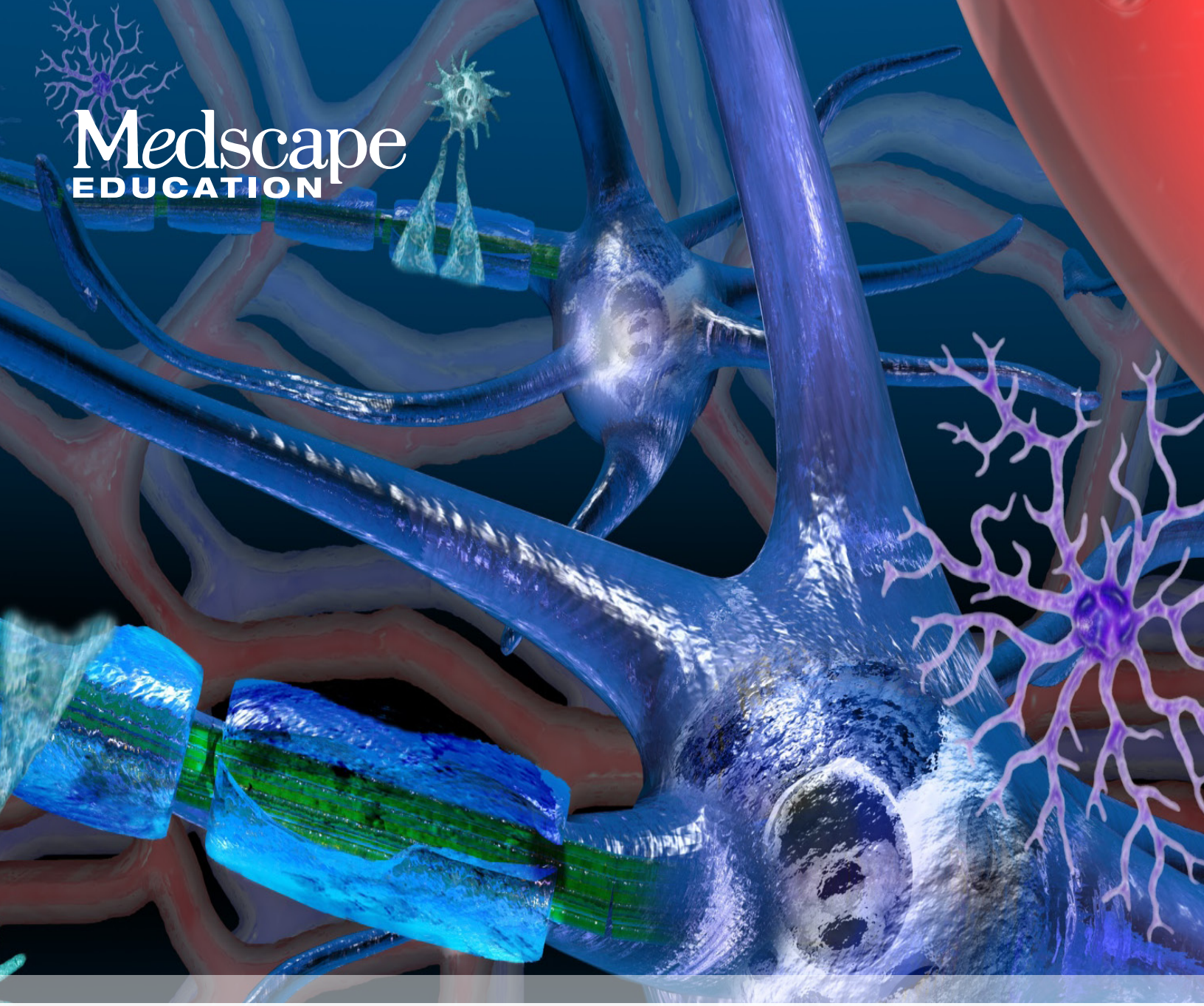

Medscape EDUCATION

Focus on Multiple Sclerosis Disease-Modifying Therapies From the 2013 Annual Neurology Meeting CME

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Focus on Multiple Sclerosis Disease-Modifying Therapies From the 2013 Annual Neurology Meeting

Editor's note:
This activity includes data that were presented in poster and platform sessions at the American Academy of Neurology Annual Meeting 2013. Such data should be considered preliminary until published in peer-reviewed journals.

