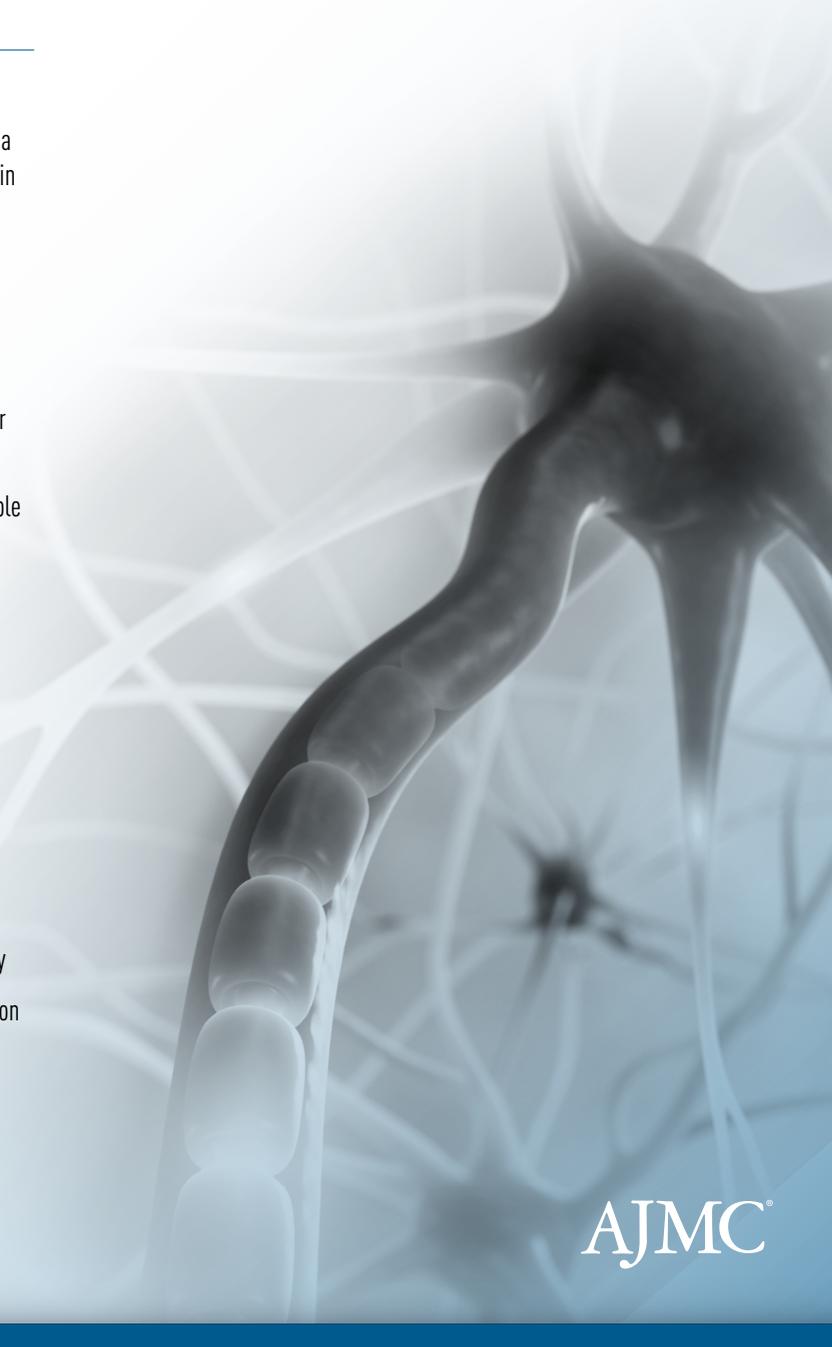


Multiple Sclerosis Compendium

SEPTEMBER 2020

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ASCLEPIOS: Ofatumumab Is Associated With a Significantly Lower Annualized Relapse Rate in Multiple Sclerosis Than Teriflunomide

Kara L. Guarini, MS

Ofatumumab received FDA approval for the treatment of relapsing forms of MS on August 20, 2020. Hauser and investigators assessed the efficacy and safety of ofatumumab compared with oral teriflunomide in 2 phase 3, randomized, double-blind, double-dummy, active-controlled clinical trials called ASCLEPIOS I and ASCLEPIOS II.

In an interview with *The American Journal of Managed Care*[®], Stephen L. Hauser, MD, director of the UCSF Weill Institute for Neurosciences and the Robert A. Fishman Distinguished Professor of Neurology at the University of California, San Francisco, discussed the changing treatment landscape for multiple sclerosis (MS). “A generation ago, [patients with] MS typically became cane- or crutch-dependent within 15 or 20 years, but now, most [individuals] with MS can anticipate lives spared from significant disability. The development of highly effective therapies for MS represents one of the great success stories of modern medicine.”

Ofatumumab, a fully human anti-CD20 monoclonal antibody, received FDA approval for the treatment of relapsing forms of MS on August 20, 2020.^{1,2} The high binding affinity and slow off-rate of ofatumumab results in prolonged B-cell depletion mediated through complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity. Hauser and investigators assessed the efficacy and safety of ofatumumab compared with oral teriflunomide in 2 phase 3, randomized, double-blind, double-dummy, active-controlled clinical trials called ASCLEPIOS I (NCT02792218) and ASCLEPIOS II (NCT02792231).³

In these trials, ofatumumab was associated with a lower relapse rate and improved disability-related measures compared with teriflunomide.³ Ofatumumab demonstrated a significantly greater reduction in adjusted annualized relapse rate (ARR), the primary end point, than did teriflunomide in ASCLEPIOS I (0.11 vs 0.22, respectively; 95% CI, -0.16 to

-0.06) and ASCLEPIOS II (0.10 vs 0.25; 95% CI, -0.20 to -0.09; $P < .001$ for both trials). In a prespecified meta-analysis of data from both trials, the percentage of patients with disability worsening confirmed at 3 months was 10.9% with ofatumumab and 15.0% with teriflunomide (HR, 0.66; 95% CI, 0.50-0.86; $P = .002$) and 8.1% and 12.0%, respectively, at 6 months (HR, 0.68; 95% CI, 0.50-0.92; $P = .01$). Although a higher percentage of patients given ofatumumab (11.0%) experienced confirmed disability improvement at 6 months compared with those given teriflunomide (8.1%), the difference was not significant (HR, 1.35; 95% CI, 0.95-1.92; $P = .09$). Hauser noted that “the trial results were remarkably consistent” across both studies.

