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MS Highlights from AAN & CMSC

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Initial high-efficacy MS therapy is associated with less disability later

The benefit of high-efficacy therapy is evident after 2 years of treatment.

Starting treatment for relapsing-remitting multiple sclerosis (MS) with high-efficacy therapy (HET) is associated with lower long-term disability, compared with a stepwise increase to reach more aggressive treatment later, new research suggests. However, there is a trade-off: in this study of nearly 300 patients, those treated with initial HET experienced more disease activity in the first 2 years than other participants.

The HET benefit emerged between 2 and 10 years into the study. For example, the mean Expanded Disability Status Scale (EDSS) scores were significantly lower at 6 years in the early, aggressive treatment group than in the later HET group (2.4 vs 3.3, respectively).

"Treatment decisions made around the time of diagnosis will affect long-term outcomes," said lead author Anna He, MBBS, of the Department of Clinical Neuroscience at the Karolinska Institute in Stockholm and the UCL Queen Square Institute of Neurology in London.

Using the most efficacious disease-modifying therapies from the start minimizes disability, "whereas those patients escalating to high-efficacy disease-modifying therapies later do not seem to catch up to those who commenced earlier," Dr. He said. "Patients and clinicians should be aware of this when choosing treatment in early MS," she added.

This research was presented online as part of the 2020 American Academy of Neurology Science Highlights.

Patient-centered outcome

Instead of measures of brain volume, lesion count, serum neurofilament, or other biomarkers that are mainly of interest to clinicians and scientists, "the main outcome of interest to our patients is their disability," Dr. He said. "The first question they ask at diagnosis is usually along the lines of: 'What will my disability be in 10 years?' This is what matters to patients and is fundamentally what motivated this study," Dr. He added.

The investigators searched international MS registries for patients with relapsing-remitting MS starting HET, which included rituximab, ocrelizumab, mitoxantrone, alemtuzumab, or natalizumab. They compared 117 participants who started HET within the first 2 years of clinical disease onset (the early group) with 181 participants who started HET after more than 4 years (the late group). All were followed for a median of 7.4 years (range, 6.4 to 8.6 years).

Difference in EDSS scores from baseline was the primary outcome. Both cohorts began the study with a mean EDSS score of 2.4, but between-group differences were significant at 10 years.

The secondary outcome of cumulative hazard of disability progression was higher in the early-treatment group from baseline to 2 years. Between the period of 2 and 10 years, the inverse was true.

In patients with highly active MS, "early exposure to high efficacy therapies is recommended," Dr. He noted. "We can already affect our patients' lives enormously by utilizing our current toolbox in the optimal way. It is our task to optimize this in a data driven manner."

Dr. He plans to look at other outcomes, including patient-reported quality of life and health economic measures, and to take a different approach to future research. Rather than assessing MS outcomes from a disease biology perspective, "I will be looking at MS outcomes from the perspective of its key stakeholders, the individual and society," and the factors that influence them, Dr. He said.

Dr. He disclosed no relevant financial relationships. ■

—Damian McNamara

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Serum NfL in early MS can help predict clinical course

An analysis of paired samples suggests a valuable role for serum NfL in predicting MS severity and treatment response.

The serum level of neurofilament light chain (sNfL) around the time of multiple sclerosis (MS) diagnosis is associated with long-term clinical disease progression, with higher baseline levels a sensitive marker of subsequent poor clinical outcomes, research suggests. The study showed that patients with higher sNfL within 5 years of MS diagnosis had a higher risk of long term-clinical disability and higher risk of developing progressive MS. The level of sNfL also predicted the rate of increase over time in the Expanded Disability Status Scale (EDSS).

Serum NfL levels can provide "useful information in both directions, adding to both an overall reassuring picture or worrying picture both at first presentation and then on subsequent visits," said Simon Thebault, MBBCh, a neurology resident at the University of Ottawa and the Ottawa Hospital Research Institute, Canada.