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UPDATE ON INJECTABLE MULTIPLE SCLEROSIS THERAPIES

Benjamin M. Greenberg, MD, MHS: Hello. My name is Benjamin Greenberg. I am an assistant professor of neurology at UT Southwestern Medical Center in Dallas, Texas, where I serve as the deputy director of the Multiple Sclerosis Clinic. This year at the 2013 American Academy of Neurology (AAN) annual meeting there were a number of presentations and posters on the topic of therapeutic advances relative to multiple sclerosis (MS) that I would like to review.

One of the biggest issues in MS therapies today involves the switching of therapies from traditional first-line disease-modifying therapies to other first- or second-line therapies.

Teter and colleagues,[1] from the New York State MS Registry, presented the characteristics of relapsing-remitting multiple sclerosis (RRMS) patients who had switched first-line disease-modifying therapies. This poster provides insight into the reasons why patients switch, and what they switch to. Out of 944 patients, approximately 44% switched therapy over a period of 7.5 years. More than half of these patients, 238, switched because of perceived efficacy issues. Of these 238, more than half switched from one injectable therapy to another. Another 27% switched therapies because of tolerability or safety issues, and 16% switched for other reasons. More than 20% of patients added a concomitant therapy. Finally, more than 23% of patients switched from an injectable therapy to natalizumab. Over a mean period of 7.5 years, 28.4% of the patients switched because of relapses. Another 14% switched because of worsening disability.

The injectable therapies were highlighted at AAN in a variety of ways. The first was a presentation from Karmon and colleagues[2] from the Jacobs Neurological Institute of the State University of New York at Buffalo, that looked at the ability of first-year magnetic resonance imaging (MRI) data and clinical activity to predict long-term clinical responses to glatiramer acetate. These investigators looked at data from 148 patients who were beginning therapy with glatiramer acetate, comparing their baseline and 1-year MRIs to determine whether the 1-year MRI findings were predictive of ultimate disability. About one-third of patients had new T2 or gadolinium-enhancing lesions at the 1-year mark. Of these, there was no predictive impact on Expanded Disability Status Scale (EDSS) assessor outcome 1 to 5 years out of the study. Of note, one of the limitations of this study was the relatively small number of patients followed for 5 years--less than one-third of the patients. Although this study is discordant from others that have found that 1-year MRI can predict outcome over the first 5 years, the authors recognize that more prospective studies are needed to determine the ultimate value of early MRI screening relative to prognostics.

On the topic of interferons, Edan and colleagues[3] presented data from the long-term impact of early interferon treatment after a first clinical event suggestive of multiple sclerosis. These were data from the BENEFIT trial, which randomized patients to interferon β-1b versus placebo in a 2-to-1 fashion and followed them for 2 years. An extension study was then performed in which 61% of the original enrollees were followed for several more years. The maximum follow-up obtained was more than 8 years. The authors found that in the first 2 years there was a lower annualized relapse rate in the treated arm compared with the placebo arm. When looking at the extension study of years 3 through 8, the annualized relapse rate remained low in the early treatment group and was slightly lower than that seen among the delayed treatment group. This study supported the use of early intervention at the first sign of demyelinating disease and showed that early intervention may have long-term impacts. Of note in this study, more than 86% of the patients remained at a relatively low EDSS scale scores of 0 to 2.5 through the last study visit. This number is quite reassuring to patients because it suggests that treatment with a therapy, in this case interferon, leads to the overwhelming proportion of patients having relatively little disability over a long period of follow-up.

