Growing research in the fast-evolving field of multiple sclerosis (MS) has led to better insights into the pathophysiology of the disease and advances in available treatment options. However, our understanding of the disease remains incomplete. As new information becomes available, controversies concerning optimal management strategies arise. Precise biomarkers that can better predict the disease course and response to treatment and that provide more sensitive outcome measures for clinical studies are critically needed. In addition, studies that are better designed, that take into account the heterogeneity of progressive MS, that evaluate novel therapeutics aimed at countering specific disease mechanisms, and that use more sensitive outcome measures are in great demand. Until the available treatment options.

At an interactive Controversies in the Treatment of Multiple Sclerosis session held during the joint 28th Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC) and the 19th Annual Meeting of the Americas Committee for Treatment and Research in Multiple Sclerosis, experts took sides in discussing important controversies that face neurologists treating patients with multiple sclerosis (MS). Participants discussed continuation of disease-modifying therapies (DMTs) in cases of secondary progressive MS. In addition, they debated whether oral or self-injectable DMTs should be used as first-line therapy of relapsing MS and whether the toxicity of alemtuzumab may limit its widespread use in MS patients. In addition, these experts pinpointed subjects for future research.

Abstract
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At an interactive Controversies in the Treatment of Multiple Sclerosis session held during the joint 28th Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC) and the 19th Annual Meeting of the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) in Dallas, Texas, four Veterans Administration (VA) experts in the management of MS provided arguments for and against taking sides in three controversies. They included Dennis Bourdette, MD, of the Oregon Health and Science University Multiple Sclerosis Center and Co-Director of the VA Multiple Sclerosis Center of Excellence–West in Portland, Oregon; Michael Carrithers, MD, of the William S. Middleton Memorial Veterans Hospital, in Madison, Wisconsin; Olaf Stüve, MD, PhD, of the VA North Texas Health Care System in Dallas, Texas; and Mitchell Wallin, MD, of the Washington DC VA Medical Center in Washington, DC, and Baltimore VA Medical Center in Baltimore, Maryland.

During this interactive session, the audience participated in polls and discussions. The panel took on discussions about whether disease-modifying therapies (DMTs) should continue in cases of secondary progressive MS (SPMS), whether oral DMTs should replace self-injectable drugs as a first-line strategy for treating relapsing forms of MS, and whether alemtuzumab is too toxic for use in most MS patients. In addition, these experts identified directions of future research.

■ SHOULD DMTs BE STOPPED IN PATIENTS WITH SPMS?

Based on a presentation by Michael Carrithers, MD, and Olaf Stüve, MD, PhD.

To introduce this debate, the chair, Dr. Bourdette, described a 55-year-old man who initially was diagnosed with relapsing-remitting MS (RRMS) and treated with interferon β-1a. This patient now is transitioning to SPMS without evidence of relapse or findings on magnetic resonance imaging (MRI). An audience poll revealed that 56% of attendees favored a change to another therapy.

Study Population Demographics

Influence Outcomes of SPMS Clinical Trials: Importance of Patient Age and Time Since Disease Onset/Transition to SPMS

Dr. Stüve proposed that DMTs should be stopped in patients who once had relapsing disease and now clearly have SPMS. However, there is no finite, universally accepted strategy for this practice because of the inconsistency of data from studies of the efficacy of DMTs in SPMS patients. In Dr. Stüve’s experience, patients who transitioned to SPMS several years ago and who have no evidence of relapses or MRI activity have not benefitted from continuing therapy. After describing large-scale studies that evaluated the use

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of DMTs in patients with SPMS and their conflicting results, he went on to propose the reasons for this discrepancy.

In 1998, the European multicenter trial on alternate-day dosing with interferon β-1b versus placebo in patients with SPMS showed a significant delay in time to confirmed progression of disability in the active treatment arm. Two years later, the North American Study Group released results on the use of two doses of interferon β-1a versus placebo. No treatment benefit was seen in terms of time to confirmed progression of disability. Both dosing regimens elicited significant benefit in terms of relapse- and MRI-related outcomes, which was consistent with the outcomes of earlier clinical trials.