This research was presented online as part of the 2020 American Academy of Neurology Science Highlights.

Prognostication from day one

Many studies have shown a correlation between MS disease activity (clinical relapses, EDSS progression, MRI lesions) and elevated sNfL. Other studies have also looked at the prognostic value of NfL in serum and cerebrospinal fluid (CSF), but the data are limited by the lack of long-term biobanked samples and subsequent follow-up, Dr. Thebault explained.

The new study took advantage of the Ottawa MS biobank, which contains carefully frozen and stored samples from more than 3,000 patients with MS going back up to 25 years.

The team identified patients with serum collected within 5 years of first MS symptom onset (baseline) who were followed for a median of 18.9 years (range, 15 to 27 years). They quantified levels of sNfL in 67 patients and 37 matched controls.

In patients with MS, the median baseline sNfL level was 10.1 pg/mL – 38.5% higher than the median level in controls (7.26 pg/mL).

The baseline sNfL level was "most helpful as a sensitive predictive marker to rule out disease progression," the researchers reported in their meeting abstract.

Patients with baseline sNfL levels less than 7.62 pg/mL were 4.3 times less likely to develop significant disability (EDSS score ≥ 4) and 7.1 times less likely to develop progressive MS by end of follow-up.

The most rapid disease progression was seen in patients with the highest baseline NfL levels (3rd-tertile, > 13.2 pg/mL). Higher baseline sNfL level was associated with faster rate of EDSS progression even after adjusting for confounders of age, sex, and disease-modifying treatment.

"We were able to show that serum neurofilament levels collected very early in the disease, usually at the time of first diagnosis, were predictive of the clinical progression [by EDSS score] and the risk of evolving to secondary progressive MS on average 19 years later," Dr. Thebault said. A baseline level less than 7.6 pg/mL was "reassuring."

"Prognostication in MS from day one is important," he emphasized. "If we know someone is on a bad trajectory, neurologists might recommend more aggressive therapies up front. Equally, if a patient has a very reassuring picture, then maybe it is more appropriate to start with safer treatments [the so called 'platform therapies'] that may serve a patient well for many years, as they did for many in the years before higher-efficacy therapies were available," Dr. Thebault said.

"In the hands of an expert MS neurologist who understands both the pearls and pitfalls of this test ... serum neurofilament is already a useful clinical tool, and we have implemented it in our daily practice in Ottawa," he concluded.

Funding for the study was provided by The Ottawa Hospital Pilot Project Grant. Dr. Thebault disclosed no relevant financial relationships.

—Megan Brooks

No benefit of three commonly used medications for MS fatigue

The TRIUMPHANT study found no difference between amantadine, modafinil, methylphenidate, and placebo in Modified Fatigue Impact Scale (MFIS) scores.

A new placebo-controlled trial has shown no benefit over placebo for three different drugs commonly used to treat fatigue in patients with multiple sclerosis (MS). The TRIUMPHANT study found no difference between the effects of amantadine, modafinil, methylphenidate, and placebo in the Modified Fatigue Impact Scale (MFIS) in a study involving 141 patients with MS.

There was also no difference between any of the drugs and placebo in any of the preplanned subgroups which included different Expanded Disability Status Scale scores, depressive scores, use of disease-modifying therapy, or type of MS (relapsing remitting or progressive).

The research was presented online as part of the 2020 American Academy of Neurology Science Highlights.

"These three drugs are used very commonly used for MS fatigue by neurologists, psychiatrists, and primary care doctors, but they don't seem to be any better than placebo. They were all associated with increased side effects compared with placebo even with short-term use," said lead investigator Bardia Nourbakhsh, MD, assistant professor of neurology at Johns Hopkins University, Baltimore.