To be eligible for these trials, patients had to be aged 18 to 55 years; have a diagnosis of MS with a relapsing-remitting course or a secondary progressive course with disease activity; have an Expanded Disability Status Scale score of 0 to 5.5; had to experience at least 1 relapse in the year before screening, at least 2 relapses in the 2 years before screening, or at least 1 gadolinium-enhancing lesion on MRI in the year before randomization; and have a neurologically stable condition for at least 1 month before randomization. Patients were randomly assigned 1:1 to receive ofatumumab 20 mg subcutaneously every 4 weeks after 20-mg loading doses on days 1, 7, and 14; or oral teriflunomide 14 mg once daily, for up to 30 months. Patients received their first injection by a health care provider at the trial site. After proper training and demonstration of their ability to self-administer treatment on subsequent visits, patients could inject themselves at home after 1 month.³

The primary end point of ARR was defined as the number of confirmed relapses of multiple sclerosis per year, according to prespecified criteria. Secondary end points were defined as disability worsening

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confirmed at 3 months, disability worsening confirmed at 6 months, and disability improvement confirmed at 6 months. Additional secondary end points were the number of gadolinium-enhancing lesions per T1-weighted MRI, the number of new or enlarging lesions on T2-weighted MRI per year, and the annual rate of brain-volume loss. Efficacy was assessed in the intention-to-treat population. All patients who received any study drug were included in the safety analysis. Separately, each study provided enough power to detect differences in the primary end point (ARR).³ However, disability-worsening measures were analyzed via a prespecified meta-analysis of data from both studies. As confirmed by Hauser, data were pooled for these measures for the sole reason of providing the required sample size for statistical power to compare ofatumumab and teriflunomide.

A total of 1882 patients were enrolled in ASCLEPIOS I (N = 927) and ASCLEPIOS II (N = 955). The identically designed trials ran concurrently among 358 sites in 37 countries. Patient demographics and baseline characteristics were similar among both trials and treatment groups. Across both trials, approximately two-thirds of participants were women and the mean age was 38 years. Most patients were diagnosed with MS an average of 6 years prior, and symptoms were present for an average of 8 years. Patients had experienced a mean

of 1.3 relapses in the past 12 months. The median time of trial enrollment was 1.6 years, and more than 30% of patients participated for more than 2 years.³

In ASCLEPIOS I, ofatumumab was associated with a significantly lower mean number of gadolinium-enhancing lesions per T1-weighted MRI scan compared with teriflunomide (0.01 vs 0.45, respectively; 97% fewer lesions with ofatumumab; $P < .001$). In ASCLEPIOS II, these values were 0.03 and 0.51, respectively, with 94% fewer lesions with ofatumumab versus teriflunomide ($P < .001$). Similarly, in ASCLEPIOS I, the mean number of new or enlarging lesions per year on T2-weighted MRI was significantly lower with ofatumumab versus teriflunomide (0.72 and 4.00, respectively; 82% fewer lesions with ofatumumab; $P < .001$). In ASCLEPIOS II, these values were 0.64 and 4.15, respectively, indicating 85% fewer lesions with ofatumumab than with teriflunomide ($P < .001$). Brain-volume loss was not significantly different among the ofatumumab and teriflunomide groups in either study.³

Combined data from both trials indicated that 83.6% of patients in the ofatumumab group and 84.2% of patients in the teriflunomide group experienced adverse events (AEs). The most common AEs (occurring in >10% of patients) with ofatumumab were injection-related reactions, nasopharyngitis, headache, injection

site reactions, upper respiratory tract infection, and urinary tract infection. Nasopharyngitis, injection-related reactions, alopecia, upper respiratory tract infection, headache, and diarrhea were the most common AEs with teriflunomide. Serious AEs occurred in 9.1% of patients given ofatumumab and 7.9% of those given teriflunomide.³

As mentioned earlier, patients could self-administer treatment at home after 1 month.³ “Some patients required a few dosings with observation, [but] most were very confident and satisfied with their self-administration,” Hauser reported. Moreover, ofatumumab could “spare the inconvenience and cost of visits to infusion centers.”

Trials of longer duration and with greater numbers of patients are needed to determine the long-term efficacy and safety of ofatumumab.³ Additional studies will enable comparisons with other disease-modifying treatments, including other anti-CD20 monoclonal antibodies. ●

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Multiple Sclerosis Management Challenges and Opportunities: A Q&A With Thomas Leist, MD, PhD

Thomas Leist, MD, PhD, director of the Comprehensive Multiple Sclerosis Center and professor of neurology at Thomas Jefferson University Hospital, discusses the changing therapeutic landscape for multiple sclerosis, the challenges of selecting an optimal treatment regimen, and his thoughts on the future of treatment. This interview was originally published in November 2019.

**THE AMERICAN JOURNAL OF
MANAGED CARE® (AJMC®): With 2 new**

agents approved by the FDA in 2019, what are your impressions of the changing multiple sclerosis (MS) treatment landscape?

