

MS RESEARCH UPDATE



Multiple Sclerosis
Association of America

The logo features the letters 'MS' in a large, bold, black font inside a teal square. Below this, the words 'RESEARCH' and 'UPDATE' are stacked in a bold, black, sans-serif font, with 'RESEARCH' on the top line and 'UPDATE' on the bottom line.

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The Multiple Sclerosis Association of America (MSAA) is pleased to present this 2020 edition of its *MS Research Update*. The Update highlights important new data on approved and experimental treatments for MS, and is provided to serve as a comprehensive resource for the entire MS community. Please note that the *MS Research Update* focuses on research related to approved and experimental medications and therapies for the long-term treatment of multiple sclerosis. It does not include information on symptom-management medications or therapies.

For additional information about MS, symptoms and symptom management, as well as MSAA's programs and services, please visit mymsaa.org or call **(800) 532-7667**. Also, please note that due to the timing of national and international MS conferences, study data from 2020 conferences generally could not be included in the Update. Information in this publication includes data presented at 2019 conferences, as well as important updates that occurred in the early months of 2020. Please visit MSAA's website at mymsaa.org for future summaries of 2020 conference highlights.

The 2020 *MS Research Update* is made possible through contributions in honor of:
Dr. Jules Kernan and Ms. Hannah Dennehy Lee and an anonymous supporter



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MSAA strives to provide useful, up-to-date information on matters of concern to MS patients and their families. This material is intended for general informational purposes only, and it does not constitute medical advice. You should not use the information presented as a means of diagnosis or for determining treatment. For diagnosis and treatment options, you are urged to consult your physician.

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Introduction

The 2020 *MS Research Update* reviews new data and findings on:

- Disease-modifying therapies (DMTs) approved by the FDA, including recently approved medications and those that have been available for several years
- Experimental drugs under investigation for the long-term treatment of multiple sclerosis (MS)
- New therapeutic approaches and treatment targets, such as stem cell therapy and the gut microbiome
- Promising areas of inquiry that are enhancing researchers' and clinicians' understanding of MS, such as genetics and biomarkers

While this 2020 edition of MSAA's *MS Research Update* provides a comprehensive overview of important areas of inquiry and study findings, it is not an exhaustive compilation of all relevant data released in the past year. There is - fortunately - far too much ongoing research for summation in a single

report. Rather, the items presented here were selected for their relevance to current or future patient care, and with a view toward showcasing the breadth of work being done to understand and treat MS. The information that follows is drawn from a variety of sources, including journal literature on MS and its management, a review of ongoing clinical trials, and presentations at major national and international conferences.

Please note that this *MS Research Update* reports on the most recent study results available at the time of publication. While every effort has been made to provide meaningful, timely, and balanced information, keeping the amount of information equal for each medication covered is not possible. Please understand that the different degree of coverage given to the various therapies should in no way be considered as favoritism toward any one medication or treatment approach. Additionally, references have been cited only for newer study results.

While medications for management of MS symptoms are beyond the scope of this report, information on the specific symptoms

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of MS and their treatment is available in the **symptoms section** of MSAA's website.

Providing these resources is at the heart of MSAA's mission of being a leading resource for the entire MS community, improving lives today through vital services and support. Feedback and thoughts on the 2020 *MS Research Update* are welcomed. These can be directed to MSAA at editor@mymsaa.org.

Overview of MS Research Progress

Never before have so many people been so keenly aware of the importance of medical research. With the arrival of the COVID-19 pandemic in early 2020, people who just a few months earlier had only a passing familiarity with the drug-development process, now understand more about the different trial phases.

This widespread appreciation for therapeutic innovation is just one of many ways the coronavirus has changed life for all people. For those with MS, however, the pandemic brings additional concerns and considerations. Does taking a disease-modifying therapy (DMT) that affects the immune system increase the risk of contracting COVID-19? Does having a chronic condition, such as MS, suggest more severe symptoms and worse outcomes should a person become infected? For information on those topics and related issues, visit **the Coronavirus and MS** section of MSAA's website.

Beyond its impact on the daily lives of people with MS, the COVID-19 pandemic also is affecting the course of multiple sclerosis research. For example, GeNeuro, a

biotechnology company investigating the monoclonal antibody temelimab for use in primary- and secondary-progressive MS, in March announced the postponement of a planned Phase II trial of the medication in order to "prioritize healthcare resources behind the fight of COVID-19 and to reduce the risk for MS patients." ¹ Meanwhile, MediciNova, the company developing the oral medication ibudilast for potential use in relapsing forms of MS, announced in April that it also will study the medication for use in acute respiratory distress syndrome (ARDS) caused by COVID-19. ²

While some temporary delays, detours, and distractions may be part of the near-term impact of COVID-19 on the MS research agenda, the long-term effect hopefully will include an enduring commitment to funding research against the full range of conditions – acute and chronic – that harm health and threaten lives. Meanwhile, investigators in clinics, hospitals, and laboratories around the world continue to explore the biological processes that lead to MS onset and progression, and the treatment approaches that can reduce or even halt disease activity.

There is abundant evidence that this research effort is making progress on many fronts. One of the most tangible markers of success is the expanding array of disease-modifying therapies (DMTs) available to treat MS.

Since the publication of MSAA's 2019 *MS Research Update*, the FDA has approved three more DMTs. In April 2020, Bafiertam™ (monomethyl fumarate) received approval for use in relapsing forms of MS. The Banner Life

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Sciences' medication is an oral agent taken twice daily. It is a fumarate-type medication, as is Biogen's Tecfidera® (dimethyl fumarate). Bafiertam obtained FDA approval after Banner Life Sciences showed that the medication is a "bioequivalent alternative" to Tecfidera, meaning that the active ingredient and site of action do not differ significantly between the two medications.³ Because Tecfidera can cause gastrointestinal (GI) effects - including nausea, vomiting, and diarrhea - in some patients,⁴ biopharmaceutical companies have explored formulations of fumarate medications that would have efficacy against MS - as Tecfidera has demonstrated - with fewer GI side effects. In the case of Bafiertam, this goal is being pursued through use of a daily dose lower than that for Tecfidera.^{4,5} However, whether or not Bafiertam causes fewer GI side effects has not yet been determined and has not been evaluated in clinical trials in people with relapsing forms of MS.

Another of the three recently approved medications pursues the same goal of reducing GI side effects by other means. In October 2019, the FDA authorized use of Vumerity® (diroximel fumarate) in relapsing forms of MS. Also an oral medication taken twice daily, Vumerity was developed by Biogen - which markets Tecfidera - and the Irish pharmaceutical company Alkermes plc. In this case, the chemical structure of Vumerity differs from that of Tecfidera, and the recently approved medication has been shown to cause fewer GI side effects than Tecfidera.⁶

The third medication recently approved by the FDA is Zeposia® (ozanimod), a once-daily oral medication from Bristol Myers Squibb. In

March 2020, the FDA approved the sphingosine 1-phosphate (S1P1)-receptor modulator for use in relapsing forms of MS. Two other S1P1-receptor modulators, Gilenya® (fingolimod) and Mayzent® (siponimod), also are FDA-approved for MS. How this class of medication exerts a therapeutic effect in MS is not completely understood. However, the mechanism of action may involve reducing the number of lymphocytes - white blood cells involved in immune function - that migrate to the central nervous system (CNS), where they may contribute to damaging the myelin sheath that protects nerves.⁷

Turning from medications approved by the FDA to those now being evaluated by the FDA, Janssen/Johnson & Johnson is requesting that another S1P1-receptor modulator, ponesimod, be approved for treating adults with relapsing forms of MS.⁸ The request is based on data from the Phase III OPTIMUM trial, in which patients treated with ponesimod had lower average annualized relapse rates than those receiving an already approved DMT, Aubagio® (teriflunomide).^{9,10}

Meanwhile, the FDA is conducting a priority review of ofatumumab for the treatment of relapsing forms of MS. Novartis, which markets the agent collaboratively with Genmab, says ofatumumab could be approved as early as this summer.¹¹ The monoclonal antibody, which already is indicated for treating chronic lymphocytic leukemia,¹² binds to the CD20 molecule located on the surface of lymphocytes, a type of white blood cell. Lymphocytes trigger the

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abnormal immune response that damages the protective sheath (myelin) surrounding nerve cells in the brain and spinal cord. By binding to CD20, the lymphocytes are destroyed and neuronal damage is prevented or delayed.

