated as possible predictors of infection risk following treatment. Of note, patients were ineligible for the CARE-MS studies if they had an active serious infection or were at high risk for a serious infection; if they were infected with human immunodeficiency virus (HIV) or hepatitis B or C virus; or if they had active tuberculosis, a history of fungal infection, or cervical human
papillomavirus positivity with a high-risk strain.\(^2,3\)

A total of 1,200 patients were included in this safety analysis. The frequency of infection was higher in the alemtuzumab-treated group than in the group that received interferon beta-1a (72.6% vs 56.8%, respectively). The majority of infections were mild to moderate in both groups, with 2.8% of the alemtuzumab cohort and 1.3% of the group given interferon beta-1a experiencing a serious infection (Table 1).\(^4\) The incidence of infection was highest during the first month after the first treatment with alemtuzumab and did not increase after the second treatment a year later.

Of note, herpetic infections were noted in 16% of the alemtuzumab group and only 2.8% of the interferon beta-1a-treated group. Beginning in late-2008, alemtuzumab-treated patients received prophylactic acyclovir starting on the first day of each treatment course and continuing for the following 28 days. The incidence of herpetic infections was lower in these patients than in those who did not receive prophylaxis (Figure 1).\(^5\) Finally, as lymphocyte counts were routinely monitored, patients who developed infections were not more lymphopenic than were those who did not.\(^6\)

### PEGINTERFERON BETA-1A

Over the past several years, interferon beta-1a has been one of the first-line immunomodulatory treatments for MS. Use of this immunomodulatory agent reduces the relapse rate, disease progression, and lesion burden in a subset of patients, but its efficacy and tolerability may be improved.

Pegylation, the process of attaching one or more molecules of polyethylene glycol to a therapeutic agent, can boost the stability, half-life, and efficacy of small-protein molecules like interferon beta-1a.\(^9\) Pegylation can also reduce renal clearance and protect the molecule from proteolytic degradation, so its circulation time is prolonged and half-life is extended—all of which may allow for less-frequent dosing.\(^10\) Lastly, pegylation can reduce the impact of receptor- and antibody-mediated clearance mechanisms and may also diminish antigenicity and immunogenicity.\(^11\)

Pegylated interferon beta-1a, or peg-interferon beta-1a, was developed by attaching a 20-kDa methoxy-peg-O-2-methylpropionaldehyde group to the alpha-amino group of the N-terminus of interferon beta-1a.\(^11\) It has now completed preclinical evaluations and phase 1 testing and currently is the subject of a 2-year randomized, phase 3 clinical trial known as ADVANCE. This ongoing, multicenter, double-blinded, parallel-group trial with a 1-year placebo-controlled period is designed to evaluate the safety and efficacy of peginterferon beta-1a injected SC once every 2 or 4 weeks in patients with RRMS. Study participants must be 18–65 years old, have a confirmed diagnosis of RRMS with an EDSS score ≤ 5, and have had at least two relapses within the preceding 3 years and at least one relapse within the preceding year.\(^9,12\)

The primary goal of the ADVANCE study is to determine the treatment efficacy of peginterferon beta-1a by measuring the change in the annualized relapse rate at 1 year. Secondary goals include determining the effect of peginterferon beta-1a on the total number of new or newly enlarging T2 hyperintense lesions on MRI, the proportion of patients with relapses, health-related quality of life, and sustained disability progression. Some of the key data from year 1 of the ADVANCE study are summarized below.

### Efficacy of Peginterferon Beta-1a

Based on presentations by Peter Calabresi, MD, Department of Neurology, Johns Hopkins University, Baltimore, Maryland, and Bernd Kieseier, MD, Department of Neurology, Heinrich-Heine University, Dusseldorf, Germany.