Changes in the way we prescribe disease-modifying therapies are imminent. One of the presentations from Khan and colleagues[4] at Wayne State University (Detroit, MI) summarized data from the GALA study, which looked at an alternate dosing regimen for glatiramer acetate. This study randomized more than 900 patients into a placebo-controlled trial comparing placebo and glatiramer acetate, 40 mg subcutaneously 3 times weekly. The study did not compare this dosing regimen with the traditional 20-mg daily dose of glatiramer acetate. The investigators found that the patients on 3-times-weekly dosing performed similarly to those in previous trials of glatiramer acetate. Specifically, the annualized relapse rate of patients was 0.33, compared with an annualized relapse rate of 0.5 for the placebo arm, representing a 34.4% reduction in the annualized relapse rate. Khan and associates[4] noted that we may be seeing the use of 3-times-weekly dosing of glatiramer acetate in the future, although it is unclear whether or not this dosing would need to be preceded by daily dosing. Further studies are underway.

Calabresi and colleagues[5] presented data around the safety and tolerability of a PEGylated form of interferon using an autoinjector device. This study, known as the ATTAIN substudy, looked at patients who had been involved in a placebo-controlled phase 3 study of PEGylated interferon β-1a in 2 different dosing regimens. One dosing regimen used 125 µg every 2 weeks, and the other regimen used 125 µg every 4 weeks in a subcutaneous injection. The ATTAIN study looked at the use of an autoinjector versus prefilled syringes and confirmed that there was a reduced annualized relapse rate for patients in both the twice-a-month and the once-a-month dosing regimens, using either the autoinjector or the prefilled syringe. This study highlights the fact that, in the future, we may see dosing changes, not just with glatiramer acetate but with the interferons as well.

Newer therapies were highlighted at the AAN meeting this year, one of which was daclizumab. Vollmer and colleagues[6] presented data from the SELECT trial examining the rate of daclizumab's effect on patient-reported outcomes. These health-related quality of life measures were followed during the SELECT trial, which was a placebo-controlled, double-blind, randomized trial looking at the use of daclizumab for RRMS. Two different doses were studied. Both showed an impact on annualized relapse rate with a reduction of 50% to 54%. Furthermore, there was a reduction of sustained accumulated disability in the daclizumab-treated group in the range of 43% to 57%, depending on the dose that was analyzed. Vollmer and colleagues[6] focused on patient-reported outcomes using a variety of scales, including the Short Form-12® Health Survey (Medical Outcomes Trust, Boston, MA)and Multiple Sclerosis Impact Scale-29. These patient-reported scales provide a quantification of the physical and psychological impact of MS. Vollmer and colleagues[6] found that daclizumab reduced the rate of relapses; however, they also found that, in patients who experienced a relapse while on daclizumab, the physical and psychological impact on their lives tended to be less than the impact seen in the placebo-treated group, suggesting that relapses on daclizumab are milder than they are among untreated patients.

Additional data about daclizumab were presented by Havrdova and colleagues.[7] The notion of disease-activity free status has been gaining momentum in the world of MS. Instead of comparing therapies just on their impact of relapse rate, a composite score based on relapse-free status, lack of sustained accumulated disability, lack of new T2 lesions, and lack of new gadolinium-enhancing lesions is used to assess the impact of a therapy on a patient's disease. In this placebo-controlled trial, 39% of daclizumab-treated patients were disease-activity free compared with 11% in the placebo arm.

Compare this with data presented by Hartung and colleagues[8] regarding the disease activity-free status of patients treated with alemtuzumab. These data were acquired from the CARE-MS II trial, which randomized patients to 2 different doses of alemtuzumab versus subcutaneous interferon β-1a. The study found that, over 2 years, 32.2% of patients treated with alemtuzumab fulfilled the criteria for disease activity-free status, compared with 13.6% of the patients treated with interferon. The subgroups of clinical and radiographic criteria and provide insight about the robust impact alemtuzumab has compared with interferon.

Finally, I would like to end by briefly mentioning data from the CARE-MS I and CARE-MS II trials regarding the safety and tolerability of alemtuzumab compared with subcutaneous interferon β-1a . These trials found that, in general, there was a higher rate of adverse events within the alemtuzumab treatment arm, including a higher rate of antibody-mediated thyroid disease,[9] and a higher rate of infections when compared with interferon.[10] The rates of serious infections were relatively low. Multiple strategies were suggested by the authors for tracking patients on interferon or alemtuzumab.

The 2013 AAN annual meeting provided a great deal of data about both existing and emerging therapies in MS. The presentations underscored the need for clinicians to stay abreast of the newest information, because the therapeutic options we will see over the next several years will be different from the ones we have had over the past decade.