Ofatumumab is self-injected subcutaneously once a month, allowing for at-home administration.¹³ Novartis and Genmab are seeking approval for use of ofatumumab in MS based on data from the Phase III ASCLEPIOS I and ASCLEPIOS II trials, in which ofatumumab outperformed Aubagio in slowing disease progression in RMS.¹¹

Phase III trials, which generate the main data used to pursue FDA approval, are under way or planned for other potential MS treatments. TG Therapeutics hopes to provide results later this year from two simultaneous Phase III trials assessing the safety and effectiveness of its monoclonal antibody ublituximab in relapsing forms of MS.¹⁵ EMD Serono will evaluate its oral investigational agent evobrutinib in patients with relapsing MS in the Phase III EVOLUTION RMS 1 and EVOLUTION RMS 2 studies.¹⁶ Evobrutinib inhibits Bruton's tyrosine kinase (BTK), an enzyme that contributes to the development and function of B lymphocytes, a type of white blood cell that can attack and destroy the neuroprotective myelin sheath that surrounds nerve cells.¹⁶

MediciNova is organizing a Phase III trial that will determine whether its oral medication ibudilast, also known as MN-166, can slow disease progression in more-severe, non-relapsing MS. Ibudilast is a small molecule macrophage migration inhibitory factor (MIF) inhibitor and phosphodiesterase (PDE) -4 and

-10 inhibitor that suppresses pro-inflammatory molecules and promotes nerve-growth factors.¹⁷

On another research front, investigators continue to assess previously approved medications, examining their long-term effectiveness and safety, both in the overall MS population and in specific groups of people with MS. This *MS Research Update* reports on studies evaluating the impact of starting specific DMTs earlier rather than later following diagnosis, and of switching from one DMT to another. Inquiries are also examining how approved DMTs are affecting efficacy measures beyond relapse rates and MRI findings, such as confirmed disability progression, and the need for wheelchair use.

In terms of safety, research is examining the frequency and nature of adverse events with multi-year use, how DMTs affect maternal and fetal outcomes when used during pregnancy, and whether altering dosing schedules can reduce the incidence of adverse effects. Beyond evaluating pharmacologic agents, a plethora of research is probing the therapeutic potential of interventions ranging from stem cell therapy and dietary adjustments, to Vitamin D supplementation and altering the gut microbiome. Other studies are looking at the role genetics and other factors may play in the development and course of MS, and at how biomarkers such as serum neurofilament light (NfL) can help in monitoring MS status and informing treatment decisions. All of these topics are addressed in the sections that follow.

In short, thousands of clinicians and researchers around the world are exploring

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various aspects of MS, and their collective efforts promise even further progress in the years just ahead. It is important to remember, however, that the work of these physicians, nurses, biochemists, pharmacologists, and others would not be possible without the selfless participation of even larger numbers of people with MS. The patients who enroll in clinical trials, submit data to registries, and otherwise contribute to research, play an invaluable role in the effort to better

understand, more effectively manage, and one day defeat multiple sclerosis. If you already are counted among their ranks, you have our deepest gratitude. If you have not participated to date, we would encourage interested readers to ask their providers about possible opportunities to become involved in MS research. For more information about participating in clinical trials for the treatment of MS and its symptoms, readers may visit mymsaa.org/clinicaltrials.

Editor’s note: Initial study results for therapeutic agents under investigation should be considered preliminary because additional studies and/or evaluations may be needed to determine the long-term safety and efficacy of these agents. MSAA does not endorse or recommend any specific products or therapies. Readers are advised to consult their physician before making any changes to their medication, diet, exercise, or other treatment regimen.

TRIAL PHASES FOR INVESTIGATING TREATMENTS

Phase I	Phase II	Phase III	Phase IV
Phase I studies are primarily concerned with assessing the drug’s safety. This initial phase of testing in humans is done in a small number of healthy volunteers, and is designed to determine what happens to the drug in the human body – how it is absorbed, metabolized, and excreted.	Once a drug has been shown to be safe, it must be tested for efficacy. This second phase of testing may last from several months to two years, and involve up to several hundred patients. Phase II studies are often “double-blinded,” meaning that the participants, medical staff, and investigators are not told who is receiving the drug and who is receiving the placebo.	In a Phase III study, a drug is usually tested in several hundred to several thousand patients, usually in multiple medical facilities around the world. Phase III studies typically last two or more years. Only after a Phase III study is successfully completed can a pharmaceutical company request FDA approval for marketing the drug.	Phase IV clinical trials are conducted after a drug has been approved. Participants are enrolled to further monitor safety and side effects, while evaluating long-term efficacy.

Medications Recently Approved

Three more medications have joined the ranks of FDA-approved therapies for MS since the 2019 *MS Research Update* was posted. They are: Zeposia® (ozanimod), approved in March 2020; Bafiertam™ (monomethyl fumarate), approved in April 2020; and Vumerity® (diroximel fumarate), approved in October 2019. To follow is information on these medications, their approved uses and dosages, and their clinical data.

Zeposia® (ozanimod)

Company: Bristol Myers Squibb

- *Starting dose: 0.23 mg orally once daily on Days 1-4, followed by 0.46 mg orally on Days 5-7*
- *Maintenance dose: 0.92 mg orally once daily on Day 8 and thereafter*
- *Approved in March 2020 for relapsing forms of MS, including clinically isolated syndrome, relapsing-remitting disease, and active secondary-progressive disease, in adults.*

Zeposia® (ozanimod) is a sphingosine 1-phosphate (S1P1)-receptor modulator, meaning that it binds to two receptors – S1P1 and S1P5 – on the surface of cells.⁷ While the exact mechanism by which Zeposia exerts a therapeutic effect in MS is not completely understood, the medication’s impact may involve reducing the number of lymphocytes that migrate to the central nervous system (CNS), where lymphocytes may contribute to damaging the myelin sheath that protects nerves. This damage results in lesions, or areas of sclerosis (scarring/hardening), at different locations along the myelin sheath, giving rise

to the term “multiple sclerosis.”

Two other S1P1-receptor modulators, Gilenya® (fingolimod) and Mayzent® (siponimod) are also approved by the FDA for treating MS. Additionally, Janssen/Johnson & Johnson has asked the FDA to approve another medication in this class, ponesimod, for the treatment of relapsing forms of MS in adults.

Zeposia is an oral medication taken once daily. The initial dose of 0.23 mg on Days 1-4 is followed by a dose of 0.46 mg on Days 5-7, with a once-daily dose of 0.92 mg starting on Day 8 and continuing thereafter.⁷ This approach to increasing the starting dose over a few days, which clinicians call “up-titration,” is necessary because some people starting Zeposia may experience initial but temporary decreases in heart rate and delays in the way electrical signals are transmitted in the heart.⁷

Before beginning Zeposia, people should have a complete blood count (CBC), an electrocardiogram (ECG), and liver function tests (which involve analyzing a sample of blood that can be obtained from the same blood draw performed for the CBC). Physicians are advised to consider what other medications a person is taking in order to be aware of any potential interactions between

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those medications and Zeposia. They also need to conduct an eye examination in patients with a history of certain ophthalmologic problems, and to vaccinate patients against varicella zoster virus (VZV) if their blood does not contain antibodies against that virus, which causes chickenpox and shingles.

Zeposia is contraindicated in people who in the last six months experienced a heart attack, stroke, coronary-related chest pain, or certain other cardiovascular conditions.⁷ Unlike other approved S1P1-receptor modulators, however, the FDA-approved prescribing information for Zeposia does not direct that people taking the medication be monitored after their first dose for possible cardiac issues.¹⁸

The FDA's approval of Zeposia is based on data from two large Phase III trials, SUNBEAM and RADIANCE Part B, which together enrolled more than 2,600 people with MS. Both trials examined the safety and efficacy of Zeposia relative to Avonex® (interferon beta-1a). This interferon-based treatment is one of the first therapies approved for multiple sclerosis.¹⁸

In the two studies, people taking Zeposia had an annualized relapse rate (ARR) – a measure of the average number of relapses a group of patients will experience over the course of 12 months – of 0.18 at one year compared to 0.35 for Avonex, and of 0.17 versus 0.28 for Avonex over two years. Those rates translate into Zeposia providing a relative reduction in ARR of 48% at one year and 38% at two years compared to Avonex.^{7,19,20}

Further, at one year, Zeposia reduced the

number of T1-weighted gadolinium-enhanced brain lesions more than Avonex (0.16 vs 0.43), which is a relative reduction of 63%, and reduced the number of new or enlarging T2 lesions (1.47 vs. 2.84), which is a relative reduction of 48%.^{7,20} At two years, Zeposia achieved a 53% relative reduction in T1-weighted gadolinium-enhanced brain lesions and a 42% relative reduction in new or enlarging T2 lesions, compared to the interferon-based therapy.^{7,19}

However, in two other measures examined in the trials – impact on three-month and six-month confirmed disability progression (CDP), there was not a statistically significant difference between patients in the Zeposia group and those in the Avonex group over the course of two years.⁷

In the Phase III clinical trials, the most common adverse reactions (occurring in 4% or more of people receiving Zeposia) were upper respiratory infection, liver enzyme elevations, a fall in blood pressure upon standing (orthostatic hypotension), urinary tract infection, back pain, and hypertension. Please note that in clinical trials, all adverse effects reported by study subjects are recorded; these events may or may not be related to the medication. This is why control or placebo groups are used to compare with groups receiving the experimental medication being studied.⁷

People who participated in SUNBEAM, RADIANCE Part B, and earlier, Phase II studies of Zeposia were eligible to enter an extension study assessing the long-term safety and efficacy of the medication. Researchers recently reported on an interim analysis of

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data on almost 2,500 patients who participated in that extension trial.