However, in a post hoc analysis there was an improvement in daytime sleepiness with two of the drugs – methylphenidate and modafinil. "These two agents reduced daytime sleepiness in patients with high daytime sleepiness scores at baseline, with about a 4-point difference versus placebo, which was significant. But as this was not a preplanned analysis, we have to be cautious in its interpretation," Dr. Nourbakhsh said. "However, this finding may not be too surprising as both these drugs are licensed as stimulants for use in narcolepsy patients with excessive daytime sleepiness."

"Our recommendations are that as amantadine was not better than placebo in any subgroup its use should be discouraged in MS fatigue," Dr. Nourbakhsh commented. "Modafinil and methylphenidate may possibly be considered for MS patients with excessive daytime sleepiness, but this should really be confirmed in further studies."

Fatigue is a common and debilitating symptom of MS, occurring in about 70%-80% of patients with MS. There is no approved drug treatment. However, nonpharmacologic therapies have shown some success: studies of exercise and cognitive-behavioral therapy (CBT) have shown these may be effective without causing side effects, Dr. Nourbakhsh noted. "So we should be getting patients to try exercise and CBT before jumping to medication."

Dr. Nourbakhsh said he was disappointed with the results of the study but not terribly surprised. "We use these three medications frequently in the clinic and we have not been seeing great benefits so we wondered whether they were actually effective."

He said that the trial was adequately powered and the question has been answered. "These are valuable results – they will hopefully encourage doctors to think twice before prescribing these medications that could be harmful and have no clear benefit," Dr. Nourbakhsh concluded.

For the randomized, double-blind, placebo-controlled, four-sequence, four-period crossover trial, 141 patients with MS and fatigue received twice-daily oral amantadine (maximum 200 mg/day), modafinil (maximum 200 mg/day), methylphenidate (maximum 20 mg/day), or placebo, each given for up to 6 weeks with a 2-week washout between each medication.

Patients had a mean baseline MFIS score of 51.3 and were randomly assigned to one of four medication administration sequences. Data from 136 participants were available for the analysis of the primary outcome (change in MFIS score), and 111 participants completed all four medication periods.

In the intent-to-treat analysis, the least-squares means of total MFIS scores at the maximally tolerated dose were as follows: 40.7 with placebo, 41.2 with amantadine, 39.0 with modafinil, and 38.7 with methylphenidate. "All medications and placebo reduced the MS fatigue score by 10-12 points from baseline, so there was quite a substantial placebo effect," Dr. Nourbakhsh noted. There was no statistically significant difference in the physical and cognitive subscales of MFIS and quality of life measures between any of the study medications and placebo. All three drugs were associated with an increase in adverse effects versus placebo.

Dr. Nourbakhsh says he is hopeful that this negative study may stimulate further research into new targets and medications for MS fatigue.

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Telerehabilitation may be effective in MS

Patients with MS may achieve equivalent benefits and increased cost savings with telerehabilitation, compared with outpatient rehabilitation.

Telerehabilitation is safe and may offer functional benefits comparable to those of outpatient rehabilitation for patients with multiple sclerosis (MS) and impaired mobility. Telerehabilitation also saves time and travel cost, compared with outpatient rehabilitation. "This model of home-based telerehabilitation offers a safe and cost-effective method for improving function and quality of life for MS patients with mobility deficits," said Heather Barksdale, DPT, a neurological clinical specialist at UF Health Jacksonville in Florida.

The study was presented at the virtual meeting of the Consortium of Multiple Sclerosis Centers (CMSC).

The Centers for Medicare & Medicaid Services do not reimburse for telerehabilitation services. Patients with MS have difficulty accessing rehabilitation specialists because of impaired mobility and lack of access to transportation. "We are based in Jacksonville, Florida, and often have patients who have to travel from Tallahassee, Panama City, Daytona Beach, and Brunswick, Georgia, to receive specialty services," said Dr. Barksdale. "Telerehabilitation would allow these patients to get access to high-quality rehab services with clinicians that specialize in MS."