UPDATE ON ORAL MS THERAPIES

Michael K. Racke, MD: Hello. I am Michael Racke, chairman of the department of neurology at the Ohio State University Wexner Medical Center in Columbus, Ohio. I would like to talk to you about some of the recent updates regarding oral agents in the treatment of MS.

As you know, in 2012 teriflunomide was approved for the treatment of MS, and it has been in use over the past year. Teriflunomide is related to the leflunomide molecule, and it works by inhibiting dihydroorotate dehydrogenase, an important enzyme in the synthesis of pyrimidine, which is used by the rapidly proliferating T cells and B cells that are thought to play a role in the pathogenesis of MS. At the 2013 AAN annual meeting, results were discussed regarding the TOWER clinical trial.[11] This, in many ways, was a similar trial design to the earlier TEMSO study, comparing the 7-mg and 14-mg doses of teriflunomide with placebo. However, in the TOWER study, there were no evaluations regarding MRI. As in TEMSO, the higher dose was much more effective, showing a 30% reduction in relapse rate. The higher dose also showed an inhibition of disability progression, which was not observed with the lower dose. As was true in TEMSO, teriflunomide continued to have a few issues related to effects on the immune response. Probably the biggest concern was that of autoimmune hepatitis and elevated liver enzymes. One of the other side effects that may affect the usage of this drug is hair thinning, or alopecia, which may be of concern to any patient, but perhaps especially so for women, who constitute about 75% of patients with RRMS.

The other oral drug in current use, fingolimod, continues to have a growing role in the care of patients with MS. There is ongoing concern about how to use fingolimod in conjunction with other medications. One of the situations where it is increasingly used is in patients who become JC virus (JCV) antibody-positive while on natalizumab and who switch to fingolimod as a way of continuing with a very active drug. In a study by Francis and colleagues,[12] one of the patients who made the transition from natalizumab to fingolimod developed progressive multifocal leukoencephalopathy (PML). It is unclear whether this was a result of the natalizumab, the fingolimod, or the combination of the 2 drugs. This is something that we, as neurologists, will continue to monitor in the future, particularly when we add more new drugs to our armamentarium, such as alemtuzumab, which has a very profound effect on CD4-positive T cells and their depletion. One of the things that we are going to have to evaluate going forward is not only the combination of drugs, but perhaps the order in which we use these medications. It will require a long period of time to accumulate the data we need to ensure we know how to use these drugs safely.

One oral drug that continues to generate a great deal of interest is dimethyl fumarate, or BG-12, which was approved by the US Food and Drug Administration shortly after the 2013 AAN meeting concluded. Dimethyl fumarate has been used in combination with monomethyl fumarate to treat psoriasis for almost 20 years in Europe, commonly in patients who failed on methotrexate and subsequently switched to this combination of fumaric acid esters. In those 20 years, there has been little concern regarding malignancy or opportunistic infections, so there is a lot of interest in the possibility of using a drug such as dimethyl fumarate, which appears to have a good safety profile in patients with MS. There is some gastrointestinal upset and flushing seen in patients when they first start taking the drug, but once the patient has grown accustomed to these effects, the drug seems to be fairly well tolerated.

The studies regarding BG-12, DEFINE and CONFIRM, were both published in the *New England Journal of Medicine* late in 2012[13,14] As was seen with teriflunomide, there appears to be a significant reduction in annualized relapse rate--almost 50%--with BG-12. Interestingly, there was a difference between the 2 trials with regard to the effects on disability progression. In CONFIRM, glatiramer acetate was used as an active comparator and essentially had an identical reduction in relapse rate to that seen in its prior phase 3 clinical trial.[14] Such results suggest that this MS patient cohort was similar to other trial cohorts in the past.

One of the other interesting things regarding BG-12 is its potential as a neuroprotective agent. No drugs currently used in the treatment of MS offer what we might call "primary neuroprotection," in which a neuron under stress would not synthesize proteins to promote its own apoptosis. There are some indications that BG-12 might have this property. That differs from how we think about neuroprotection in MS. One could argue that monoclonal antibodies such as alemtuzumab or natalizumab can be thought of as neuroprotective agents, because their potent anti-inflammatory effects result in less damage to the nervous system and therefore provide secondary neuroprotection.