In terms of efficacy, the reduction in the annualized relapse rate with peginterferon beta-1a was statistically significant in both treatment groups (dosing every 2 weeks, 36%; dosing every 4 weeks, 28%) as compared with the placebo group.\(^11\) In terms of secondary endpoints, peginterferon beta-1a given either every 2 weeks or every 4 weeks significantly reduced the risk of relapse within 1 year when compared with the administration of placebo; like-

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**TABLE 1**

<table>
<thead>
<tr>
<th>Patients with infections, n (%)</th>
<th>Interferon β-1a, 44 μg (n = 389)</th>
<th>Alemtuzumab, 12 mg (n = 811)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related</td>
<td>36 (9.3)</td>
<td>303 (37.4)</td>
</tr>
<tr>
<td>Unrelated</td>
<td>212 (54.5)</td>
<td>503 (62.0)</td>
</tr>
<tr>
<td>Grade 1 (mild)</td>
<td>116 (29.8)</td>
<td>371 (45.7)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>172 (44.2)</td>
<td>480 (59.2)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>6 (1.5)</td>
<td>30 (3.7)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Grade 5 (fatal)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infections leading to treatment withdrawal, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infections leading to study discontinuation, n (%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Serious infections, n (%)</td>
<td>5 (1.3)</td>
<td>23 (2.8)</td>
</tr>
</tbody>
</table>

Source: Havrdova et al\(^8\)
wise, the active-treatment groups showed a significantly reduced risk of disability progression (38%) when compared with the group receiving placebo. A reduction in the number of new or newly-enlarging T2 hyperintense lesions was also seen in the every-2-week dosing group (67%) and every-4-week dosing group (28%) when compared with those receiving placebo. When given every 2 weeks, peginterferon beta-1a significantly reduced the number of new gadolinium-enhancing lesions and T1 hypointense lesions when compared with placebo administration.

In a post hoc analysis by Calabresi and colleagues, the proportion of patients deemed to be free of overall disease activity, as determined by the absence of clinical and radiologic disease activity over 48 weeks, was significantly higher in the every-2-week treatment group than in the every-4-week dosing group or the group given placebo.

In terms of disability, when compared with the placebo group, both active-treatment groups showed a statistically significant reduction of 38% over 48 weeks in the risk of 12-week sustained disability progression, as measured by the change in EDSS scores (more than a one-point increase in EDSS score in patients having an EDSS score ≥ 1 at baseline or a 1.5-point increase in EDSS score in patients with an EDSS score of 0 at baseline that was sustained over 12 weeks) in both treatment groups.13

**Immunogenicity of Peginterferon Beta-1a**

Based on a presentation by Joleen White, PhD, Principal Scientist, Biogen Idec Inc., Cambridge, Massachusetts.

The presence of neutralizing anti-drug antibodies may negatively impact the therapeutic efficacy of all immunomodulatory therapies. This phenomenon has been seen with interferon beta in three clinical studies, where the presence of neutralizing antibodies was associated with a reduction in the drug’s clinical and radiologic efficacy.14-16

The immunogenicity of peginterferon beta-1a and the impact of this immunogenicity on the safety, efficacy, and pharmacodynamics of the drug was determined in patients enrolled in the ADVANCE trial. Immunogenicity was assessed by evaluating for antibodies that bind to interferon beta-1a, neutralizing antibodies to interferon beta-1a, and antibodies that bind to polyethylene glycol. Overall, the incidence of binding antibodies, neutralizing antibodies, and anti-polyethylene glycol antibodies was low in both treatment groups, and the majority of treatment-emergent antibodies appeared to be transient.17 The presence of antibodies was not associated with adverse safety events or hypersensitivity reactions (although the analysis was limited by the low incidence of treatment-emergent antibodies). There also was no discernible impact of antibody status on efficacy as evidenced by the annualized relapse rate, MRI endpoints, or disability progression.

**MRI Results from the First Year of the ADVANCE Study**

Based on a presentation by Douglas Arnold, MD, Montreal Neurological Institute, McGill University, and NeuroRx Research, Montreal, Quebec, Canada.

Treatment with peginterferon beta-1a reduced the number of new or newly-enlarging T2 hyperintense lesions on brain MRI scans by 67% in the every-2-week dosing group and by 28% in the every-4-week dosing group at 48 weeks, both of which were statistically significant when compared with those given placebo.12,18 Additionally, peginterferon beta-1a given every 2 weeks significantly reduced the number of new T1 hypointense lesions, gadolinium-enhancing lesions, and new active lesions at 24 and 48 weeks when compared with placebo administration. Peginterferon beta-1a given every 4 weeks also significantly reduced the number of new active lesions when compared with the use of placebo at 24 and 48 weeks. The proportion of patients free of MRI disease activity at 48 weeks was significantly higher in both the every-2-week and every-4-week treatment groups as compared with the placebo cohort.