Dr. Barksdale and colleagues conducted a pilot study to evaluate the feasibility of a physical therapy–guided telerehabilitation program for patients with confirmed MS and mobility impairments. They enrolled patients at the MS Center of Excellence at University of Florida Health Jacksonville into a telerehabilitation group. A board-certified neurologist and a physical therapist specializing in MS examined participants in person at baseline. The latter underwent an 8-week program of physical therapy–guided telerehabilitation that used the Jintronix software platform and a kinetic tracking system.

By reviewing charts during January 2018 to September 2019, Dr. Barksdale and colleagues selected patients with MS who were seen on an outpatient basis by the same physical therapists who were administering telerehabilitation. This outpatient comparison group was matched to the telerehabilitation group on duration of treatment and outcome measures completed. Dr. Barksdale and colleagues reviewed the data for the effects of the two interventions on mobility and travel.

Eight patients completed the telerehabilitation program, and all had improvements in fatigue, quality of life, or mobility measures. The investigators did not observe any adverse events during or after the intervention. The total savings in projected travel costs for all eight participants was $8,487.23, compared with the outpatient group. Participants in the telerehabilitation and outpatient groups achieved minimal detectable changes in the outcome measures examined at equivalent rates.

"The game-based model with virtual visits by a physical therapist can be modified to include exercises specific for other motor, coordination, spasticity, and movement dysfunctions and may be useful for other chronic and progressive dysfunction seen in Parkinson's disease, stroke, and other movement and neuromuscular disorders," said Dr. Barksdale.

"Future studies are needed to further establish guidelines for patient selection and mode of delivery, as well as design of future telerehabilitation programs," she added. "Duration of treatment and types of exercises to be included should also be examined. Further research into use of telerehabilitation for the treatment of upper-extremity, cognitive, speech, and swallowing dysfunction should also be examined."

The investigators conducted their study without outside funding and reported no disclosures.

—Erik Greb

No benefit of three commonly used medications for MS fatigue

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His group has recently conducted a pilot study of intravenous ketamine in MS fatigue with some encouraging results, but he stressed it needs to be tested in a larger study before it can be recommended for use in clinical practice. "While an IV medication is not ideal, the effect did seem to be quite long-lived with a difference still evident at 28 days, so it could perhaps be dosed once a month, which could be feasible," he said.

Dr. Nourbakhsh has reported receiving personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities for Jazz Pharmaceuticals.

—Sue Hughes

CMSC MRI guidelines evolve into international consensus protocol

Internationally accepted consensus guidelines will improve lagging conformity with the recommendations.

Proposed updates to guidelines for magnetic resonance imaging (MRI) in patients with multiple sclerosis (MS) are in the works to make the Consortium of Multiple Sclerosis Centers (CMSC) protocol and other international guidelines more similar, with the hope that internationally accepted consensus guidelines will improve lagging conformity with the recommendations.

"We've always envisioned the guidelines as being international, but now we have harmony with the groups, so this is truly a global protocol," Anthony Traboulsee, MD, a professor of neurology and director of the MS clinic and neuromyelitis optica clinic at the University of British Columbia in Vancouver, said in presenting the proposed updates during the virtual meeting of the CMSC.

The updates reflect the input of an international expert panel convened by the CMSC in October 2019, made up of neurologists, radiologists, magnetic resonance technologists, and imaging scientists with expertise in MS. Attendees represented groups including the European-based Magnetic Resonance Imaging in MS (MAGNIMS), North American Imaging in Multiple Sclerosis Cooperative, National MS Society, Multiple Sclerosis Association of America, MRI manufacturers, and commercial image analysis.

Standardizing scans

While the mission was to review and update the current guidelines, an important overriding objective was to boost universal acceptance and improve the utilization of the protocol, which research shows is surprisingly low. According to one poster presented at the meeting, a real-world MRI dataset of 1,233 sessions showed only 8% satisfied criteria for the T1 sequence outlined in the 2018 guidelines, and only 7% satisfied criteria for the T2 sequence. "In a real-world MRI dataset of patients with MS, the conformance to the CMSC brain MRI guidelines was extremely low," concluded the authors, who were with Icometrix, in Chicago and Belgium.