There is a great deal of anticipation regarding role of dimethyl fumarate, now that it has been approved. Given the recent data presented at the 2013 AAN, clinicians should be optimistic about the growing use of oral agents in the treatment of patients with RRMS.

I am Michael Racke. Thanks for being with us today.

WOMEN, MEN, AND MS

Rhonda Voskuhl, MD: Hello. My name is Rhonda Voskuhl. I am a professor in the department of neurology at the University of California in Los Angeles (UCLA) and the director of the UCLA MS program. Today I am going to talk about an exciting poster session at the 2013 AAN that addressed issues related to pregnancy and hormonal influences in MS.

One of the exciting findings was that endogenous testosterone may have a protective effect in men with MS. Bove and colleagues,[15] from Harvard University examined testosterone levels and MS clinical outcomes in men with early RRMS. They found that 41% of 96 men with MS were hypogonadal, as defined by testosterone levels less than 300 ng/dL. Lower testosterone levels were associated with higher or worse EDSS clinical disability scores. Further, when patients were followed longitudinally for 2 years, the men with lower testosterone levels had greater declines in cognitive testing, as determined by the symbol digit modality test. Together, these data suggest that low testosterone levels in men with MS may be associated with more severe clinical disability. Based on this, further studies regarding testosterone supplementation in MS men may be warranted.

Pregnancy was another important topic during the AAN meeting. Although late pregnancy is known to be associated with decreased MS relapses and the postpartum period with increased relapses, the net effect of pregnancy on long-term disability has remained controversial. A new study by Teter and colleagues[16] followed patients from 17 sites in New York and assessed the effect of parity on long-term disability. Six-year assessment revealed that the parous group (n=1195) was significantly less likely than the nulliparous group (n=328) to reach EDSS scores of 6. To address a potential selection bias, whereby differences in disability at baseline might affect a woman's choice to become pregnant, the investigators also showed no differences in disability levels between groups at baseline. These data suggest a potential beneficial effect of parity on long-term disability in MS. However, pregnancy is a very complex situation, involving a decision whether to discontinue use of disease-modifying therapies. Extensive counseling is needed with MS patients before they get pregnant to properly manage their disease-modifying treatments.

A third important point that was brought up in several posters at the 2013 AAN was related to the safety of some of the newer disease-modifying therapies in MS. Given that MS affects women of childbearing age and these women are often on disease-modifying agents, natalizumab and fingolimod are being examined for their effects on pregnancy outcomes and congenital abnormalities. A pregnancy registry is currently ongoing to collect data from women with MS who were exposed to natalizumab at any time within 90 days before the first day of the last menstrual period or during pregnancy.[17] The rate of spontaneous abortion in this registry was consistent with that expected in the general US population. Various birth defects were observed in 30 of 356 prospective pregnancy registry cases. The types of congenital defects also were consistent with those observed most frequently in the general population. Final data will be available at a later date and will be very important in assessing the potential risk of natalizumab exposure during pregnancy.

A similar registry has recently been launched to prospectively collect safety data on maternal and fetal outcomes associated with exposure to fingolimodup to 8 weeks before the last menstrual period and during pregnancy.[18] Thus far, 16 women, 9 in the United States and 7 in the European Union, have been enrolled. Data from this registry will ultimately be important in assessing the potential risks of fingolimod exposure during pregnancy.

Such registries have been very important in the past in assessing the effect of interferon treatment and glatiramer acetate treatment on pregnancy risks. Future registries are also being planned for other new drugs, such as BG-12 and teriflunomide. Participation in and attention to these registries is critical in determining the safety of all of these drugs during pregnancy.

To summarize, there is a growing appreciation of the important roles of pregnancy and hormonal factors in MS. Research in this area is providing useful information that can help physicians and patients better manage the disease.

THE EVOLVING MS TREATMENT LANDSCAPE

By Michael K. Racke, MD

As we learned in the audio segments of this program, there are numerous developments on many fronts in the ongoing effort to improve treatment and outcomes for patients with MS. This brief article offers a broader look at the field as represented by presentations at the 2013 AAN, to anticipate new developments in the coming years and to place recent findings into a broader context.