Among patients who took 1 mg of Zeposia in any of the earlier trials and who then continued that dose over an average of 19.2 months in the follow-up study, the ARR was 0.126. Meanwhile, people who had taken an interferon-based medication in an earlier trial and then switched to Zeposia in the extension study, had a very similar annualized relapse rate - 0.123 - over an average of 18.3 months in the follow-up study.

The incidence and nature of adverse events were similar to those seen in the Phase III studies. The most common adverse event during the extension study was nasopharyngitis (a cold or sore throat), which was reported by 11.3% of participants. Just under 6% of participants reported a serious treatment-emergent adverse event, and just over 1% of participants stopped participating in the study due to an adverse event.²¹

Bafiertam™ (monomethyl fumarate)

Company: Banner Life Sciences

- *Starting dose: 95 mg twice a day, orally, for 7 days*
- *Maintenance dose after 7 days: 190 mg (administered as two 95 mg capsules) twice a day, orally*
- *Approved in April 2020 for relapsing forms of MS, including clinically isolated syndrome, relapsing-remitting disease, and active secondary-progressive disease, in adults.*

Bafiertam™ (monomethyl fumarate) is an oral medication taken twice daily for relapsing forms of MS. It is a fumarate-type medication, as is Tecfidera® (dimethyl fumarate). Bafiertam secured FDA approval after its developer, Banner Life Sciences, demonstrated that the medication is a “bioequivalent alternative” to Biogen’s Tecfidera, meaning that the active ingredient and site of action do not differ significantly between the two medications.^{3,5}

The issue of bioequivalence is important because Tecfidera has demonstrated efficacy in treating relapsing forms of MS but can cause significant gastrointestinal (GI) effects - including nausea, vomiting, and diarrhea - in some patients.⁴ As a result, drug developers have sought to find formulations of fumarate medications that offer similar efficacy but have fewer GI side effects. These efforts include Biogen partnering with Ireland-based Alkermes to develop the recently approved Vumerity® (diroximel fumarate), as detailed below, and Banner Life Science’s development of Bafiertam.

The starting and maintenance doses of Bafiertam are lower than those for Tecfidera.^{4,5} With the daily doses assumed to be equivalent in terms of their efficacy, the hope is that the reduced amount of Bafiertam will result in fewer GI side effects while providing similar benefit against relapses and other manifestations of MS. Although not studied in MS patients, a recent study compared the gastrointestinal tolerability of Bafiertam to Tecfidera in 210 healthy adults without MS. The five-week study has been completed, but results were not posted at the time of this writing.^{22,23}

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The exact mechanism of action by which fumarate medications exert their therapeutic effect in MS is not completely understood. However, the monomethyl fumarate molecule is thought to activate an antioxidant protein that reduces oxidative stress, which in turn slows damage to protective nerve fibers in the brain. Clinical trials with Tecfidera showed a reduction in relapse rate, a delay in progression of physical disability, and a slowing in the development of brain lesions, as compared to placebo.

According to the prescribing information for Bafiertam, the starting dose is one 95-mg oral capsule taken twice daily for the first seven days. The maintenance dose after seven days is two 95-mg capsules (for a total of 190 mg) taken twice daily. The prescribing information also warns not to crush, chew, or mix contents of the delayed-release oral capsules with food. However, Bafiertam may be taken with or without food.

Warnings, side effects, and adverse events are similar to those listed for Tecfidera. Bafiertam is contraindicated in patients with known hypersensitivity to monomethyl fumarate, dimethyl fumarate, diroximel fumarate, or to any of its inactive ingredients. Allergic reactions, PML (progressive multifocal leukoencephalopathy), herpes zoster and other serious opportunistic infections, decreases in white blood cell counts, and liver injury, are among the potential serious adverse events that could occur. Blood tests, including a complete blood count (CBC) and lymphocyte count, need to be performed prior to starting treatment, six months after starting treatment, and every six to 12 months

thereafter (as well as when clinically indicated).⁵

According to Banner, Bafiertam may cause flushing, which may be experienced as warmth, redness, itching, and/or a burning sensation. In clinical trials with Tecfidera, 40% of treated patients experienced flushing, which in most cases was mild to moderate in severity. As noted earlier, other common side effects include: redness, itching, or rash; nausea, vomiting, diarrhea, stomach pain, or indigestion. Flushing and stomach problems are the most common reactions, especially at the start of therapy, and may decrease over time.³

Vumerity® (diroximel fumarate)

Company: Biogen Inc. and Alkermes plc

- *Starting dose: 231 mg twice a day, orally, on Days 1-7*
- *Maintenance dose after seven days: 462 mg (administered as two 231-mg capsules) twice a day, orally*
- *Approved in October 2019 for relapsing forms of MS, including clinically isolated syndrome, relapsing-remitting disease, and active secondary-progressive disease, in adults*

Vumerity® (diroximel fumarate) is a fumarate agent, as is Biogen's Tecfidera® (dimethyl fumarate). However, it has a chemical structure that is distinct from Tecfidera, and has been shown to cause fewer gastrointestinal (GI) side effects – such as diarrhea, nausea, vomiting, and abdominal pain – than Tecfidera. The exact mechanism of

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action by which diroximel fumarate exerts its therapeutic effect in MS is not completely understood. However, upon entering the body, the medication is rapidly converted into the molecule monomethyl fumarate. The converted molecule is thought to activate an antioxidant protein that reduces oxidative stress, which in turn slows damage to protective nerve fibers in the brain.⁶

The FDA's October 2019 approval of Vumerity was based on a new drug application (NDA) that included data from pharmacologic studies comparing Vumerity and Tecfidera. By demonstrating that the two agents were similar in many key respects, or had "bioequivalence," Biogen and Alkermes were able to ask the FDA to consider findings on the safety and efficacy of Tecfidera as part of the evidence supporting Vumerity.⁶

The application also included interim exposure and safety findings from EVOLVE-MS-1, an ongoing, Phase III, single-arm, open-label, two-year safety study evaluating Vumerity in patients with relapsing-remitting MS. Interim results from EVOLVE-MS-1 at the time the application was submitted included a low overall rate of Vumerity treatment discontinuation due to adverse events (6.3%), which included less than 1% of patients discontinuing Vumerity due to gastrointestinal (GI) adverse events. Additional exploratory efficacy endpoints in the ongoing EVOLVE-MS-1 study showed changes in clinical and radiological measures compared to baseline.⁶

A few weeks after the FDA approved Vumerity, Biogen presented data from another Phase III study, EVOLVE-MS-2, that directly

compared the GI tolerability of Vumerity with that of Tecfidera.²⁴

EVOLVE-MS-2 was a multi-center, double-blind, active-controlled, five-week study involving 506 patients with relapsing forms of MS. The primary endpoint was the number of days patients reported GI symptoms with a symptom intensity score ≥ 2 on the Individual Gastrointestinal Symptom and Impact Scale (IGISIS) rating scale. Secondary endpoints included the number of days (relative to exposure) that patients reported GI symptoms with IGISIS intensity scores of ≥ 1 or ≥ 3 in the overall population. Patients who completed the five-week treatment period were eligible to enroll in EVOLVE-MS-1, the 96-week, open-label, safety study referenced above.

Results for the primary endpoint showed that patients treated with Vumerity reported 46% fewer days with intensity scores of ≥ 2 on the IGISIS, compared to Tecfidera.

The EVOLVE-MS-2 results also found that compared to people taking Tecfidera, patients receiving Vumerity had:

- Lower discontinuations due to GI adverse events (0.8% vs. 4.8%).
- Fewer days with IGISIS intensity scores of ≥ 1 and ≥ 3 (29% relative reduction and 44% relative reduction, respectively).
- Fewer days with a self-reported intensity score of ≥ 1 (30% reduction on the Global Gastrointestinal Symptom and Impact Scale [GGISIS], which assessed the overall intensity of GI symptoms, their impact on daily activities and how bothersome they were). Fewer days with GGISIS intensity scores of ≥ 2 and ≥ 3 were also observed.

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- A gradual decline in worst IGISIS intensity scores over the five-week treatment period.