**Safety and Tolerability of Peginterferon Beta-1a**

Based on a presentation by Bernd Kieseier, MD, Department of Neurology, Heinrich-Heine University, Dusseldorf, Germany.

The overall incidence of adverse events in both peginterferon beta-1a treatment groups was 94% (compared with 83% in the placebo group), with most of these events being mild or moderate.19 The most frequent adverse events were erythema at the injection site, influenza-like illness, pyrexia, and headache (Table 2).19 Influenza-like illness was the most common adverse event leading to treatment discontinuation. There was no increased risk of serious infection or malignancy in the peginterferon beta-1a–treated groups or the placebo group.

Similar to the changes seen in hemato logic parameters with the use of unmodified interferon beta-1a, reductions in white blood cell counts were noted in patients treated with peginterferon beta-1a. Elevations in liver transaminase levels also occurred, but they were not associated with increases in hepatic adverse events.

**DACLIZUMAB HIGH-YIELD PROCESS**

Daclizumab high-yield process (DAC HYP) is a humanized monoclonal antibody that modulates interleukin 2 (IL-2)-receptor signaling by targeting the alpha chain (CD25) of the IL-2 receptor.20

The efficacy and safety of DAC HYP in adults with RRMS were evaluated in the SELECT trial,20 a 52-week, randomized, double-blind, placebo-controlled study. Patients were randomized to receive 150 or 300 mg of DAC HYP or placebo every 4 weeks for 52 weeks. A significant decrease in the annualized relapse rate, slowing of disability progression, and reduction in the number of new MRI lesions were noted among patients treated with DAC HYP as compared with the placebo group. Patients who completed the SELECT trial were eligible for SELECTION, a 52-week extension study.

**Reduction of Brain Atrophy with Extended Treatment with DAC HYP**

Based on a presentation by Ernst-Wilhelm Radue, MD, Medical Image Analysis Center, University Hospital Basel, Basel, Switzerland.

A retrospective study previously showed use of DAC HYP to reduce the rate of brain volume loss in patients with
RRMS. Radue and colleagues evaluated the rate of brain atrophy in patients who received 2 years of treatment with DAC HYP as part of the SELECT and SELECTION studies. During the first 6 months of the study, patients treated with DAC HYP (150 mg) showed a greater loss of whole-brain volume than those given placebo; this finding was considered to be secondary to pseudoatrophy, or reduced brain volume related to lessened inflammation-associated edema. This phenomenon of pseudoatrophy was thought to resolve by the end of year 1; however, patients receiving DAC HYP or placebo exhibited a similar rate of decline in brain volume at that point. During year 2, however, the percentage change in whole-brain volume was 27% lower in the DAC HYP treatment groups than in the placebo group at year 1 and 24% less than in the DAC HYP combined-treatment group at year 1.

These promising results showed that treatment with DAC HYP for 2 years may result in a reduction of brain atrophy in patients with RRMS. However, it would be helpful to correlate this finding with disability progression, quality of life, and cognitive outcomes to further determine its clinical relevance.

### TABLE 2
**ADVANCE Trial: Number and Frequency of Adverse Events in ≥ 10% of Patients in Each Treatment Group at Year 1**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (n = 500)</th>
<th>Peginterferon β-1a Every 4 weeks (n = 500)</th>
<th>Peginterferon β-1a Every 2 weeks (n = 512)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection-site erythema</td>
<td>33 (7)</td>
<td>282 (56)</td>
<td>315 (62)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>63 (13)</td>
<td>234 (47)</td>
<td>239 (47)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>76 (15)</td>
<td>218 (44)</td>
<td>228 (45)</td>
</tr>
<tr>
<td>Headache</td>
<td>165 (33)</td>
<td>204 (41)</td>
<td>224 (44)</td>
</tr>
<tr>
<td>Relapse of multiple sclerosis</td>
<td>159 (32)</td>
<td>111 (22)</td>
<td>96 (19)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>30 (6)</td>
<td>97 (19)</td>
<td>97 (19)</td>
</tr>
<tr>
<td>Chills</td>
<td>23 (5)</td>
<td>92 (18)</td>
<td>88 (17)</td>
</tr>
<tr>
<td>Injection-site pain</td>
<td>15 (3)</td>
<td>67 (13)</td>
<td>77 (15)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>38 (8)</td>
<td>70 (14)</td>
<td>68 (13)</td>
</tr>
<tr>
<td>Back pain</td>
<td>57 (11)</td>
<td>64 (13)</td>
<td>61 (12)</td>
</tr>
<tr>
<td>Injection-site pruritus</td>
<td>6 (1)</td>
<td>56 (11)</td>
<td>68 (13)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>77 (15)</td>
<td>69 (14)</td>
<td>53 (10)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>35 (7)</td>
<td>54 (11)</td>
<td>57 (11)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>49 (10)</td>
<td>55 (11)</td>
<td>51 (10)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>49 (10)</td>
<td>54 (11)</td>
<td>44 (9)</td>
</tr>
</tbody>
</table>