Early Stage Drugs

The results of a phase 2, randomized, multicenter trial assessing the safety and efficacy of ocrelizumab in patients with RRMS were presented.[19] In the initial 24 weeks of the study, patients were randomized to placebo, high-dose (2000 mg) or low-dose (600 mg) ocrelizumab, or interferon β-1a. All patients then received ocrelizumab and were followed an additional 48 weeks for a total of 144 weeks of follow-up. At 144 weeks, patients still were not experiencing significant disease activity as evaluated by MRI. The significant effects of B-cell depletion by ocrelizumab on both relapse rate and MRI disease activity suggest that B cells play an important role in the pathogenesis of MS.

Data were also presented from the SELECT study, which evaluated 2 doses of daclizumab (300 mg or 150 mg subcutaneously) versus placebo in patients with RRMS.[20] Several markers of disease activity favored treatment with daclizumab over placebo, including no clinical activity, no radiological activity, and no relapses. There was a 50% reduction in the annualized relapse rate in daclizumab-treated patients and a significant reduction in disability progression. Of the 517 patients who went on to enter a second year of therapy in the SELECTION study, 88% were free of confirmed disability progression at the end of the second year of the study. These data suggest that interleukin-2 receptor blockade can have a significant effect on disease activity in MS.

Data were presented on several new sphingosine-1-phosphate (S1P) receptor modulators at various stages in early development. Results for siponimod (BAF312), a selective $S1P_1/S1P_5$ agonist, showed a 73% reduction in T2 lesions at 12 months for the 10-mg dose.[21] Results for ponesimod, a selective $S1P_1$ agonist, showed reductions in annualized relapse rate in a dose-dependent fashion.[22] The DreaMS study examined ONO-4641, a selective $S1P_1/S1P_5$ agonist, in a placebo-controlled, 26-week, phase 2 study[23] There was a reduction in gadolinium-enhancing lesions of 75% to 90% compared with placebo, depending on the dose of drug. Another $S1P_1$ agonist, RPC1063, is also undergoing phase 1 clinical trials.[24] All of these studies suggest that S1P receptor modulators can have beneficial effects on various measures of inflammatory activity in MS.

Therapies in Late Development

Data from the open-label, 1-year extension trial of ALLEGRO, which used laquinimod, 0.6 mg/day, in the treatment of RRMS, were presented at the 2013 AAN.[25] Most (97%) of the patients who completed ALLEGRO (laquinimod n=423; placebo n=419) entered the open-label extension. In ALLEGRO, oral administration of laquinimod was found to reduce both relapse rate and disability progression.[26] As in other clinical trials, patients who received daily laquinimod during the 2-year double-blind phase and who continued throughout the 1-year extension had less disease progression than did placebo-treated patients who then switched to the active drug; 88.2% of the early-start patients were disease progression-free compared with 84% of delayed-start patients who were disease progression-free. This demonstrates the important principle of initiating disease-modifying therapy as early as possible in patients with MS. No additional unexpected safety concerns occurred during year 3. One patient suffered a myocardial infarction and one patient committed suicide during the extension.

Three-year follow-up results were presented from the CARE-MS studies.[9,10] During these 2-year phase 3 trials, patients were allocated to alemtuzumab (12 mg/d for 5 days in year 1 and 12 mg/day for 3 days in year 2) or to interferon β-1a, 44 µg 3 times weekly. In both studies, alemtuzumab was shown to produce a significantly reduced annualized relapse rate in comparison with the interferon arm. CARE-MS II also showed that alemtuzumab demonstrated a beneficial effect on disability.[27] During year 3, patients from both CARE-MS trials were entered into the open-label extension in which all patients were followed and offered retreatment with alemtuzumab if indicated. Patients allocated to alemtuzumab in CARE-MS I experienced an annualized relapse rate of 0.22 in year 1, 0.12 in year 2, and 0.24 in year 3. Similarly, those in CARE-MS II had an annualized relapse rate of 0.28 in year 1, 0.25 in year 2, and 0.25 in year 3. Adverse events were similar across the 3-year combined studies except for thyroid events, which occurred more frequently during year 3. During the extension, approximately 80% of patients did not require retreatment with alemtuzumab. These results demonstrate that the beneficial effects on annualized relapse rate persist through year 3.