THOMAS LEIST, MD, PHD: Siponimod, a recently approved second-generation sphingosine-1-phosphate (S1P) receptor agonist, has a shorter half-life and is more lipophilic than fingolimod, the first S1P

receptor agonist that was approved. With an initial dose titration, a first-dose observation that is mandatory with fingolimod is only needed for individuals with certain risk factors [when initiating siponimod]. Siponimod was specifically studied in secondary progressive MS (SPMS) patients. Despite this, the FDA has given it a broad indication that includes clinically isolated syndrome (CIS), relapsing-remitting MS

(RRMS), and active SPMS. On the other hand, the FDA approval does not include secondary MS without disease activity, likely due to the fact that the clinical effect of siponimod appears to be more muted, based on the clinical results of the phase 3 trial in this population.

The second agent approved in 2019 is oral cladribine. Unlike other MS disease-modifying therapies, [this] medication is given in short annual courses. Cladribine leads to selective depletion of peripheral lymphocytes, followed by gradual recovery of B and T cells. The aspiration of this treatment approach is that repopulation favors B and T cells that are naïve and not self-reactive.

At the 2019 European Committee for Treatment and Research in Multiple Sclerosis meeting, data from successful phase 3 trials of ofatumumab and ponesimod were presented. [Editor's note: Ozanimod received FDA approval in March 2020 and ofatumumab received FDA approval in August 2020.]

AJMC®: Can you discuss the increased emphasis on timely intervention and the implications that has for clinical trial design?

LEIST: As noted, there are now agents with different modes of action available for the treatment of relapsing forms of MS, including patients with a first attack and with additional evidence of characteristic central nervous system (CNS) lesions. It is difficult to justify placebo cohorts in longer and later-stage MS trials, as patients assigned to the placebo cohort carry, in my opinion, a greater risk-burden than necessary to evaluate the efficacy of a new agent. The field is not necessarily interested in new agents that cannot surmount a minimal degree of efficacy. Once agents have been shown to be more efficacious than currently marketed products, the benefits of such enhanced efficacy need to be readily accessible to patients with the condition. Placebo cannot be justified in phase 3 trials, and probably also phase 2 trials, in relapsing forms of

MS. It is also difficult to justify the step approach applied by many payers to require patients to fail certain treatments—that is, to incur the risk of enduring consequences of potentially avoidable inflammatory events in the CNS—before they can access more effective therapies [in] a disease where the benefit of effective early treatment has been demonstrated across numerous studies.

AJMC®: Given the number of therapies available for the treatment of MS, what are some of the challenges of selecting a regimen?

LEIST: Although there are an increasing number of treatments, access to them may not be equal. Particularly in patients with less-favorable characteristics at presentation, first-line access to highly effective therapies would afford patients a better chance for a successful long-term outcome. With an increasing number of medications, it is important to consider whether a patient has already been treated with a given mode of action. A patient who experienced breakthrough disease on one product is unlikely to respond to another product with the same mode of action.

AJMC®: What are your impressions of the FDA's inclusion of the first attack (ie, CIS) as part of its classification of relapsing forms of MS, and how much do these classifications matter from a treatment perspective?

LEIST: Trials completed in patients with a first demyelinating event and evidence of additional lesions in the CNS have uniformly proved that early treatment beats a wait-and-see approach. I don't think that the FDA changed its approach to relapsing forms of MS, but calling out CIS more specifically formalizes the agency's position that a first demyelinating event is the initial clinical manifestation of MS or, at minimum, a significantly increased risk of developing MS. I interpret it as the agency's acknowledgment of the 2017 McDonald criteria.¹ Patients with a first

demyelinating event and no additional lesions on brain MRI have a 1-in-5 chance of developing MS. One characteristic lesion increases the risk to about 1 in 2, and when 2 or more lesions can be demonstrated, the risk is about 90%. Patients with a first event who demonstrate enhancing and nonenhancing lesions meet 2017 McDonald criteria, provided there is no alternate cause.

“Early effective management of MS affords patients better long-term outcomes. What is lost, in reality, cannot be regained.”

AJMC®: Based on the current landscape of research and drug development, how do you expect the MS treatment spectrum to change over the next several years?

LEIST: It is probably the majority view that MS is a syndrome and not a single disease. The current emphasis on RRMS, SPMS, and primary progressive MS is limited by the fact that these are phenomenological and not biological categorizations. It is very possible that there are unappreciated characteristics that would allow for the subcategorization of patients who could more favorably respond to a certain treatment mode of action. The evolution of treatment approaches of oncologic conditions serves as an example. Without the ability to personalize treatment approaches, patients will likely have to step through generic medications before they gain access to the higher-efficacy newer agents. This is concerning, as early effective management of MS affords patients better long-term outcomes. What is lost, in reality, cannot be regained. ●

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Greater Disease-Modifying Therapy Use Is Associated With a Drop in Hospitalizations for Patients With Multiple Sclerosis

Maggie L. Shaw

The first disease-modifying therapies were introduced in the United States and Canada in the 1990s.

Canada has one of the highest estimated prevalences of multiple sclerosis (MS) in the world, and the economic burden of these cases (total annual costs) was almost \$950 million in 2001. This number is expected to more than double by 2031 to \$2 billion, reflective of the disease's long-term nature and significant treatment costs, especially those related to disease-modifying therapies (DMTs).

With conflicting results from previous studies on the cost-effectiveness of DMTs, a group of investigators in Saskatchewan and Manitoba, Canada, used data from Saskatchewan government health administrative databases to investigate health care utilization rates at the population level for patients with MS who were taking DMTs versus the general population in Saskatchewan, hoping to shape future health care policy decisions on therapy reimbursement and coverage. Their results were published in *BMJ Open*.¹

All patients in both cohorts were at least 18 years old. The general population cohort comprised drug plan beneficiaries, while

those in the MS group were identified by having at least 3 MS-related claims for a hospital stay, physician visit, or medication. Only DMT dispensations that occurred between January 1, 1997, and December 31, 2016 were included, with the same period used to assess hospitalization and physician claims. The authors tested for the impact of yearly DMT dispensations on 3 measures:

- total inpatient hospitalizations (MS and all-cause);
- mean length of all-cause inpatient hospitalizations; and
- yearly physician claims (MS and all-cause).