Source: Kieseier et al

### TRANSITIONING PATIENTS WITH RRMS TO IMMUNOMODULATORY THERAPY

With the ongoing development of new immunomodulatory therapies for MS, decisions about when and how to switch a patient’s medication are becoming increasingly complex. Additionally, the safety and efficacy of treatment escalation in patients who do not respond to first-line therapies have not been well established.

**FIRST Study**

Based on a presentation by Giancarlo Comi, MD, Department of Neurology, Vita-Salute San Raffaele University, San Raffaele Scientific Institute, Milan, Italy.

Comi and colleagues completed a post hoc analysis of patients enrolled in the Fingolimod Initiation and Cardiac Safety Trial (FIRST). This study compared the tolerability, efficacy, and safety of fingolimod, a once-daily oral sphingosine 1-phosphate receptor modulator, in patients given glatiramer acetate or any interferon-beta formulation during the preceding 6 months versus treatment-naïve patients. The three patient groups studied had received glatiramer acetate or interferon beta in the 6 months prior to the study or were treatment-naïve.

The calculated annualized relapse rate for each patient group during the 4-month study was lower than the calculated annualized relapse rate for that group in the year before the study, regardless of whether patients had been treatment-naïve or treated with interferon beta or glatiramer acetate. There were no significant differences in the overall incidence of adverse events or serious adverse events among the three groups.

This relatively short study evaluated only a limited subgroup of patients previously treated with disease-modifying therapy, but the authors concluded that fingolimod could be used as an effective and safe escalation therapy for patients previously treated with either interferon beta or glatiramer acetate. These results are useful, but a longer study with an additional control group and more complete information on the patients’ treatment history could be more informative.

**EPOC Trial**

Based on a presentation by Bruce Cree, MD, PhD, University of California, San Francisco, School of Medicine, San Francisco, California.

Cree and colleagues sought to describe patient- and physician-reported satisfaction after switching from first-line disease-modifying therapy to fingolimod. Specifically, an open-label phase 4 study (EPOC) evaluated patient-reported outcomes and physician-reported assessments in patients with relapsing forms of MS who switched to fingolimod versus remained on glatiramer acetate, the standard of care. All patients enrolled were deemed to be candidates for a therapy change if their physicians so identified them or if they evidenced poor tolerance or an inadequate response to standard disease-modifying therapy.

Patients were randomized to receive fingolimod or standard-of-care therapy with glatiramer acetate for 6 months. A post hoc analysis evaluated the change from baseline using the Treatment Satisfaction Questionnaire for Medication, the Beck Depression Inventory-II, the Fatigue Severity Scale, and the physician-assessed Clinical Global Impression of Improve-
ment. After 6 months of treatment, both patients and physicians believed that a switch to fingolimod provided benefit. In particular, the investigators found a significant improvement in patient treatment satisfaction, especially with regard to convenience and patient-perceived effectiveness.

**CONCLUSION**

Many of the posters presented at ECTRIMS 2013 highlighted the breadth of research dedicated to developing immunomodulatory therapies. Many studies featured drugs with novel mechanisms of action and alternative routes of administration for patients with RRMS. Ongoing research, data collection, and analysis will help to determine whether these new therapies are truly safe, effective, and ready for routine clinical use.

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