Approved Therapies

Data presented at this meeting analyzed results from both the DEFINE and CONFIRM studies, which examined the use of BG-12. In both studies, which involved patients with RRMS, BG-12 significantly reduced relapse rates and improved MRI outcomes.[28] Fox and colleagues[29] presented data demonstrating that a significant reduction in relapse rate occurred at 12 weeks for patients on BG-12 in comparison with placebo. Serious infections did not appear to be observed over the other cohorts in patients receiving BG-12.[30] In addition, BG-12 appeared to be efficacious in RRMS patients previously treated with an immunomodulatory agent[31] In the analysis of patient subgroups, BG-12 appeared to favor patients with younger age and a lower baseline EDSS, suggesting a more favorable effect in patients with a more inflammatory profile. The DEFINE and CONFIRM cohorts have entered a 5-year extension study called ENDORSE. In this trial, RRMS patients receiving BG-12 will remain on the same dose of BG-12 and patients who were on glatiramer acetate or placebo will be randomized to either 2-times-daily or 3-times-daily dosing of BG-12.

Use of fingolimod resulted in a consistent reduction in brain volume loss compared to interferon β-1a in 3 clinical trials, FREEDOMS, FREEDOMS II, and TRANSFORMS (reductions of 36%, 33%, and 31%, respectively).[32]Fingolimod also demonstrated reduced disability progression in both FREEDOMS studies.[33] In patient subgroup analyses, fingolimod reduced annual relapse rate regardless of patient characteristics or disease severity.[34] In long-term follow-up for patients enrolled in the extension of FREEDOMS II, there were few reports of bradycardia (2 in the group who switched from placebo to the 0.5-mg dose of fingolimod and 1 in the group who switched from placebo to the 1.25-mg dose).[35]

One of the patient populations using fingolimod includes those who switch from natalizumab, particularly those patients receiving natalizumab who become anti-JCV antibody-positive. The ENIGM observational study involved 198 patients from 36 tertiary care centers in France who were on natalizumab for a mean duration of 30 months and who were switched to fingolimod[36] The study demonstrated that 40% of patients switched due to JCV positivity and 30% due to efficacy or intolerance issues. There was an increased risk of relapse for patients who waited for a 6-month washout period before starting on fingolimod compared with those that waited 3 to 6 months or less than 3 months (58% vs 29% vs 19%, respectively). Interestingly, a higher risk of relapse was detected in patients who switched to fingolimod due to concerns regarding natalizumab efficacy or intolerability.

As mentioned in the audio segments of this program, results from the TOWER study were presented; those results are briefly summarized again here. In TOWER, teriflunomide (7 mg or 14 mg) was compared with placebo in patients with RRMS.[11] Both the 7-mg and 14-mg doses showed a significant reduction in annualized relapse rate (22.3% vs 36.3%, respectively). Although the higher dose showed a significant reduction in disability progression (31.5 %), the lower dose did not show a significant reduction in this measure. Adverse events that were more common in the teriflunomide treatment groups compared with placebo included headache, nausea, liver enzyme increases, and hair thinning. A major difference between the TOWER and TEMSO studies was that TOWER did not have imaging outcomes, whereas TEMSO showed a significant reduction in MRI evidence of disease activity.[37]

Results of the STRATIFY-1 study, measuring anti-JCV antibodies, were also presented at the 2013 AAN meeting.[38]The original assay found 47% of RRMS patients were JCV antibody-positive, and a second-generation assay found 52% of patients were JCV antibody-positive. In addition, 56% of the patients who were on natalizumab and who tested anti-JCV positive switched their treatment; 60% of those who did changed from natalizumab to fingolimod.