Despite 159,396 DMT dispensations over the study period, hospitalization rates decreased for both cohorts, with the drop greater among the MS cohort. Also, although increases were seen in the mean lengths of stay for both all-cause and MS-specific hospitalizations, non-MS claims were constant. For the 3 measures of yearly DMT dispensations impact, there was a drop in risk, the mean length increased but was considered insignificant, and no association was recorded, respectively, with an increase in DMT use.

However, the authors do not view this in a negative light because their results matched those of previous studies of patients with MS in the United States and Canada, in which results showed that greater DMT use correlated with drops in inpatient hospitalizations, emergency department visits, and intensive care unit admissions.

Still, their outcomes need to be considered in light of several study limitations. The analyses did not cover Registered First Nations and Inuit people in Saskatchewan, whose drug costs are covered by another government agency; the authors could not account for all potential confounders; and administrative data do not include clinical details that could have influenced the results.

"Additional research on cost-benefit [ratios] and differing treatment strategies would provide further insight into the true impact of DMTs on health care utilization at a population level," the investigators noted. ●

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Comorbidities Do Not Increase Odds of Multiple Sclerosis-Specific Hospitalizations

Rachel Lutz

What is the relationship between comorbidities and multiple sclerosis-related hospitalizations?

Recognizing and managing comorbidity in the population of patients with multiple sclerosis (MS), especially in their early disease, likely will reduce hospital admissions for these

patients, according to the results of a study published in *Multiple Sclerosis and Related Disorders*.¹

Canadian investigators conducted a retrospective cohort study to examine the risk of comorbidity on hospitalizations in 2275 patients with MS. The investigators gathered incident MS cases between 1996

and 2017 and identified every hospitalization that occurred after the date for the first claim of MS or a demyelinating condition. They assessed the link between comorbidity and MS-related hospitalizations in patients with at least 1 hospitalization within the follow-up period, which was about 8.7 years.

In their analysis, the investigators centered on 8 specific comorbidities: hypertension, diabetes, hyperlipidemia, ischemic heart disease, chronic lung disease, migraine, epilepsy, and mood and anxiety disorders (depression, anxiety, and bipolar disorder were grouped together). They selected these 8 on their prevalence in or relevance to MS.

Comorbidities were identified a year prior to the index MS date, then reevaluated every year throughout the follow-up period. Once a comorbidity was identified, it was considered prevalent throughout the follow-up period.

During the study period, the investigators identified 3312 hospitalizations, occurring in about half of the MS patients. They also reported that more than half of the cohort had at least 1 existing comorbidity at their index date, most commonly mood and anxiety disorders (26.6%), hypertension (16.9%), migraine (14.6%), and chronic lung disease (13.5%).

Having any comorbidity increased the rate of all-cause hospitalization, the study authors noted. This remained true whether the MS patients had a comorbidity at MS index or it was acquired over the study period. The number of comorbidities also increased the rate of all-cause hospitalizations in a dose-response manner.

However, the presence of any comorbidity did not increase the odds of having an MS-specific hospitalization. An increase in the number of comorbidities was associated with lower MS-specific hospitalization rates.

The only comorbidity to be associated with MS-specific hospitalization rates was hypertension, which was associated with 33% lower odds of an MS-related hospitalization, the study authors said.

All-cause hospitalization also increased with age, more than doubling in MS patients 60 and older compared with those less than 40 years, the study authors said. On the other hand, MS-related hospitalizations were more likely to occur in

younger adults, and those rates decreased consistently with increasing age. Finally, a hospitalization prior to the index date was associated with an increased rate of all-cause hospitalizations, but not of MS-specific hospitalizations.

“Comorbidity increases the rate of all-cause hospitalizations, but appears to have little impact on MS-related hospital admissions,” the study authors concluded. “We also observed increased hospitalization rates during the earlier stages of MS, when the disease is typically more active. These findings highlight the importance of recognizing and managing comorbidity in the MS population, especially early in the disease course, as this will likely have the biggest impact on reducing overall hospital admissions.” ●

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Analysis of Real-World Data Shows Better Outcomes in Multiple Sclerosis After Early Intensive Therapy

Valerie Sjoberg, MWC

Investigators analyzed long-term outcomes in a population-based cohort according to initial treatment strategy. The results of this study demonstrate higher efficacy profiles associated with therapies used in early intensive treatment therapies compared with therapies used in escalation treatment.

Current disease-modifying therapies (DMTs) for multiple sclerosis (MS) do not effectively prevent long-term disability associated with the disease. DMTs mainly target the inflammatory phase of MS rather than the neurodegenerative phase that leads to long-term disability; this selectivity may be driven by differing pathological mechanisms between the 2 phases. Although MS treatment has demonstrated greatest efficacy when aggressive, high-efficacy therapies are initiated during the

early stages of the disease, most patients with early MS receive moderate-efficacy DMTs; treatment is escalated when symptoms worsen or due to exacerbations, and only those with indication of a poor prognosis at baseline are treated with high-efficacy DMTs. Generally, the DMTs with greatest efficacy exhibit complex safety profiles, which is why they are typically reserved to treat only aggressive or resistant forms of MS. To explore the potential long-term benefits of intense DMT therapy during early stages of MS versus escalation therapy, investigators conducted a population-based, retrospective cohort study on patients with MS in southeast Wales, United Kingdom.¹