These findings that use the patient-assessed symptom intensity scales were supported by lower investigator-reported incidences of GI adverse events with Vumerity (34.8%) compared to Tecfidera (49.0%). Overall, adverse events occurred in 78.3% of patients receiving Vumerity and 83.7% taking Tecfidera, but most of those

adverse effects were mild or moderate in severity. Overall, 1.6% of patients receiving Vumerity and 5.6% of those taking Tecfidera experienced adverse effects that caused them to stop participating in the study. Among those patients who discontinued due to any adverse effect, 0.8% in the Vumerity group stopped due to GI effects, as compared to 4.8% in the Tecfidera group.²⁴

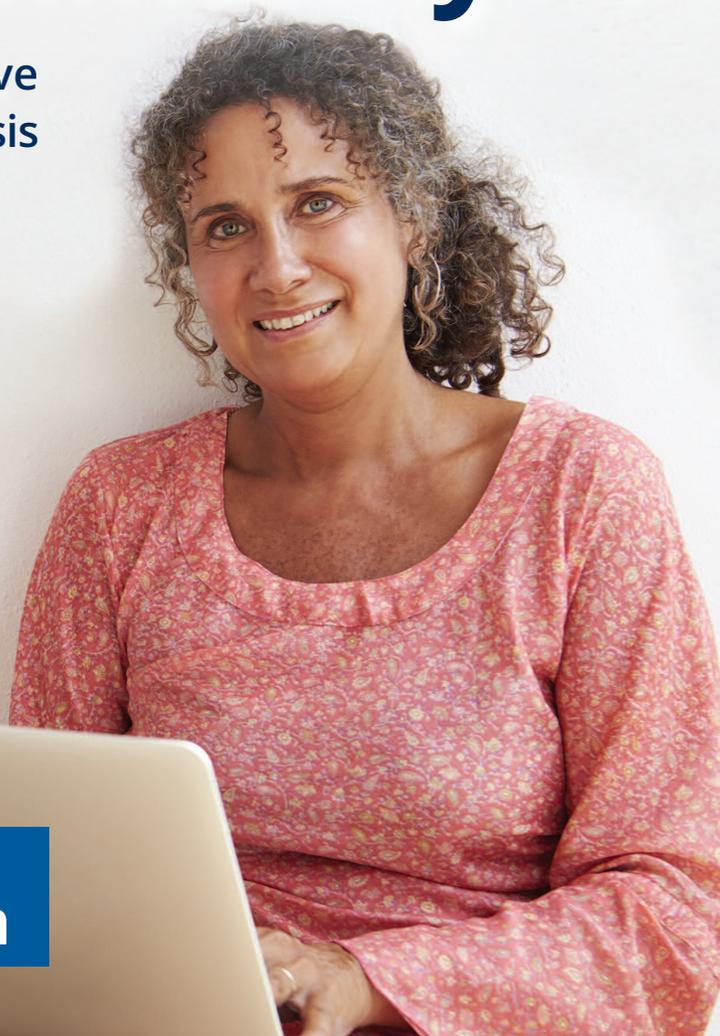
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FDA-APPROVED MEDICATIONS: NEW DATA ON PREVIOUSLY APPROVED MEDICATIONS

Please note that not all of the approved treatments for MS have been included in this section. For a full listing, please see **MSAA's treatment chart** giving an overview of the approved DMTs.

INFUSED MEDICATIONS

Ocrevus® (ocrelizumab)

Company: Genentech and Roche Pharma AG

- *Starting dose: 300 mg given via IV infusion, followed two weeks later by a second 300-mg infusion*
- *Subsequent doses: 600 mg given via IV infusion every six months*
- *Approved in 2017 for relapsing forms of MS (RMS) and primary-progressive MS (PPMS)*

Ocrevus® (ocrelizumab) is a humanized monoclonal antibody, meaning that it is an antibody from a non-human species whose protein sequences have been modified to increase their similarity to antibodies produced naturally in humans. Ocrevus works by destroying the CD20 receptor, a molecule that helps B cells receive messages from throughout the body. Destroying the CD20 depletes the B cells that can trigger neurodegeneration in MS.

A recent study found that people with relapsing-remitting MS (RRMS) who start Ocrevus early and respond to the monoclonal antibody may continue to benefit from the medication many years later. The findings, from an open-label extension of the OPERA I and OPERA II Phase III clinical trials, offer solid evidence for sustained first-line use

of Ocrevus in RRMS, researchers said.

During the OPERA trials, Ocrevus showed superiority over an interferon-based medication in slowing disease activity and progression over 96 weeks.²⁵ Patients who completed the 96-week, double-blind comparison trial entered a four-year, open-label extension phase, during which they either stayed with or switched to Ocrevus.

Among patients who switched from the interferon medication to Ocrevus, adjusted annualized relapse rates (ARR) fell from 0.20 in the year before the switch to 0.04 at Year 4 of the open-label phase. Patients who stayed on Ocrevus after the comparison phase also saw a decrease in ARR during the same period, from 0.13 to 0.05.²⁶

Another analysis suggests that early and intensive intervention with Ocrevus may provide meaningful benefit for people with MS who suffer early severe disability.

Researchers performed a post-study analysis of the OPERA I, OPERA II, and ORATORIO trials, in which Ocrevus showed efficacy in slowing disease activity and progression in patients with relapsing-remitting MS over 96 weeks, and in patients with primary-progressive MS (PPMS) over 120 weeks or longer. Drawing on data from those trials, investigators identified 882 patients with baseline Expanded Disability Status

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Scale (EDSS) scores of 4.0 or greater, 92 patients with baseline EDSS scores >5.0, and 88 patients with baseline EDSS scores >6.0. (On the EDSS scale, a higher score indicates a greater degree of disability.) The patients had received Ocrevus or a comparator – interferon beta-1a in OPERA or placebo in ORATORIO.

The researchers found that the incidence of EDSS score increases over a given 24-week period were significantly lower among patients who received Ocrevus compared with those who received interferon beta-1a or placebo. Ocrevus-treated patients from the ORATORIO trial who had high baseline EDSS scores also saw significant reductions in disability compared with placebo.²⁷

Another team of investigators recently examined the safety of Ocrevus in widespread, “real world” use. Researchers regularly compare clinical trial data on a medication’s safety with data collected after the medication has been approved by the FDA and prescribed by clinicians across the country. The purpose is to ensure that no new “safety signals” or other concerns emerge as a medication that had been tested in hundreds or thousands of patients in clinical trials now is given to a much larger number of people.

In one such study of Ocrevus, researchers analyzed safety outcomes data from the medication’s Phase II and Phase III trials, and from related open-label extension periods and sub-studies. Because length of exposure to Ocrevus varied among participants, rates of adverse events were calculated per 100 patient years, or the number of adverse

effects 10 patients would suffer in 10 years.

A total of 4,501 people with MS received Ocrevus in the clinical trials, amounting to 12,559 patient years of exposure. Side-effect rates per 100 patient years were:

- Adverse events: 255
- Serious adverse events: 7.52
- Infections: 77.1
- Serious infections: 2.01
- Malignancies: 0.47
- Adverse events prompting treatment discontinuation: 1.15

Using United States’ claims data and number of vials sold, the researchers then estimated that as of April 2019, 96,000 patients in the general population with MS had received Ocrevus, and that the prevalence of adverse events in this “real world” group is similar to the data reported for the clinical trials group.¹³

Turning from safety assessments to measures of effectiveness, investigators in the Phase III OPERA I, OPERA II, and ORATORIO clinical trials measured serum and plasma neurofilament light (Nfl) levels in study subjects. Nfl levels are an important marker of disability and disease progression in MS, with those levels tending to be higher in patients experiencing progressive disability than in patients with stable disease.²⁸

After 96 weeks, NfL levels were significantly lower among patients who received Ocrevus relative to levels in the studies’ comparator groups. Among 621 people with either RRMS or PPMS whose baseline NfL levels were above the 90th

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percentile of normal, a higher proportion of individuals treated with Ocrevus saw their NfL decrease to normal levels, compared with those who received interferon beta-1a (81.4% vs 58.9% in RRMS) or placebo (40.4% vs 16.6% in PPMS). Higher baseline NfL levels also predicted increased disability progression in PPMS, and were linked to worse outcomes for patients with RRMS treated with interferon beta-1a, as evidenced by changes in Expanded Disability Status Scale, Nine-Hole Peg Test, and Timed 25-Foot Walk scores.²⁹

Tysabri® (natalizumab)

Company: Biogen

- *300 mg given via one-hour IV infusion every four weeks*
- *Approved in 2004 for relapsing forms of MS*

Tysabri® (natalizumab) is a monoclonal antibody that acts against a molecule involved in the activation and function of lymphocytes, immune system cells produced to fight infection and disease. Tysabri also acts against the passage of lymphocytes into the central nervous system (CNS), which consists of the brain, spinal cord, and optic nerves.