Patients with natalizumab-associated PML are typically diagnosed because of symptoms of PML, although 7% of patients are diagnosed by MRI and the presence of JCV DNA in the cerebrospinal fluid when they are asymptomatic. Those patients with asymptomatic PML had a 100% survival rate (n=21), whereas only 76.5% (228/298) with symptomatic natalizumab-associated PML survived.[39] Another interesting factor regarding PML risk in MS patients appeared to be lower body mass, which was associated with higher natalizumab concentrations and higher very late antigen-4 lymphocyte saturation.[40]

The ADVANCE study examined the usage of PEGylated interferon (PEGinterferon) β-1a in a multicenter, randomized, double-blind, placebo-controlled study in 1512 patients with RRMS.[41] PEGinterferon β-1a was given either every 2 weeks or every 4 weeks and resulted in significant reduction in relapses (39%), disability progression (38%), and gadolinium-enhancing lesions (86%) compared with placebo. Incidence of neutralizing antibodies to peginterferon β-1a was less than 1%.

The GALA study was a multicenter, randomized, double-blind, placebo-controlled trial comparing subcutaneous glatiramer acetate, 40 mg 3 times weekly, and placebo.[4] Glatiramer acetate reduced the annualized relapse rate by 34.4% and reduced gadolinium-enhancing lesions by 44.8%. Although this study showed that reducing the frequency of glatiramer acetate injections maintained its therapeutic effect, it is unclear whether this reduction will have a significant effect on the injection site complications (particularly lipoatrophy) during long-term use of the drug.

Data were also presented on the 7-year extension of CombiRx, which compares the combination of interferon β-1a and glatiramer acetate with each of the drugs individually. At the end of the trial, 84% of patients entered into the extension. Protocol-defined exacerbations were 0.09 relapses per year for the glatiramer acetate group, 0.10 relapses per year for glatiramer acetate plus interferon group, and 0.13 relapses per year for the interferon-only group.[42] Although the combination was not found to be superior to either of the treatments alone, the results of GALA confirm that both of these agents continue to be highly efficacious.

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Abbreviations
AAN = American Academy of Neurology
ADVANCE = Efficacy and Safety Study of BIIB017
ALLEGRO = Assessment of Oral Laquinimod in Preventing Progression in Multiple Sclerosis
ATTAIN = A Dose-Frequency Blinded, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of PEGylated Interferon Beta-1a (BIIB017) in Subjects With Relapsing Multiple Sclerosis
BENEFIT = Betaseron/Betaferon in Newly Emerging Multiple Sclerosis for Initial Treatment
CARE-MS = Comparison of Alemtuzumab and Rebif Efficacy in Multiple Sclerosis
CombiRx = Combination Therapy in Patients With Relapsing-Remitting Multiple Sclerosis
CONFIRM = Comparator and an Oral Fumarate in Relapsing-Remitting Multiple Sclerosis
DEFINE = Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting Multiple Sclerosis
DREAMS = Drug Research Evaluation for Multiple Sclerosis
EDSS = Expanded Disability Status Scale
ENIGM = Enquete Nationale Concernant l'Introduction du Fingolimod en Relais au Natalizumab
FREEDOMS = Fingolimod in Patients With Relapsing-Remitting Multiple Sclerosis
GALA = Glatiramer Acetate Low-Frequency Administration
JCV = JC virus
MRI = magnetic resonance imaging
MS = multiple sclerosis
PEGinterferon = PEGylated interferon
PML = progressive multifocal leukoencephalopathy
RRMS = relapsing-remitting multiple sclerosis
S1P = sphingosine-1-phosphate
SELECT = Safety and Efficacy Study of Daclizumab HYP to Treat Relapsing-Remitting Multiple Sclerosis
SELECTION = Safety and Efficacy Extension Study of Daclizumab High Yield Process (DAC HYP) to Treat Relapsing-Remitting Multiple Sclerosis
STRATIFY = JCV Antibody Program in Patients With Relapsing Multiple Sclerosis Receiving or Considering Treatment With Tysabri
TEMSO = Teriflunomide Multiple Sclerosis Oral
TOWER = Teriflunomide Oral in People With Relapsing Multiple Sclerosis
TRANSFORMS = Trial Assessing Injectable Interferon versus FTY720 Oral in Relapsing-Remitting Multiple Sclerosis
UCLA = University of California – Los Angeles

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