David Li, MD, also of the University of British Columbia and cochair of the MRI guideline committee, said the nonconformity has important implications. "Nonstandardized scans, with inconsistent slice thickness and gaps, nonstandardized slice acquisition (not in the subcallosal plane), and incomplete brain coverage, all contribute to scans that are difficult to compare," he said. Those factors "allow for assessment of new lesions and lesion activity that are invaluable for diagnosis as well as determining the effectiveness of therapy or the need for initiating/changing therapy."

Dr. Traboulsee said the lack of adherence to guidelines may simply have to do with a mistaken perception of complexity. "Part of the challenge is MRI centers don't realize how easy it is to implement these guidelines," he said in presenting the proposed updates.

Dr. Traboulsee noted that the CMSC has been working with manufacturers to try to incorporate the protocol into the scanners "so that it's just a button to press" for the MRI. "I think that will get us over a major hurdle of adaptation," Dr. Traboulsee said. "Most radiologists said once they started using it they were really happy with it. They found they were using it beyond MS for other basic neurologic imaging, so just raising awareness and making things more of a one-step process for individuals to use will be helpful," he said.

Repositioning consistency is key

Among key suggestions that the expert panel proposed for guideline updates include the use of the subcallosal plane for consistent repositioning, which should allow for more accuracy and consistency in the identification of lesions in MS, Dr. Traboulsee said. "A major change reflecting improvements in MRI technology is the ability to acquire high-resolution 3-D images and that's particularly helpful with fluid attenuation inversion recovery [FLAIR] sequences, which is what we do to identify lesions," he explained. "The repositioning along the subcallosal line is important because it allows us to easily compare studies over time. It takes very little time but allows us to prepare studies over time much more easily," he said.

Central vein sign

Another update is the establishment of a new category of optimum plus sequences allowing for the monitoring of brain atrophy and identifying lesions with a central vein sign, which has gained high interest as a marker on 3T MRI of demyelinating plaques in MS. As described in recent research, the central vein sign shows high accuracy in differentiating between MS and non-MS lesions.

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Newest oral DMTs haven't yet made a big impact in the MS world

"Now there are six oral DMTs competing among themselves for a relatively limited pool of patients."

The three oral disease-modifying therapies (DMTs) for multiple sclerosis (MS) approved last year in the United States haven't made a big splash in the marketplace. So far, it's more like a ripple, according to a study of neurologists' prescribing patterns. "The recently approved therapies will initially be niched as later line options," predicted Virginia R. Schobel, MSc, nephrology franchise head at Spherix Global Insights, an independent market intelligence firm in Exton, Pennsylvania.

At the virtual annual meeting of the Consortium of Multiple Sclerosis Centers, Ms. Schobel presented the results of a retrospective chart audit Spherix conducted in February 2020 of 1,006 patients with MS who were switched to a new DMT by 199 U.S. participating neurologists within the previous 3 months. About 72% of the patients had relapsing remitting MS (RRMS).

Assessing the three new oral DMTs The purpose of the study was to gain an understanding of the early adoption patterns for the three recently approved oral DMTs: Siponimod (Mayzent), cladribine (Mavenclad), and diroximel fumarate (Vumerity).

The first surprise was that only 41% of medication switches to a new DMT among the RRMS group were to oral DMTs; that is a substantially lower proportion than in prior Spherix chart audits. Instead, the most popular switch was to ocrelizumab (Ocrevus), a monoclonal antibody.

"Things to keep in mind when we see the switch shares for the newer products are just how crowded this market has become and how much Ocrevus has really changed the market," Ms. Schobel explained in an interview. "Ocrevus has become increasingly dominant in the RRMS segment, so that now there are six oral DMTs competing among themselves for a relatively limited pool of patients."