According to Dr. Stüve, the European study involved younger patients with a more recent onset of MS (7-year difference in average time since disease onset) and transition to SPMS (3-year difference in average time to onset of progression between the two studies). The baseline Expanded Disability Status Scale (EDSS) scores in the two studies were similar. In his opinion, these studies had different outcomes because the study populations differed in age, along with time since onset of MS and progression to SPMS. He proposed that DMTs were more likely to work in younger patients with a more recent onset of MS and transition to SPMS. Thus, the demographics of the patient population are an important consideration in interpreting studies of drug treatments for patients who have transitioned to SPMS.

**A Role for Interferon β-1a in SPMS?**

In 2001, the SPECTRIMS study group examined the effect of interferon β-1a therapy in patients with SPMS. This multicenter study involved 22 centers in Europe, Canada, and Australia. The results failed to show a significant impact on time to sustained progression of disability. Subgroup analyses suggested maximal benefit among women and patients still experiencing relapses when treatment was started. Thus, interferon β-1a treatment for such patients is reasonable.

In the IMPACT trial of interferon β-1a versus placebo, the primary outcome measured was the Multiple Sclerosis Functional Composite (MSFC), which consists of quantitative tests of ambulation (Timed 25-Foot Walk), arm function (Nine-Hole Peg Test), and cognition (Paced Auditory Serial Addition Test). The change in MSFC was significantly smaller in the active treatment arm; however, no significant effect on EDSS scores was observed in the IMPACT study. Thus, the EDSS may not be a particularly sensitive measure of disability, and other large-scale studies are needed to explore the utility of the MSFC as an outcome measure in SPMS.

**Treatment of Progressive MS with Mitoxantrone**

A multicenter, randomized, double-blind, placebo-controlled trial that examined the use of mitoxantrone in patients with SPMS and progressive relapsing MS resulted in regulatory approval of the drug for progressive MS. The MIMS trial compared 5 and 12 mg/m² of mitoxantrone with placebo. Only results among patients given the higher dose were significant. The preplanned ordered analyses of each of the five components of the composite outcome showed significant treatment effects for change in EDSS score, change in ambulation index, number of relapses treated with corticosteroids, time to first relapse, and change in standardized neurologic status.

According to Dr. Stüve, however, these results should be viewed cautiously, since the cohort was not made up solely of SPMS patients but also included those with worsening RRMS. When compared with participants in other studies, the subjects were younger and more recently diagnosed; further, they had an average EDSS score of only 4.5 and more evidence of relapses. The study population appeared to have “active MS” and not “burned-out” disease. Few practitioners disagree with using DMTs when clinical or radiologic evidence of inflammation is present. However, whether or not the SPMS patient who is showing no evidence of inflammation should be treated remains controversial.

**Analysis of Opposing Conclusions**

The conflicting outcomes of these clinical trials reflect fundamental important differences in patient cohorts. On average, patients in the European and MIMS trials were younger, were less likely to be free of exacerbations, and had a more recent onset of MS symptoms and SPMS. Therefore, the effects of interferon therapy, as measured by the EDSS, are more readily demonstrable in early SPMS, when exacerbations are commonly superimposed on gradual progression of disability.

Consistent with this interpretation, the National Institute for Clinical Excellence in the United Kingdom recommended that approval of interferon β-1b as a treatment option for patients with SPMS without superimposed relapses be withdrawn. Hence, these patients are a heterogeneous group, and better-designed clinical trials that account for SPMS patients with and without clinical and radiologic evidence of inflammation are needed. All clinical trials conducted so far have included SPMS patients who have relapses. It is difficult to draw conclusions about best management strategies in SPMS patients who have no relapses or MRI activity (burned-out disease). More sensitive measures of disability than EDSS, such as the MSFC as suggested by the IMPACT trial, should be explored.

Thus, in the absence of convincing evidence, Dr. Stive believes that there is no role for DMTs in treating the SPMS patient who has progressed for several years and who has no clinical or radiologic evidence of inflammation.
years and who has no clinical or radiologic evidence of inflammation, since these drugs have no proven benefit in SPMS but do have side effects. Instead, these patients should undergo frequent clinical and radiologic monitoring, and DMTs should be restarted if relapse or new MRI activity is observed. In the absence of sufficient evidence of efficacy, and given the potential for side effects, continuation of therapy to prevent the patients from feeling abandoned is not justified.