In the study, data from January 1998 to December 2016 were collected through a

systematic review of all patient clinical records. The mean (SD) age of patients at onset of MS symptoms was 27.0 (9.4) years (N = 592). Patients were grouped on the basis of first-line therapy with either high-efficacy, early intensive treatment (EIT) (n = 104) or moderate-efficacy, escalation treatment (ESC) (n = 488). EIT therapies were monoclonal antibodies (alemtuzumab and natalizumab), and ESC therapies comprised all other DMTs (interferons, glatiramer acetate, dimethyl fumarate, fingolimod, and teriflunomide). It should be noted that during data analysis, fingolimod was also considered an EIT (because switching from injectable to fingolimod could otherwise be considered escalation therapy). The primary end point was change in Expanded Disability

Status Scale (EDSS) score at 5 years, and the secondary end point was sustained accumulation of disability (SAD).¹

Of the 488 patients in the ESC group, 58 (11.9%) moved to EIT, with a median time to escalation of 2.4 years (95% CI, 2.1-3.5). This intensification of treatment was primarily due to relapses. For both groups, the median time spent on any DMT was 2.0 years (95% CI, 1.8-2.4).¹

“There may be a short period during early stages of disease during which aggressive treatment could modify biology for better long-term outcomes.”

At the 5-year follow-up, 41 patients receiving EIT therapies and 138 patients receiving ESC therapies had EDSS scores to compare baseline and 5-year results. For the EIT and ESC groups, the mean (SD) baseline EDSS scores were 4.2 (1.7) and 3.5 (1.7), respectively, and the mean changes in EDSS score at 5 years were +0.3 and +1.2,

respectively ($\beta = -0.92$; 95% CI, -1.45 to -0.41 ; $P < .001$). With covariate adjustments, at 5 years the EIT group experienced a significantly lower change in EDSS score than did the ESC group ($\beta = -0.85$; 95% CI, -1.38 to -0.32 ; $P = .002$).¹

The median time to SAD was 6.0 years (95% CI, 3.4-8.2) for those in the EIT arm and 3.1 years (95% CI, 2.8-4.0) for patients in the ESC arm (log-rank test $P = .05$). Those who escalated from ESC to EIT experienced a median time to SAD of 3.3 years (95% CI, 1.8-5.6). Although there were no identified differences between the groups in hazard of SAD, 60% of the patients who switched from ESC to EIT developed SAD while in the ESC group.¹

Regarding safety, of those patients receiving EIT with alemtuzumab, 87% experienced adverse events related to infusion and 47% developed autoimmunity; there were no serious infections or deaths related to this treatment. Patients receiving EIT with natalizumab experienced no serious adverse events, no progressive multifocal leukoencephalopathy, and no deaths related to treatment. Patients in the ESC group also did not experience any deaths related to treatment, but did have 7 cases of serious adverse events

involving necrotic skin reactions, anaphylaxis (with injectable DMTs), and severe infection (with fingolimod).¹

The results of this study demonstrate higher efficacy profiles associated with EIT therapies than those of ESC therapies, despite the poor prognostic factors among patients receiving EIT. Importantly, the results show that ESC therapies may not effectively delay disability. There may be a short period during early stages of disease during which aggressive treatment could modify biology for better long-term outcomes. Considering the potential benefits of EIT, current eligibility criteria for receiving EIT therapies may be too high. Although the escalation approach with moderate-efficacy DMTs remains the standard-of-care for patients with MS who are not considered high risk, this approach has not been tested in a randomized clinical trial. A prospective randomized clinical trial is needed to further explore optimal treatment and monitoring strategies for individuals with MS.¹ ●

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Digital Tool Aims to Catch Transition to Secondary-Progressive Multiple Sclerosis

Jared Kaltwasser

It can be difficult to notice when a patient is transitioning from relapsing-remitting multiple sclerosis to the secondary progressive form.

A digital tool could help neurologists more quickly notice when a patient with relapsing-remitting multiple sclerosis (RRMS) is transitioning to the secondary progressive form of the disease (SPMS).

About half of patients with RRMS will eventually see their disease transition to SPMS, but diagnosing exactly when that shift occurs has been difficult.

To address this need, a data-driven tool has been created that investigators believe will give physicians a better chance at catching the transition. The Multiple Sclerosis Progression Discussion Tool, or MSProDiscuss, is designed to facilitate physician-patient discussions and catch subtle changes that might indicate changes in the patient's MS.

“The problem in diagnosing SPMS is that there are no defined criteria or gold standard,” cocreator Tjalf Ziemssen, MD, told *The American Journal of Managed Care*.[®]

“Of course, at the end, the patient's history is relevant for the diagnosis. Our tool is an attempt to standardize this neurological history in an easy way.”

Ziemssen is a professor of clinical neuroscience at the Dresden University of Technology, in Germany. Ziemssen and colleagues' findings were published in the *Journal of Internet Medical Research*.¹

In addition to helping to collect and process information, MSProDiscuss is designed to produce an easy-to-interpret output.

The tool pairs a mix of qualitative and quantitative information with a scoring algorithm. To evaluate the tool, the research team asked 20 neurologists to use the tool to diagnose 198 patients whose MS status was already known. Of those patients, 89 had been diagnosed with RRMS, 47 had been diagnosed as transitioning to SPMS, and 62 had already transitioned to SPMS.

The results from MSProDiscuss evaluation were highly accurate.

“The sensitivity for SPMS was consistently around 80% (true positive rate) and specificity (true negative rate) for RRMS [was] above 86%,” the authors noted. “Overall, the draft tool demonstrated excellent interrater reliability, and good evidence of construct validity using the known-groups method.”

The data showed that the impact and severity of symptoms for individuals transitioning to SPMS was markedly different from patients with RRMS, meaning it was possible to create meaningful cutoff values. Although the tool was more accurate when Expanded Disability Status Scale (EDSS) scores were included, the tool was found to be accurate even without EDSS numbers.