Because of grandfathering by the Food and Drug Administration, most of the oral DMTs now share identical indications

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CMSC MRI guidelines evolve into international consensus protocol

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"Many people have a few white spots on neuroimaging, but with MRI so much more available around the world, many of them are being misdiagnosed with MS," Dr. Traboulsee said. "But the central vein sign, using a very simple MRI technique, can identify lesions with a vein in the center that [distinguishes them as] MS lesions."

Though the process is still several years from routine clinical use, the proposed update would better implement susceptibility weighted imaging, which has traditionally been used for functional MRI.

PML surveillance

The updates also include recommendations to help in the detection of the rare but potentially serious complication of some disease-modifying therapies of progressive multifocal leukoencephalopathy (PML). "We need a very quick and comprehensive way to monitor patients for PML before symptoms develop," Dr. Traboulsee said. "The sequences we recommended were based on expert opinion of people who have worked quite a bit with PML in MS, and if one wants to survey for PML it's only about a 10-minute scan."

International protocol

The CMSC updated imaging guidelines are expected to be published in coming months. The most recent previous updates are available online.

Dr. Traboulsee disclosed relationships with Biogen, Chugai, Roche, Sanofi, and Teva. Dr. Li disclosed no relevant financial relationships. ■

—Nancy A. Melville

SUGGESTED READING

Sinnecker S, et al. Evaluation of the central vein sign as a diagnostic imaging biomarker in multiple sclerosis. *JAMA Neurol*. 2019;76(12):1446-1456.

Newest oral DMTs haven't yet made a big impact in the MS world

continued

for clinically isolated syndrome, RRMS, and active secondary progressive MS. Ocrevus, she noted, has the same indications.

Only 1% of MS patients who switched to a different DMT in late 2019 or early 2020 moved to diroximel fumarate. Three percent switched to siponimod, and another 3% switched to cladribine. Switches to the three older, established oral DMTs were collectively five times more common, with 15% of patients moving to dimethyl fumarate (Tecfidera), 11% to fingolimod (Gilenya), and 9% to teriflunomide (Aubagio).

Ms. Schobel said that the three latest oral DMTs offer advantages over the older ones in terms of various combinations of efficacy, dosing schedule, and tolerability, which may make them attractive options as first-line therapy. She predicted that over time, as neurologists gain increasing familiarity with these drugs as first line therapies, they also will gradually become more comfortable in turning to them as switch options.

First-time switches to an oral DMT among patients with RRMS were most often made in search of improved efficacy. Neurologists cited this as their main reason for 73% of switches to cladribine and 36% of switches to teriflunomide, with the other oral agents falling at various points in between. A switch to fingolimod was most often driven by a wish for a high-efficacy DMT with once-daily oral dosing. Improved tolerability figured prominently in switches to teriflunomide, and even more so in the relatively few changes to diroximel fumarate.

Drug switching in the pandemic era

Ms. Schobel said Spherix has been serially tracking neurologists' prescribing for MS during the COVID-19 pandemic, which has clearly had an enormous dampening effect on medication switching. In mid-April, neurologists' switching volume was down by 70%, compared with prepandemic figures. A slow recovery began in May, but by the end of the month, prescription-switching volume was still down by 52%.

Of the neurologist prescriptions that are being run for switching thus far during the coronavirus pandemic, 82% are being done via telemedicine. Therein lies a tale. Neurologists are using telemedicine to a lesser extent than physicians in the other specialties that Spherix monitors, according to Ms. Schobel.

"COVID is definitely changing the MS world. Within MS, drug switching is now much more likely to involve a switch to a DMT that doesn't impact the immune response and is not immunosuppressant, such as an injectable interferon or glatiramer acetate," she said. "In this COVID world, safety and conservatism may end up trumping the move toward 'time is brain' which we've been talking so much about in recent years: the importance of getting patients on high-efficacy DMTs from the start in order to give them the best chance for positive outcomes."

Ms. Schobel noted that Spherix received no industry funding to conduct these studies. ■

—Bruce Jancin