However, Dr. Carrithers argued for continuing the use of DMTs in SPMS patients. He agreed that the label of “SPMS” is a heterogeneous entity, and there is almost uniform consensus among practitioners about continuing treatment in SPMS patients who show evidence of ongoing relapses or MRI activity. Nevertheless, more sensitive outcome measures for assessing disease activity in these patients are needed, especially because opportunities exist for studying potential neuroprotective and repair agents. Although the trials in SPMS patients have yielded conflicting results, the IMPACT trial did confirm a significant effect on the MSFC score, which may be more revealing than changes in the EDSS score.

Interestingly, no large studies have investigated the effect of stopping DMTs in SPMS patients who are already on therapy. One small study from Finland looked at the effect of discontinuing subcutaneous (SC) interferon β-1a, 44 µg three times a week, in 21 SPMS patients. Discontinuation of SC interferon β-1a after 12 months of treatment resulted in a significant increase in both EDSS scores and the volumes of cerebral T2- and T1-weighted lesions on MRI. Systematic trials in larger populations are needed to further study the effects of continuing or stopping DMTs in SPMS patients.

Summary

Overall, the experts agreed that the heterogeneous nature of the SPMS cohort confounded the results of existing studies. In addition, better-designed studies must examine SPMS patients with no relapses or MRI activity as a separate entity from SPMS patients with clinical or radiologic evidence of ongoing inflammation. Traditional DMTs should be given to SPMS patients who relapse or have MRI activity. More sensitive outcome measures than the EDSS score and better study designs incorporating precise SPMS definitions are needed, and more information about the effects of ending the use of DMTs is vital. Until more convincing data become available, the decision of whether or not to treat SPMS in the absence of clinical or radiologic activity remains at the physician’s discretion on a case-by-case basis, taking into account the patient’s wishes.

FIRST-LINE ORAL OR PARENTERAL DMTs IN RELAPSING MS?

Based on a presentation by Mitchell Wallin, MD, and Michael Carrithers, MD.

Dr. Bourdette described the case of a 28-year-old woman with newly diagnosed MS. Two years earlier she noticed her first symptoms of numbness and tingling from the waist down; the symptoms resolved spontaneously, and no workup was done. More recently, she developed left optic neuritis with a subsequent return of vision to baseline. Physical examination was remarkable for a left afferent pupillary defect and a mild decrease in vibration in her toes. Her brain MRI showed six T2 lesions and a single gadolinium-enhancing lesion. She was willing to consider both oral and injectable DMTs. About half of the audience was in favor of starting oral DMTs for this patient.

The Case for Oral DMTs

Dr. Wallin advocated for starting oral agents as first-line therapy in newly diagnosed RRMS patients. He based his argument on the superior efficacy, better adherence, and patient preference for oral therapy observed in clinical trials of these agents. It is a good strategy to start treatment early and more aggressively, since patients who experience more early relapses are more likely to progress. In clinical trials, oral DMTs have the same or better efficacy as injectable agents in terms of relapse rate, MRI activity, and disability. The deciding factor, in his opinion, is better adherence with oral agents.

Dr. Wallin cited the results from a retrospective cohort study that analyzed pharmacy claims from Medco Health Solutions, Inc, for patients who began using DMTs between October 2010 and February 2011.11 Initiation was defined as no prescription fills over the previous 12 months. Patients who had not received a DMT prescription during the 12 months before the index date were considered treatment-naïve users. Compliance was measured by the proportion of days covered and medication possession ratio for 12 months post index. Discontinuation was defined as a 60-day gap of index DMT. Patients started on fingolimod therapy were more compliant and less likely to discontinue treatment than were patients who started using self-injected DMTs, and they also tended to discontinue therapy later.