“Why should neurologists use this tool?” Ziemssen asked. “Because it is easy and quick to enter [data,] and it is possible to get semiquantitative standardized data which can be used in the long term and integrated in the holistic symptomatic management of MS patients.”

Now that the system has been validated in a study, Ziemssen said that his research team must work to validate it in a clinical setting. The team has already integrated

the tool into another ongoing study that longitudinally monitors individuals with SPMS and individuals at high risk of SPMS. Based on the results of this ongoing study, the tool could then be used to help optimize early interventions, which may slow the progression of the disease.

“[MSProDiscuss] may be useful in clinical practice for a more informed physician–patient discussion supporting the successful management of MS,” Ziemssen and colleagues concluded.

MSProDiscuss may be accessed online at <https://www.neuro-compass.education/en-gb/msprodiscuss/>. ●

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Patients With Multiple Sclerosis Have Increased Risk for Cardiovascular Disease, Related Mortality

Rachel Lutz

Patients with multiple sclerosis (MS) had a 3.5-fold increase in all-cause mortality and a 1.5-fold increase in cardiovascular disease mortality, compared with those without MS, even after controlling for traditional risk factors, and women were more at risk than men.

Multiple sclerosis (MS) is associated with an increased risk of cardiovascular and cerebrovascular disease, according to the results of a study published in *JAMA Neurology*,¹ and women are more severely affected than men.

Traditional vascular risk factors may not account for the higher risk, said the investigators, who examined UK data. The investigators conducted a population-based, retrospective, matched cohort study involving 12,251 individuals diagnosed with MS between 1987 and 2018 to assess the risk of macrovascular events and mortality for patients. The information came from the UK Clinical Practice Research Datalink, a large repository

of anonymized longitudinal electronic medical records from primary care offices.

Each patient was matched to 6 individuals without MS by age, sex, and general practice (the clinic where they received care). While the first MS diagnosis was considered the index date, the analysis included individuals with 3 or more MS events recorded through their study period to improve case finding. The average follow-up time was 10.3 years for individuals with MS and 11.5 for their matched controls.

The investigators noted that individuals with MS have a higher prevalence of hypertension and hyperlipidemia, being overweight or obese, having ever smoked, and having lower levels of physical activity. Mortality among individuals with MS remains higher than that of the general population, but evidence about the efficacy of tighter control of vascular risk factors in this population is lacking, they added.

Two-thirds of the patients with MS were women, compared with 69.8% in the control group, the study authors said. The mean age was 44.9 years in both groups. The proportion of individuals using cardiovascular medications in the MS and non-MS groups were similar, but there were more patients with MS who smoked compared with controls (37.9% vs 29.4%, respectively).

The incidence of acute coronary syndrome in MS patients was 204.5 per 100,000 person-years, the study authors found, compared with 116.8 in the control group. For cerebrovascular disease, the incidence was 159.6 per 100,000 person-years, compared with 81.4 in the controls.

Having MS was linked with a 28% increased hazard of acute coronary syndrome (HR, 1.28; 95% CI, 1.09-1.51), 59% increased hazard of cerebrovascular disease (HR, 1.59; 95% CI, 1.32-1.92), 32% increased hazard of any macrovascular disease (HR, 1.32; 95% CI, 1.15-1.52), 3.5-fold

increased hazard of all-cause mortality (HR, 3.46; 95% CI, 3.28-3.65), and 1.5-fold increased hazard in cardiovascular disease mortality (HR, 1.47; 95% CI, 1.27-1.71).

The observed mortality rate was 2223.3 events per 100,000 person-years for individuals with MS but 619.5 events for the control groups. The investigators wrote that the individuals with MS had an increased risk of all-cause mortality and cardiovascular disease mortality.

Women, especially, were at risk, according to their analysis: Compared with women without MS, women with MS had a 3.5-fold increase in all-cause mortality (HR, 3.52; 95% CI, 3.28-3.77)

and a 1.3-fold increase in cardiovascular disease mortality (subhazard ratio [SHR], 1.30; 95% CI, 1.04-1.62). Women with MS had an increased hazard of acute coronary syndrome, cerebrovascular disease, and any macrovascular disease compared with women without MS, the authors said.

Men with MS had a 2.7-fold increased risk of all-cause mortality (HR, 2.74; 95% CI, 2.35-3.18) and a 1.5-fold increased risk of cardiovascular disease mortality (SHR, 1.54; 95% CI, 1.06-2.23) than men without MS.

These findings are consistent with those of prior studies that used matched cohort designs, the study authors wrote. This includes a Swedish study that found the

risk for acute myocardial infarction was 85% higher and the risk of stroke was 71% higher in the MS population. The study results also showed a greater increased risk for women, the study authors added.

“This study suggests that MS is associated with an increased risk of cardiovascular and cerebrovascular disease that is not completely accounted for by traditional vascular risk factors,” the study authors concluded. ●

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Immediate Disease-Modifying Therapy After Relapse Reduces Multiple Sclerosis Disability

Alison Rodriguez

Study results suggest that delaying initiation of disease-modifying therapy, especially after a poorly recovered relapse, decreases the likelihood of remaining disability free by age 45.

Patients with multiple sclerosis (MS) who do not experience good recovery after initial relapse, but who immediately initiate disease-modifying therapy (DMT), have an increased likelihood of a benign disease course, according to the results of a recent study.

“Patients with good recovery and immediate DMT initiation after first relapse have about 65% chance of remaining at a minimal disability level by age 45 years.”

Published in *Neurology Neuroimmunology & Neuroinflammation*,¹ the study was a double-blind trial of interferon

beta-1a 30 mc once a week versus placebo in clinically isolated syndrome. The main trial period was followed by a 10-year follow-up extension.