The FDA approved Tysabri in 2004 based on positive results in the Phase III AFFIRM trial. Tysabri was voluntarily withdrawn from the market in 2005, after three cases of progressive multifocal leukoencephalopathy (PML), a rare but potentially fatal brain infection caused by the JC virus, were

identified in patients taking the medication. Tysabri became available again in 2006, based on the implementation of a comprehensive risk-management program that includes testing potential Tysabri users to see if they have anti-JC virus antibodies.³⁰

In an attempt to reduce the risk of PML, some clinicians are extending the interval between Tysabri doses, adopting a personalized dosing strategy that has been used to mitigate the adverse effects of extra-strength antibiotics and other medications.³¹ As more physicians stretch out the time between doses beyond the recommended four weeks, researchers decided to assess how this risk-reduction approach affects the medication's therapeutic effects.^{4,31}

Investigators leading a two-year study are recording several measures of disease progression in 61 adults with MS who had no disease activity in the 12 months before enrollment. Treatment intervals are being adjusted to maintain the lowest therapeutic concentration of Tysabri (10 mcg/mL) for each patient before the next dose is given.

At the time interim study results were released, the 10 mcg/mL level had been maintained with extended dosing intervals of five to seven weeks in 84% of patients. No gadolinium-enhanced lesions or new or enlarging T2 lesions had been reported. Also, Expanded Disability Status Scale and MS Functional Composite scores had not increased, and serum levels of neurofilament light, an important indicator of MS disease activity, had remained low.

While biomarkers suggested some degree of disease activity among a subset of

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patients, the findings suggest that Tysabri dosing intervals can be safely expanded on a patient-by-patient basis.³¹

Other researchers recently found greater cognitive improvement among people who started Tysabri early in the course of their MS than in individuals whose treatment was delayed. The findings suggest that the earlier treatment can be started, the greater the chances of maintaining a patient's cognitive function, researchers said.

A total of 2,069 patients with relapsing MS who were treated with Tysabri for at least 12 months were followed at 58 neurology clinics across Sweden. The participants were divided into two groups: those who started treatment within three years after MS onset, and those who started treatment later. Symbol Digit Modalities Test (SDMT) scores were collected at the start of Tysabri therapy, at six months and at one year after the start of treatment, and annually thereafter.

SDMT scores improved overall in both groups across the median 72-month follow-up, but the rate of improvement was an average of 0.38 points per year lower in the late-treatment group compared with patients who started treatment early.

When SDMT scores were examined by age, no difference in score trajectory was noted among patients younger than age 36 years, regardless of when they started treatment. Among patients aged 36 and older, however, SDMT score improvements were on average 0.45 points lower per year of follow-up among late-treated patients vs. early-treated subjects.

Of note, individuals who started Tysabri

early had fewer relapses (1.91 vs 3.2) and modestly higher SDMT scores (52 vs 50) in the year before starting Tysabri early, compared with late-treated patients.³²

Tysabri has long-term effectiveness in delaying relapses and slowing disability progression among people with relapsing-remitting MS, another ongoing study suggests.

The Tysabri Observational Program (TOP), begun by the medication's manufacturer after Tysabri was approved by the FDA in 2004, is an open-label, multinational, prospective study that assesses the efficacy and safety of Tysabri in real-world clinical settings. As of November 2017, the continuing study included 6,148 patients with RRMS who received or are still receiving Tysabri. Median exposure to the medication was 3.3 years, and nearly 500 patients received Tysabri for eight years or longer. Median follow-up was 62 months as of the November 2017 review.

During the analysis, the annualized relapse rate (ARR) for patients on Tysabri fell from 1.99 in the year before treatment initiation to 0.15. Of note, ARRs for individuals taking Tysabri were significantly lower among patients with baseline Expanded Disability Status Scale scores of 3.0 or less, having taken two or fewer prior disease-modifying therapies, or no more than one relapse in the year prior to treatment.

Additionally, EDSS scores were stable throughout the analysis. At 10 years, the cumulative probability of 24-week confirmed disability worsening was 27.8%, and the cumulative probability of 24-week confirmed disability improvement was 33.1%.

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Of the 5,179 patients with baseline EDSS scores of 2.0 or higher, 1,210 (23.4%) experienced a confirmed disability improvement event.

The safety profile of Tysabri was consistent with adverse events (AE) reported in clinical trials. One or more serious AE was reported in 829 patients (13.5%). Infection was the most common AE, reported by 4.1% of patients. PML occurred in 53 patients (0.9%), while breast cancer and other malignancies occurred in 1.1%.³³

Meanwhile, a recent Italian study found that use of Tysabri during pregnancy is associated with a lower risk of relapse but a greater incidence of newborn anemia compared to stopping the agent before conceiving.

Researchers followed 84 expectant mothers who were receiving Tysabri at 19 MS centers. Participants were divided into three groups: women whose last Tysabri infusion occurred before their last menstrual period (Group 0), those who were last infused during the first trimester of pregnancy (Group 1), and those who continued treatment throughout pregnancy (Group 2).

Annualized relapse rates (ARR) during pregnancy were 1.06 among Group 0 expectant mothers, 0.49 for those in Group 2, and 0.09 for women in Group 3. Among the women who restarted Tysabri after giving birth, ARR 12 months postpartum were 0.39 for women in Group 0 and 0.23 for women in Group 1.

Researchers also analyzed data on the 94 infants who were born during the study and compared pregnancy outcomes among

groups. No differences in mean gestational age or birthweight were found. However, major and minor malformations were reported in seven infants in Groups 1 and 2 (women who stopped natalizumab in early pregnancy or continued throughout), compared with one in Group 0 (women who stopped before pregnancy). Anemia was found in five newborns from mothers in Group 2, including three infants who were born prematurely.

The researchers commented that continuing Tysabri during pregnancy “is associated with lower risk of relapses compared to wash-out and early interruption. No worrisome adverse events emerged in newborns. Occurrence of anemia is consistent with previous findings and may be biased by prematurity.”³⁴

Please note that women who are pregnant or are planning to become pregnant, while considering or taking a DMT, are advised to consult their physician.

Lemtrada® (alemtuzumab)

Company: Sanofi Genzyme

- *Intravenous infusion over four hours for two treatment courses:*
- *First course: 12 mg/day on five consecutive days;*
- *Second course: At one year, 12 mg/day on three consecutive days;*
- *Approved in 2014 for relapsing forms of MS*

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Lemtrada (alemtuzumab) is a monoclonal antibody formulated to slow or prevent the immune system's destruction of the neuroprotective myelin sheath by killing white blood (immune) cells. The United States' prescribing information for the medication describes the risk of serious and potentially fatal adverse events with use of the medication, including stroke, autoimmune conditions, infusion reactions, and certain cancers.³⁵

The EMA made the recommendations after its drug-safety monitoring committee received reports of cardiovascular issues – including heart attacks and strokes – as well as immune complications in people with MS taking Lemtrada.³⁶ Because of the potential toxicity associated with Lemtrada, the manufacturer advises using the agent only in "patients who have had an inadequate response to two or more [DMTs]."³⁵

Meanwhile, findings from a recent long-term analysis suggest that people receiving Lemtrada for relapsing-remitting MS may retain function nearly a decade after starting treatment.

Over the course of four years, Lemtrada significantly improved clinical and imaging outcomes in the CARE-MS I clinical trial and a subsequent extension study. An additional five-year extension trial, TOPAZ, assessed participants' continuing function and disease progression. Patients could receive Lemtrada or another disease-modifying therapy as needed at the investigators' discretion. Among Lemtrada-treated patients in the

original CARE-MS I study, 75% stayed in the study through the entire five-year extension phase, and 55% required no additional treatment with Lemtrada or another disease-modifying therapy.

After the full nine-year study period:

- 68% of patients showed no signs of confirmed disability progression over a given six-month period, and 41% showed improvement after confirmed six-month disability progression.
- The mean increase Expanded Disability Status Score (EDSS) was 0.10, suggesting overall minimal disability progression. Also, 77% of patients had improved or stable EDSS scores.
- 89% of patients showed no gadolinium-enhanced lesions, and 68% were free of new or enlarging T2 lesions. Also, 68% showed no disease activity after magnetic resonance imaging.
- Median cumulative brain volume loss (BVL) was 1.97%. Also, median annual BVL was 0.22% or less in Years 3 through 9.

Lemtrada also maintained a consistent safety profile throughout the extended nine-year period. The cumulative incidence of thyroid-related adverse events was 46%, and the incidence of immune thrombocytopenia (an uncommon disorder marked by reduced platelet counts) was 2%. Overall, the incidence of drug-related adverse events and infections declined over the nine-year period.³⁷

ORAL MEDICATIONS

Mayzent® (siponimod)

Company: Novartis

- *Starting dose for most patients: 0.25 mg orally on Day 1, increasing in 0.25-mg increments over five days to 1.25 mg.*
- *For patients with CYP2C9*1/*3 or *2/*3 genotype, 0.25 mg on Days 1 and 2, increasing to 0.5 mg on Day 3 and 0.75 on Day 4.*
- *Maintenance dose: 2 mg daily orally for most patients; 1 mg daily orally for patients with CYP2C9*1/*3 or *2/*3 genotype*
- *Approved in 2019 for relapsing forms of MS*

Mayzent® (siponimod) is a sphingosine 1-phosphate (S1P)-receptor modulator, meaning that it binds to two receptors, called S1P1 and S1P5, on the surface of cells. By binding to these receptors, Mayzent blocks lymphocytes (a type of white blood cell) from leaving the lymph nodes and entering the peripheral blood. While the mechanism by which Mayzent exerts its effects in MS is not fully understood, it may involve reduction of lymphocyte migration into the central nervous system (CNS).²⁵ Further, Mayzent binds to S1P1 and S1P5 receptors on oligodendrocytes and astrocytes, cells within the CNS, which are thought to promote remyelination and prevent inflammation.³⁸

Mayzent was the first FDA-approved oral drug to treat secondary-progressive MS in adults experiencing active disease. Mayzent is also approved for use in clinically isolated syndrome (CIS) and relapsing-remitting MS (RRMS).³⁹

A recent study found that Mayzent may delay or prevent wheelchair dependence in some people with secondary-progressive MS (SPMS). In the Phase III EXPAND study that led to Mayzent receiving FDA approval, the medication delayed disability progression and cognitive decline among those with SPMS.