Use of injectable DMTs has been linked to flu-like symptoms (chills, 19% with interferon β-1a), injection-site reactions (2%–49% with glatiramer acetate; 3%–92% with interferon β-1a), and lipatrophy (< 2% with glatiramer acetate). Among oral DMTs, treatment with fingolimod has been associated with adverse cardiovascular effects (hypertension, 6%; bradycardia, 4%) and macular edema (0.4%).12–17 Teriflunomide therapy poses the risk of elevated liver enzyme levels (12%–14%) and hair thinning (13%) and requires the use of contraception if the patient is of child-bearing age.18–19 Use of dimethyl fumarate presents issues with tolerance—principally flushing (40%), rash (8%), and gastrointestinal symptoms (abdominal pain, 18%; diarrhea, 14%; nausea, 12%).20 However, few long-term safety data for oral DMTs are available.

In general, patients with RRMS should be treated on a case-by-case basis, with consideration for their unique characteristics and preferences. Dr. Wallin argued that oral DMTs often are the preferable therapeutic option in terms of adherence, side-effect profile, and efficacy.

The Case Against Oral DMTs

Dr. Carrithers argued against the use of oral DMTs for first-line RRMS therapy. Injectable DMTs are considered to be first-line agents by insurance companies, and a
less-expensive generic form of glatiramer acetate may soon be available. Over 20 years of safety data have shown that serious side effects rarely occur with the use of injectable DMTs. Furthermore, some patients prefer receiving once-weekly interferon β-1a injections compared with swallowing oral medications once or twice a day. Once pegylated interferon becomes available, the frequency of injections will be reduced to once every 14 days.22 [Editor's note: peginterferon β-1a was approved August 15, 2014, by the US Food and Drug Administration (FDA) for the treatment of patients with relapsing forms of MS.] Oral agents, especially dimethyl fumarate, have serious tolerability issues that must be considered. Dr. Carrithers concluded that given their proven safety, cost, availability, and side-effect profile, injectable DMTs remain good first-line agents for RRMS patients.

Members of the audience brought up the idea of starting with the least effective but safest DMT and escalating therapy, if needed. Slightly more than one third of the audience favored the use of oral agents as first-line therapy for most patients with RRMS.

Summary

With the emergence of oral agents, more options are available for first-line MS therapy. Physicians should prescribe treatment depending upon the drug’s safety profile, tolerance, efficacy, and cost, along with individual patient characteristics and preferences.

IS ALEMTUZUMAB TOO TOXIC FOR USE IN MOST PATIENTS WITH MS?

Based on a presentation by Olaf Stüve, MD, PhD, and Mitchell Wallin, MD.

Alemtuzumab is a recombinant humanized monoclonal antibody that targets CD52, a cell-surface glycoprotein present on all T and B lymphocytes, monocytes, and eosinophils; importantly, it is not found on hematologic precursors. It is currently approved in the United States for the treatment of B-cell chronic lymphocytic leukemia. In December 2013, the FDA rejected Genzyme’s bid to market alemtuzumab under the trade name Lemtrada for use in the treatment of MS, citing the lack of double-blinding in the CARE-MS I and CARE-MS II trials and safety concerns. Alemtuzumab is approved in Europe, Canada, Australia, and parts of Central and South America for the treatment of RRMS. On May 30, 2014, Genzyme resubmitted its supplemental Biologics License Application (sBLA) to the FDA seeking approval of the drug for the treatment of relapsing forms of MS, based on data from the same clinical studies as well as supplemental analyses and additional information to address the issues previously raised by the FDA. The sBLA was accepted by the FDA for review in June 2014.

Alemtuzumab was compared with interferon β-1a as first-line therapy for active RRMS in one phase 2 study and two phase 3 studies.23–25 The phase 2 trial, CAMMS-223, limited disease duration to 3 years from onset. The duration was extended to 5 and 10 years for the phase 3 studies, CARE-MS I and CARE-MS II, respectively. For CAMMS-223 and CARE-MS I, patients’ EDSS scores could not exceed 3.0. In CARE-MS II, the limitation was extended to an EDSS score of 5.0. For inclusion in the clinical trials, patients with RRMS had to have experienced at least two clinical relapses over the preceding 2 years. In the CAMMS-223 trial, patients also had to have gadolinium-enhancing lesions on one of up to four baseline scans performed 1 month apart. For the phase 3 studies, MRI disease activity was not a criterion for inclusion in the trials.