The investigators defined good recovery after presenting relapse as:

- full early recovery within 28 days of symptom onset, meaning an Expanded Disability Status Scale (EDSS) score of 0 at enrollment and maintained for at least 6 months; and
- delayed good recovery with an EDSS score of above 0 at enrollment and improvement from peak deficit to 6th month or 1-year visit that is greater than or equal to the median.

“In MS, partial recovery from relapses leads to residual disability. Limited recovery from early clinical relapses also situates patients with MS for an earlier onset of progressive disease. A single, partially recovered, symptomatic or asymptomatic, critically located lesion in the high cervical spinal cord is sufficient to set a patient up for progressive disease,” the authors

noted. “A common real-world practice in deciding immediate vs delayed DMT initiation in early MS often involves the extent and rapidity of a patient’s recovery from early relapses, a decision for which there is no evidence from a clinical trial setting.”

In total, of the 328 patients, 175 had good recovery (94 who had immediate treatment and 81 who had delayed treatment) while 153 did not have good recovery (77 immediate and 76 delayed treatment). According to these results, patients with good recovery and immediate initiation of DMT after their first relapse have about 65% chance of remaining at a minimal disability level (EDSS score <2.5) by age 45 years. However, patients with poor recovery and delayed DMT initiation have about a 20% chance of remaining at that minimal disability level of by age 45. Additionally, those with poor recovery but immediate DMT initiation or patients with good recovery but delayed DMT initiation have about a 50% chance of remaining at that minimal disability level by age 45.

The results suggest that delaying initiation of DMTs, especially after a poorly recovered relapse, decreases the likelihood of remaining disability free by age 45.

“A better understanding of the biology underlying relapse recovery in MS is of utmost importance in generating better animal models of recovery, in developing

better recovery agents, in more optimal timing of administration of recovery agents in future recovery trials, and in defining the clinical/ subclinical metrics appropriate for the recovery measurement,” the authors concluded. “It is very likely that DMTs and medications stimulating relapse recovery will be used concomitantly, and

clinical or subclinical metrics that can assess such interactions will be further relevant in future clinical trials.” ●

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Investigators Create, Validate Health Utilization Questionnaire for Multiple Sclerosis

Rachel Lutz

An efficient, concise patient questionnaire gathering health utilization information is effective for patients with multiple sclerosis, according to investigators.

The Multiple Sclerosis Health Resource Utilization Survey (MS-HRS) is an easy-to-use questionnaire that provides well-rounded, cross-sectional, longitudinal evaluations of resource utilization among patients with MS, according to the authors of a paper published in the *Journal of Medical Internet Research*.¹

“The MS-HRS is a promising option to measure costs precisely in cross-sectional and longitudinal settings instead of estimating them or using surrogates.”

Investigators from Germany—a team of neurologists, health care administrators, psychologists, and MS nurses—developed the MS-HRS in 2009 in the form of a questionnaire that could be taken via smart tablets or on paper. A more time-efficient version that can be completed in 10 to 15 minutes was created in 2016.

The study authors noted that previous studies that examined resource utilization by MS patients analyzed secondary data, such as administrative data from health

insurance or health care providers; the use of such data is associated with limitations. Thus the authors sought to develop and validate a questionnaire to capture longitudinal data on resource utilization.

The investigators looked at 3 primary steps for evaluation of costs: classification of resource consumption, qualification of resource use, and valuation of resources. Costs were divided into direct medical, direct nonmedical, and indirect. All prices from were adjusted to year 2011 prices.

There were 2207 patients with MS who completed the study. The cohort was predominantly women (72.90%), had a mean age of 41.73 years, and were mostly employed (61.03%) with full-time work (58.95%), the investigators reported. About half of the patients had experienced a relapse in the previous 12 months.

Most of the patients reported using direct medical services in the previous 3 months. However, only 44% reported indirect medical costs and just 16% had direct nonmedical costs. Besides DMTs, the study authors said, indirect costs were the main cost drivers followed by direct medical and direct nonmedical costs. Per quarter per patient, total cost was about €2462 (about US\$3427, using the 2011 exchange rate of 1.392 provided by the authors) without DMTs, and it reached €7126 (US\$9919) with DMTs.

The majority of patients (85%) received care in private practices, although care was also received during inpatient hospital

stays (6%) and through day care admissions (3%). The highest costs were for inpatient treatments (€315/\$438), with consultations in the primary sector (€210/\$292) and day admissions in hospitals (€32/\$45) following.

Annual costs for mild to moderate relapsing-remitting MS were estimated to range between €9528 (\$13,263) without DMTs and €28,203 (\$39,259) with DMTs.

The authors suggest that the MS-HRS can be used during clinical interventions as well as in noninterventional studies to gather economic data. Limitations of the study include time-limited recall intervals, particularly in those who may be cognitively impacted by MS, as well as the potential reluctance of patients to disclose confidential socioeconomic or health economic information.

Still, “in a large population, we demonstrated that the questionnaire is easy to administer and has good psychometric properties,” the authors concluded.

“These characteristics provide the necessary prerequisites for high-quality health economic studies (eg, cost-effectiveness analyses). The MS-HRS is a promising option to measure costs precisely in cross-sectional and longitudinal settings instead of estimating them or using surrogates.” ●

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Brain Fluid Flow Is Associated With Multiple Sclerosis Pathogenesis, Progression

Gianna Melillo

Investigators determined that patients with multiple sclerosis present with significant aqueduct of Sylvius enlargement over time, which may be attributable to regional atrophy changes and ex vacuo expansion of the aqueduct.