Investigators subsequently performed two analyses on data for participants in the EXPAND active treatment and placebo groups. The first analysis measured time to wheelchair dependence in 412 patients with a baseline Expanded Disability Status Scale (EDSS) score of 6.5, which indicates dependence on a walking device and high risk of progression to a wheelchair. In that group, EDSS scores increased to 7.0 (indicating wheelchair dependence) in 19.8% of Mayzent-treated patients, compared with 26.1% of those in the placebo group.

In the second analysis, researchers split the overall EXPAND population of 1,645 participants into three groups by EDSS score range: 5.0 or lower; 5.5 to 6.0; and 6.5. The investigators then calculated the time each patient stayed in an EDSS range before moving to another, and used that information to predict time to wheelchair dependence for

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patients at any EDSS range.

Based on this analysis, the researchers found that Mayzent reduced the risk of progression from an EDSS of 5 or less to EDSS 5.5 or 6 by 21%, and reduced the risk of worsening from an EDSS of 6.5 to 7.0 by 28%, compared with placebo. Assuming that the effect of Mayzent would remain stable over time, the researchers predicted that Mayzent may extend the median time to wheelchair dependence by 4.3 years in the overall study population, compared with placebo.⁴⁰

Another analysis of EXPAND data by a separate team of investigators found further evidence that Mayzent reduces the risk of confirmed disability progression (CDP) in people with active SPMS. The researchers evaluated data on 779 EXPAND study participants with active SPMS, which was defined as having suffered one or more relapses in the two years before screening, or having one or more T1 gadolinium-enhancing lesions at baseline. A total of 516 patients in the active-disease group received Mayzent, while 263 received placebo.

The analysis found that Mayzent reduced the risk of three-month CDP by 31% and the risk of six-month CDP by 37%, compared with placebo. Among patients in the treatment group, Mayzent also:

- Lowered the annualized relapse rate by 46%.
- Reduced T1 gadolinium-enhancing lesions by 85%, and new or enlarging T2 lesions by 80%. Also, T2 lesions were smaller at 12 months and 24 months in the

treatment group, compared with placebo.⁴¹

Meanwhile, a six-year analysis of Mayzent-treated patients uncovered no major safety concerns or increased incidence of adverse events (AEs), but underscored the need to monitor patients for tolerability issues. It should be noted that just because a person experiences an adverse event while taking a medication, it does not necessarily mean that the medication caused that event. Researchers record all adverse events to look for patterns that may suggest an association between the medication and the event.

Researchers typically perform long-term studies of medications to determine their safety and tolerability in real-world practice. In this analysis, researchers studied two groups of patients: a “controlled pool” of 1,755 people who received Mayzent or placebo during the medication’s core clinical trials, and a “long-term pool” of 1,737 people who received at least one 2-mg or 10-mg dose of Mayzent in either the core or extension trial phases. Mean exposure to Mayzent was 17.7 months in the controlled pool and 27.8 months in the long-term pool, and 127 people in the long-term pool received Mayzent for five years or longer.

In the long-term pool, 90% of patients had at least one adverse event, 20.7% had at least one serious adverse event (AE), and 9.6% had AEs that led to study discontinuation. Rates of infection in the long-term and controlled pools were 43.2 and 48.9, respectively, per 100 patient years (the number of infections 10 patients would suffer in 10 years). By

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comparison, the infection rate in the placebo group within the controlled pool was 53.8 per 100 patient years. Also, between 42.3% and 53% of Mayzent-treated patients with low levels of lymphocytes (an infection-fighting type of white blood cell) contracted infections, but these percentages were similar to those in the placebo group and did not indicate an increased infection rate compared with previous data.

The most common AEs in both groups were headache, urinary tract infection, falls, high blood pressure, and the common cold. The incident rates ranged from 4.9 to 11.3 per 100 patient years, and were similar between both patient pools.⁴²

A new six-month, multicenter, open-label study called EXCHANGE will examine the safety of switching patients currently taking another disease-modifying therapy (DMT) to Mayzent. The study will recruit 300 patients with relapsing-remitting MS from 80 MS treatment centers throughout the United States. Individuals with the CYP2C9*3/*3 genotype are ineligible, as this genotype slows the body's ability to process Mayzent and increases the risk of medication-related adverse effects.

Study participants will switch from their current DMT to Mayzent within 24 hours of study entry. Patients who have been taking Aubagio, which is metabolized more slowly than other DMTs,⁴³ will stop Aubagio and wait 14 days before starting Mayzent. Participants will start Mayzent at a low dose, and then be titrated over five days to 2 mg daily at Day 6. Participants will be monitored for adverse effects throughout the six-month

analysis, as well as for treatment satisfaction, treatment adherence after switching, and cardiac safety.²⁹

Mayzent is contraindicated in those who experienced a cardiovascular event or who were diagnosed with severe heart failure in the past six months. Physicians are advised to perform an echocardiogram and check for use of other medications that affect heart function before starting Mayzent.³⁹

Mavenclad® (cladribine)

Company: EMD Serono

- *3.5 mg/kg divided into two yearly treatment courses of 1.75 mg/kg*
- *Approved in 2019 for relapsing forms of MS*

Mavenclad® (cladribine) is an antimetabolite that reduces the number of lymphocytes, which are white blood cells that are part of the immune system. It long has been used to treat hairy cell leukemia, and regulatory authorities in other countries approved it to treat MS several years before the FDA granted its approval in 2019. The FDA acted later than other regulatory agencies in part because of concerns about Mavenclad potentially increasing the risk of cancer in some patients. Indeed, the prescribing information for Mavenclad includes a boxed warning that the medication may increase risk for malignancy, adding that clinicians should weigh the benefits and risks of treatment on an individual basis, considering a patient's specific history of, or risks for, cancer.

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The prescribing information also notes that, due to its safety profile, “use of Mavenclad is generally recommended for those who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for treatment of MS.” Mavenclad also is contraindicated in pregnant women, and in men and women of reproductive potential who do not plan to use effective contraception. This contraindication stems from concerns about potential birth defects.⁴⁴

However, new findings provide reassuring news regarding both the safety of Mavenclad and its ability to slow disease progression in people with MS.

Researchers reviewed safety data for 211 patients who received between one and three cycles of Mavenclad. The patients had either relapsing-remitting or progressive MS, and showed disease activity based on magnetic resonance imaging (MRI) scans and measurement of neurofilament light chains (NfL) in cerebrospinal fluid. Patients received three to four 10-mg Mavenclad doses at the start of the study, plus as many as three more 10-mg doses five weeks later if their lymphocytes (a type of infection-fighting white blood cell) were at normal levels. Mavenclad can diminish lymphocytes to dangerously low levels; the manufacturer advises regular blood testing before and during treatment.⁴⁴

A total of 154 patients completed another cycle of treatment 11 months after the initial cycle. Overall, Mavenclad was well tolerated. Severe lymphopenia (shortage of lymphocytes) occurred in less than 3% of participants, and 12 patients had skin

reactions that resolved shortly after treatment. One patient survived a heart attack, and another was diagnosed with breast cancer. Two patients died, but neither death was believed by investigators to be medication-related.

Mavenclad also showed efficacy in slowing MS disease progression. The rate of no evidence of disease activity (NEDA) was 71% among patients with RRMS, and the rate of no evidence of progression or active disease (NEPAD) was 38% among patients with progressive MS. Of 23 patients with elevated NfL initially, 22 had normal levels at follow-up.⁴⁵

Tecfidera® (dimethyl fumarate)

Company: Biogen

- *Starting dose: 120 mg twice a day, orally for seven days; ongoing dose: 240 mg twice a day, orally*
- *Approved in 2013 for RMS*

The exact means by which Tecfidera® (dimethyl fumarate) exerts its effects in MS is not known. The medication has been shown to activate a pathway involved in the cellular response to oxidative stress, which is induced by inflammation. However, it is unclear whether this pathway activation plays a role in Tecfidera’s impact on the MS disease process.⁴

In 2017, the prescribing information for Tecfidera was revised to include direction to obtain a complete blood cell count and to measure liver enzymes and other values before initiating the medication. Additionally,

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warnings were added to the prescribing information noting that progressive multifocal leukoencephalopathy (PML), a rare but serious brain infection, and liver injury, have occurred in people taking Tecfidera.⁴

A recent study found that patients with relapsing-remitting MS (RRMS) respond well to Tecfidera and generally adhere to treatment, regardless of whether they switched from a previous disease-modifying therapy or were being treated for the first time. The findings offer a glimpse into the real-world efficacy of Tecfidera, and may guide physicians' use of the oral agent at various stages of RRMS.