The alemtuzumab infusion-associated syndrome experienced by nearly all patients precluded double-blinding. It was decided that a “blinded rater” who was unaware of the treatment assignments in the three clinical trials would be used to assess efficacy outcomes, as advocated by the American Academy of Neurology.26 This step had major repercussions, culminating in the FDA’s decision in late 2013 not to license use of the drug in RRMS.

Efficacy Results

In all three randomized clinical trials, alemtuzumab significantly reduced the risk of clinical relapse when compared with interferon β-1a—by 69%, 55%, and 49% in CAMMS-223, CARE-MS I, and CARE-MS II, respectively.23–25 Alemtuzumab also appeared to reduce the risk of accumulation of significant disability when compared with interferon β-1a, but the evidence was less convincing than for the reduction in relapse rate. In CAMMS-223 and CARE-MS II (the phase 3 trial in “treatment-experienced” patients), treatment with alemtuzumab resulted in 71% and 42% fewer patients, respectively, who acquired fixed disability during the trial. In CARE-MS I, fewer alemtuzumab-treated patients accumulated disability than did those who used interferon β-1a, but the difference was not statistically significant. One explanation for this discrepancy is that some of the patients in CARE-MS I had benign disease. From prior experience, 20% of patients on interferon β-1a would have a 6-month disability event; however, only 11% met this criterion. Hence, alemtuzumab may improve disability. In CAMMS-223 and CARE-MS II, not only did alemtuzumab therapy lead to fewer people developing fixed disability, but the mean disability of alemtuzumab-treated patients actually improved over 3 and 2 years of treatment, respectively.

Safety

Some of the potential adverse effects of alemtuzumab, such as infusion reactions and increased risk of infection, malignancy, and other autoimmune diseases, could be life-threatening. Altogether, 23% of alemtuzumab-treated MS patients in CAMMS-223, 18% of those in CARE-MS I, and 16% of those in CARE-MS II developed thyroid disorders, and there was a small, albeit significant, risk of developing immune thrombocytopenic purpura (3%) or Goodpasture’s syndrome (0.5%) in the pivotal clinical trials. There has been one fatality due to immune thrombocytopenic purpura, two cases of Goodpasture’s syndrome requiring renal transplantation, and one fatal case of Burkitt’s lymphoma, along with a clustering of thyroid cancer cases. The thyroid-related side effects usually are easily manageable. However, immune thrombocytopenic purpura and
Owing to its risk profile, however, it will be able to patients with refractory disease. Dr. Wallin added to the therapeutic options available for treating relapsing MS, alemtuzumab will add more aggressive therapies (e.g., long-term corticosteroid therapy and treatment with cyclophosphamide and rituximab), which could produce additional side effects. Unfortunately, validated biomarkers to identify patients at risk for developing alemtuzumab-associated autoimmunity are lacking.27

Discussion

At the joint CMSC/ACTRIMS meeting in Dallas, Dr. Stüve supported the approval of alemtuzumab as a therapeutic alternative to natalizumab in patients with refractory RRMS. The basis for considering any therapeutic option, he argued, is its efficacy-to-safety ratio. In his opinion, alemtuzumab has superior efficacy and an acceptable safety profile for patients with aggressive MS. He also suggested that it could be used as induction therapy, followed by treatment with safer DMTs.

Dr. Wallin made the case that given the risk for serious and potentially fatal adverse effects, the use of alemtuzumab should be weighed extremely carefully. Fatalities from cerebral hemorrhage related to immune thrombocytopenic purpura and sepsis, as well as Goodpasture’s syndrome requiring renal transplantation, have been reported in patients treated with alemtuzumab. Various autoimmune diseases such as type 1 diabetes and non-specific connective tissue diseases also have been reported. The long half-life of alemtuzumab (mean, 6.1 days after repeated dosing) further complicates these situations. Adverse events also include an increased risk of malignancy, especially melanoma. The infusion reaction can be severe. Given the serious risk of toxicity from alemtuzumab, in Dr. Wallin’s opinion, there is greater potential for harm than benefit.

Summary

If eventually approved by the FDA for treating relapsing MS, alemtuzumab will add to the therapeutic options available to patients with refractory disease. Owing to its risk profile, however, it will likely remain reserved for aggressive cases, perhaps as induction therapy. Careful monitoring of patients for potential side effects will be required.

REFERENCES