Investigators determined that patients with multiple sclerosis (MS) present with significant aqueduct of Sylvius (AoS) enlargement over time, which may be attributable to regional atrophy changes and ex vacuo expansion of the aqueduct, according to the results of a study published in *Fluids and Barriers of the CNS*.¹

White matter lesions in the brain, along with neurodegenerative and vascular abnormalities, are characteristic of MS. “Hemodynamic changes such as inflammation-driver hyperperfusion or atrophy-driven hypoperfusion will significantly influence the overall brain volume,” the investigators wrote. They continued, “It is currently unknown whether the changes in cerebral fluid dynamics are driven by forces within the CSF [cerebrospinal fluid] space or due to atrophy-driven passive expansion.”

To investigate the dynamics of CSF flow, investigators performed 3T MRI with cine phase contrast with velocity-encoded

pulse-gated sequence on 40 patients with MS and 20 healthy controls (HCs). Images taken at baseline and after a 5-year follow-up were compared between the cohorts.

In addition, to evaluate atrophy, patients with MS underwent additional high-resolution 3D T1-weighted imaging throughout the study period. “Measures of AoS cross-sectional area (CSA), average systolic and diastolic velocity peaks, maximal systolic and diastolic velocity peaks, and average CSF flow rates were determined,” noted the authors, along with brain atrophy and ventricular CSF (vCSF) expansion rates.

The study found that over 5 years, patients with MS showed a significant increase in:

- maximal diastolic peak, from 7.23 cm/s to 7.86 cm/s (unadjusted $P = .037$);
- diastolic peak flow rate, from 7.76 mL/min to 9.33 mL/min (unadjusted $P = .023$); and
- AoS CSA, from 3.12 mm² to 3.69 mm² (adjusted $P = .001$)

“The only differentiator between MS patients and HCs was the greater AoS CSA (3.58 mm² vs 2.57 mm², age- and

sex-adjusted analysis of covariance $P = .045$). The AoS CSA change was associated with vCSF expansion rate (age- and sex-adjusted Spearman’s correlation $P = .019$) and not with baseline nor change in maximal velocity,” the authors wrote.

Of the 40 patients with MS included in the study, 26 had relapsing-remitting MS and 14 had progressive MS. In this population, patients demonstrated an average increase of 13.8% in total T2 lesion volume, 2.6% in whole brain atrophy rate, and 13.7% in vCSF space expansion rate.

“If brain fluid dynamics contribute toward the multifaceted pathophysiological MS mechanisms, either pharmacological or rehabilitative treatments may alleviate some of the aforementioned abnormalities,” investigators concluded.

Future studies should consider analysis of correlations between longitudinal changes in CSF measures and clinical disability accrual/phenotype progression, the investigators noted. ●

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Synthetic MRI Can Be Useful in Calculating Myelin Volume Fraction, Multiple Sclerosis Study Results Show

Jared Kaltwasser

A study compared synthetic magnetic resonance imaging (SyMRI) with other techniques for measuring myelin volume fraction in patients with multiple sclerosis. The results indicate that the technique is effective.

Synthetic magnetic resonance imaging (SyMRI) appears to be a valid option for quantifying myelin volume fraction (MVF) in patients with multiple sclerosis

(MS), according to the results of a study that compared the technology with other measurement approaches.¹

Myelin imaging can be an important clinical tool for tracking the prognosis of patients with MS and evaluating the effectiveness of therapy. But, as a team of investigators from Japan and France noted in a study in the journal *Cells*, accurately

assessing myelin can be an exceedingly difficult challenge.¹

“There is currently no recognized gold standard for myelin estimation, although myelin water fraction is one of the best validated and most commonly used quantitative measurements for noninvasive assessment of myelin content in the brain,” wrote the investigators, including

corresponding author Shigeki Aoki, MD, PhD, of Juntendo University School of Medicine, in Tokyo.¹

Technology has emerged that has the potential to improve the situation. SyMRI uses multislice, multiecho, and multidelay acquisition to simultaneously measure longitudinal T1 relaxation rate, transverse T2 relaxation rate, proton density, and local radiofrequency field B1. The latter measurement can help correct location variations in flip angle. The system is able to obtain full head coverage in about 6 minutes, Aoki and colleagues said.¹

“From these absolute parameters, it is possible to create any contrast-weighted image that is clinically useful, including T1-weighted or T2-weighted images, using SyMRI software,” said the investigators. “Using the same absolute parameters, SyMRI also allows myelin measurement.” Knowing that it was feasible to measure myelin using SyMRI, Aoki and colleagues wanted to know whether such a measure was accurate compared with other existing measurement strategies.

A total of 37 individuals with relapsing-remitting MS were recruited for this study. Sixteen were excluded because they did

not have any plaque or only small plaques on the brain or because they had diffuse extensive white matter abnormalities, leaving 21 patients eligible for inclusion in the study. The investigators then used 4 techniques to measure the white matter of the patients: SyMRI, magnetization transfer saturation, T1-weighted images divided by T2-weighted images, and radial diffusivity.¹

“*Synthetic MRI myelin volume fraction could yield additional complementary information about microstructural tissue damage in patients with MS.*”

They found the results of SyMRI MVF were comparable with the other techniques. “Moreover, it presented better sensitivity for detecting the difference between plaque or periplaque regions and [normal-appearing white matter],” they added, “which warrants further investigation for

SyMRI myelin volume fraction to be useful for diagnosis and prognosis evaluation.”¹

Aoki and colleagues said that additional research is needed and there are still other factors to be considered. Each type of imaging has its own advantages and disadvantages. Also, the authors did not compare SyMRI with myelin water imaging, one of the “best-validated techniques.” “Further studies comparing SyMRI MVF and myelin water imaging in patients with MS should be conducted to analyze the association between these metrics,” Aoki and colleagues wrote.¹

The authors concluded by noting that while subregional analysis showed a weaker, but significant, correlation in myelin estimation, particularly for normal-appearing white matter, the normal-appearing white matter SyMRI MVF result “was significantly associated with disease duration.” SyMRI MVF “could therefore yield additional complementary information about microstructural tissue damage in patients with MS.” ●

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