Researchers reviewed the records of 456 people with RRMS at six MS treatment centers in Italy. These individuals either had started treatment with Tecfidera or switched to the medication from another DMT. Two of every three patients studied were women, and the group had a mean Expanded Disability Status Scale (EDSS) score of 2.5, indicating mild to moderate disability for many of these individuals. The participants' mean age was 40 years, and mean MS disease duration was nine years.

The annualized relapse rate was reduced by 75% from baseline among those treated with Tecfidera. However, study participants with an elevated pre-treatment EDSS score (suggesting more-severe disability) were more likely to discontinue the medication, compared to those who had mild to moderate disability before treatment. Also, patients who de-escalated from a stronger but potentially more-toxic second-line therapy to Tecfidera faced an increased risk

of relapse.

Among the other findings:

- EDSS scores were stable in 88% of patients.
- The younger the patient, the lower the risk of relapse.
- The shorter patients' disease duration, the greater their chance of achieving no evidence of disease activity (NEDA) over a three-month period.⁴⁶

Meanwhile, an analysis of 665 people with MS in Denmark and Switzerland sought to measure real-world discontinuation rates for Tecfidera and determine why patients stop the medication. The average length of Tecfidera use among the study subjects was 15.3 months. The researchers found that 200 patients (30.1% of the study population) discontinued Tecfidera, with 115 of them citing adverse events as the main reason. Lymphopenia (a shortage of an infection-fighting white blood cell), gastrointestinal (GI) discomfort, and flushing were the most common adverse effects reported. Disease activity and pregnancy were also common reasons for discontinuation.

Among those who discontinued Tecfidera within three months after starting treatment, GI discomfort was the most common reason cited. Lymphopenia, GI effects, and disease activity were common reasons among those who stopped after three to 12 months, while lymphopenia and disease activity drove discontinuation after one year.⁴⁷

Pregnancy is a common reason for stopping Tecfidera and other DMTs, as

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reflected in the findings from the study just cited. While clinical trials and post-marketing data have not found evidence that exposure to delayed-release Tecfidera during pregnancy poses safety concerns for the mother or unborn child, the medication's manufacturer advises that the agent may cause fetal harm based on animal studies.⁴ However, recent research may provide reassurance for women who are weighing the risks and benefits of taking Tecfidera during pregnancy. As noted earlier, women who are pregnant or planning on becoming pregnant, and who are taking or considering a DMT, should consult with their physician.

Researchers reviewed data from an ongoing registry of women with MS who took Tecfidera one day before their last menstrual period, before conception, or during pregnancy. Data were obtained at enrollment, at six to seven months of gestation, at four weeks after estimated delivery date, and at four, 12, and 52 weeks after birth. Mean duration of fetal exposure to dimethyl fumarate was 5.7 weeks.

As of October 2018, a total of 194 births were reported, including 177 live births and 17 fetal deaths (16 miscarriages and one stillbirth). No ectopic or molar pregnancies, nor infant or maternal deaths, occurred. Of the 174 infants for whom gestational age was known, 160 were born full-term and 14 were premature. Of the 144 infants for whom gestational size was recorded, 119 were appropriately sized, 13 were small, and 12 were large. Birth defects were reported among seven (4%) of the 194 births.⁴⁸

Aubagio® (teriflunomide)

Company: Sanofi Genzyme

- *Starting dose: 7 mg once daily*
- *Approved in 2012; indicated for relapsing forms of MS*

As is the case with many other disease-modifying therapies (DMTs) used to treat MS, the exact mechanism by which Aubagio® (teriflunomide) exerts its therapeutic effect has not yet been fully determined. In the case of Aubagio, the mechanism may involve reducing the number of activated lymphocytes - immune-system cells - in the central nervous system. The medication has anti-inflammatory properties and has been shown to inhibit the synthesis of pyrimidine, an organic compound involved with various cells and processes throughout the body.⁴³

Recently reported study results indicate that Aubagio may alleviate the fatigue that commonly afflicts individuals with relapsing-remitting MS (RRMS).

Teri-FAST, an observational study conducted in France, followed 210 patients with RRMS who were receiving 14 mg daily of Aubagio. Of these patients, 110 had not received a disease-modifying therapy (DMT) prior to Aubagio, and 100 had switched to Aubagio from another DMT. Fatigue was measured using EMIF-SEP, the French version of the Modified Fatigue Impact Scale. Data on fatigue and medication adherence were collected at baseline and at six months, one year, and two years after treatment initiation.

After two years, the overall mean reduction from baseline in EMIF-SEP scores

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was 1.5 points, suggesting a decrease in fatigue with Aubagio. Significant mean two-year EMIF-SEP score reductions were also reported among those previously treated with other DMTs, suggesting that Aubagio may reduce fatigue regardless of the patient's treatment history. At the two-year point, 126 patients were still taking Aubagio, with 123 of these patients taking the medication daily. Adverse events were reported in 27.5% of the total patient population.⁴⁹

Another study showed that Aubagio helped patients maintain quality of life over two years, even though adverse effects (AEs) with the medication were common.

The Teri-LIFE study followed 200 adults in Scandinavia treated with Aubagio 14 mg daily for RRMS. Patients' quality of life assessed was every six months with the Short Form-36 (SF-36) questionnaire. Slightly more than seven of 10 participants were women. The mean age for all participants was 44.1 years, and the mean time since diagnosis at study entry was 3.6 years. The median Expanded Disability Status Scale score was 2.0, suggesting that many patients had mild to moderate disability at study initiation.

Mean SF-36 scores remained stable from baseline through Year 2, ranging from 46.5 to 47.7 for the physical component and from 46.6 to 48.8 for the mental component. The on-treatment annualized relapse rate was 0.17, and 79% of patients experienced no relapses.

At the two-year mark, 118 individuals (59%) were still taking Aubagio; 22% had discontinued because of adverse events (AEs), 9% stopped due to lack of efficacy,

and 10% discontinued for other reasons. The most common AEs reported were hair thinning (26.5%), diarrhea (23%), and fatigue (20%). Serious AEs were reported by 11% of patients. These percentages, were similar to the prevalence of AEs reported in clinical trials of Aubagio.⁵⁰

Gilenya® (fingolimod)

Company: Novartis

- *Starting dose: 0.5 mg once daily for patients weighing more than 88.2 lbs (40 kg); 0.25 once daily for patients weighing 88.2 lbs (40 kg) or less*
- *Approved in 2010; indicated for clinically isolated syndrome (CIS), relapsing multiple sclerosis (RMS), and active secondary-progressive multiple sclerosis (SPMS) in patients aged 10 years and older*

Gilenya® (fingolimod) was the first sphingosine 1-phosphate (S1P)-receptor modulator approved for the treatment of MS. In 2018, the FDA expanded the approved uses of Gilenya to include treatment of children ages 10 years and older with relapsing forms of MS, clinically isolated syndrome, and active secondary-progressive MS. Gilenya is similar in structure to a naturally occurring component of cell-surface receptors on white blood cells. (White blood cells are produced by the immune system to fight infection and disease.) Gilenya blocks potentially damaging T cells from leaving lymph nodes, lowering their number in the blood and tissues. It may reduce damage to

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the central nervous system (CNS) and enhance the repair of damaged nerves within the brain and spinal cord.⁵¹

A study comparing Gilenya with an interferon-based medication in pediatric patients found that Gilenya was more effective in slowing disease progression in children and adolescents with MS.

The study assigned 215 children and adolescents ages 10 to 18 years to receive either Gilenya at 0.25 or 0.5 daily depending on body weight, or interferon beta at 30 mcg per week. Magnetic resonance imaging (MRI) scans were taken every six months for two years or until treatment was stopped.

After two years, the children receiving Gilenya had a 66% lower annualized rate of formation of gadolinium-enhancing T1 lesions, compared with the interferon group. Annualized rates of new or enlarging T2 lesions were 52.6% lower in the Gilenya group, and rates of T1 hypointense and combined unique active lesions were 62.8% and 60.7% lower, respectively, with Gilenya than with interferon. T2 and gadolinium-enhancing T1 lesion volumes also were lower among youths receiving Gilenya. Of note, approximately 77% of children treated with Gilenya showed no gadolinium-enhancing lesions after the study, compared with 54% of the interferon group.⁵²

While Gilenya demonstrated its efficacy in the clinical trials that led to its approval, French researchers wanted to know more about its effectiveness and safety over the long term in real-world clinical settings, where patients may be in poorer overall health and

receive less-intensive management compared with a controlled trial setting.⁵³

The VIRGILE trial, a multicenter, observational study, observed 1,052 adults with highly active RRMS who received Gilenya between 2014 and 2016. For comparison, researchers also studied 331 patients treated with Tysabri, the intravenously administered disease-modifying therapy (DMT) throughout the same period. All participants were analyzed every six months. A total of 1,064 patients from either group completed two years of follow-up; 923 of them completed three years, and some patients in the Gilenya group continued treatment in an additional two-year extension study.

Annualized relapse rates (ARRs) at baseline were 1.0 in the Gilenya group and 2.1 among patients treated with Tysabri. The ARR rates decreased to 0.3 in both groups after two years and three years, and ARR rates for the Gilenya patients were 0.2 after 4 years. Also, mean Expanded Disability Status Scale (EDSS) scores remained stable for both groups, changing from 2.7 to 3.0 over four years for Gilenya patients and from 3.2 to 2.9 over three years in the Tysabri group. The findings suggest that oral Gilenya may be an alternative to second-line IV therapy in those with active MS, the researchers said.

Over the entire study period, 59.4% of the Gilenya group and 52.3% of Tysabri patients reported one or more adverse events (AEs). One or more serious AEs were reported in 13.5% and 7.9% of Gilenya and Tysabri patients, respectively. The AE incidence was similar to that seen in clinical trials.⁵³

INJECTABLE MEDICATIONS

Rebif® (interferon beta-1a)

Company: EMD Serono

- *Dose: 22 mcg or 44 mcg injected subcutaneously three times per week*
- *Approved in 1996 for relapsing forms of MS*

Rebif® is an interferon medication. Interferons are a group of proteins that signal the body's immune system to respond to threats, such as a virus. While the exact means by which Rebif and other interferon-based medications exercise their therapeutic effects in multiple sclerosis is not known, interferons are among the earliest disease-modifying therapies (DMTs) used to treat MS.

A recent head-to-head comparison of Rebif and the oral disease-modifying therapy (DMT) Aubagio showed no significant differences between the two medications in terms of slowing MS disease progression over the course of two years.

A total of 932 patients with relapsing-remitting MS (RRMS) were started on Rebif or Aubagio, and were followed for two years regardless of whether they discontinued either medication. Relapse rates and lesion activity were measured during that period, and disability progression was calculated based on Expanded Disability Status Scale (EDSS) scores. Individuals who were pregnant or who had RRMS for 10 years or longer were excluded from the study.

After two years, the prevalence of disability progression was low but similar

among both treatment groups (8.5% with Rebif vs 11.4% with Aubagio). The percentage of participants who suffered one or more relapses in two years was lower in the Rebif group (39.4%) than in the Aubagio group (49.2%). Also, a higher proportion of individuals in the Rebif group were free of disease activity over a given three-month period (73.1%) vs Aubagio (55.1%).

The researchers warned, however, that differences in baseline EDSS scores and past disease-free periods were not considered when the percentages were calculated, so the results are not definitive.⁵⁴ Ultimately, individual response, patient preference, tolerability, and accessibility to medication go far toward determining which patients are best suited to a specific DMT.

Plegridy® (peginterferon beta-1a)

Company: Biogen

- *Dose: 125 micrograms injected subcutaneously every 14 days*
- *Approved in 2014 for relapsing forms of MS*

Plegridy is a form of interferon beta-1a that is pegylated, meaning that its chemical structure allows for longer duration of the medication's effect. Like other interferon-based agents used in multiple sclerosis, however, the exact means by which Plegridy exercises its therapeutic effect in MS is not fully understood.

An evaluation of the long-term safety and effectiveness of Plegridy in adults with

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relapsing forms of MS has yielded reassuring findings, researchers reported recently.

The Plegridy Observational Program (POP) is an initiative sponsored by Biogen, the company that markets Plegridy. It is a five-year project involving patients in 14 countries who are taking Plegridy. The effort is a “post-marketing study,” meaning that it collects data on real-world use of a medication following the medication’s approval by regulatory authorities.

The study includes a safety analysis involving 1,126 patients, plus an effectiveness analysis that examines data on 1,125 patients. Results for both analyses are grouped according to whether individuals are newly diagnosed (those diagnosed with MS within one year before consenting to the study) and those who were previously diagnosed. The newly diagnosed individuals are younger (mean age 38.0 vs 45.9 years), have less MS-related disability, and have a higher rate of relapse before entering the study (mean

relapses: 0.9 vs 0.3) than those diagnosed more than one year before entering the study.

As of September 11, 2018, annualized relapse rates were similar between the newly and previously diagnosed patients (0.12 vs 0.14). Serious adverse events were reported in 5.3% of those who were newly diagnosed, compared with 7.0% of previously diagnosed individuals. Transient, post-injection flu-like symptoms were common in both groups (reported in 47.7% of newly diagnosed and 38.6% of previously diagnosed patients) as were injection-site reactions (35.8% vs 38.6%). Of note, newly diagnosed individuals had a significantly shorter MS-treatment history (mean duration 21.5 months), compared with non-newly diagnosed individuals (mean duration 87.3 months).

No birth defects, premature births, or ectopic or molar pregnancies relating to Plegridy exposure were reported among expectant mothers in the study. Nineteen live births and two miscarriages were recorded.⁵⁵

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EXPERIMENTAL MEDICATIONS: MONOCLONAL ANTIBODIES

About Monoclonal Antibodies

Monoclonal antibodies are medications derived from identical cells that are cloned from a single cell and then replicated. They are produced from animal tissue, most commonly laboratory mice. Humanized monoclonal antibodies are antibodies from non-human species, again, commonly a mouse, whose protein sequences have been modified to increase their similarity to antibodies produced naturally in humans.

Monoclonal antibodies can be extremely powerful and effective, as they can specifically target a certain segment of one of the body's systems - such as the immune system - while leaving the other parts of the system unaffected. This can be very desirable when trying to impact a structure as complex as the immune system.

The names of all monoclonal antibodies end with "mab," including alemtuzumab (Lemtrada®), ocrelizumab (Ocrevus®), and natalizumab (Tysabri®), which are already approved for MS. Several other monoclonal antibodies have shown promise in MS, and five of these are reviewed in this section.

Ofatumumab

Company: Novartis and Genmab

- *Injected subcutaneously, being studied at 20 mg monthly*
- *Being studied in RMS*

The Food and Drug Administration (FDA) is conducting a priority review of the cancer medication ofatumumab for the treatment of relapsing forms of MS (RMS). Executives at Novartis, which markets ofatumumab collaboratively with Genmab, say the medication could be approved as early as mid-2020. The European Medicines Agency (EMA), the drug regulatory agency for the European Union, is also reviewing ofatumumab and may approve the medication in early 2021. ⁵⁶

Ofatumumab, a monoclonal antibody

used for treating chronic lymphocytic leukemia,¹² binds to the CD20 molecule located on the surface of lymphocytes, a type of white blood cell. Lymphocytes are believed to trigger the abnormal immune response that damages the protective sheath (myelin) surrounding nerve cells in the brain and spinal cord. By binding to CD20, the lymphocytes are destroyed and neuronal damage is prevented or delayed. ⁵⁷

This treatment approach is similar to that of ocrelizumab, a monoclonal antibody that is FDA-approved for RMS and primary-progressive MS, as well as rituximab, which is often used off-label to treat MS. But while ocrelizumab and rituximab are administered intravenously, ofatumumab is self-injected subcutaneously (under the skin) once a month. For this reason, ofatumumab could provide the benefits of a CD20 monoclonal

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antibody with convenient at-home dosing, and could be an option for individuals looking for an alternative to periodic infusions or frequent self-injections.¹³

The application for FDA approval to use ofatumumab in MS is supported by data from the Phase III ASCLEPIOS I and ASCLEPIOS II trials, in which ofatumumab outperformed Aubagio in slowing disease progression in RMS.⁵⁶ A total of 1,881 adults with RMS in the two simultaneous trials received a subcutaneous 20-mg injection of ofatumumab plus an oral placebo tablet, or oral Aubagio at 14 mg once daily plus a sham (placebo) injection, for up to 2½ years. Neither the investigators nor the participants knew which treatment was active and which was placebo. Those who received active ofatumumab injections received loading doses of 20 mg upon study entry and then seven and 14 days later before switching to monthly dosing.¹³

At the end of the two trials, annualized relapse rates were 50.5% and 58.5% lower, respectively, among ofatumumab-treated individuals compared with the Aubagio group (0.11 vs. 0.22) and (0.10 vs 0.25). Those treated with ofatumumab also showed a relative risk reduction of 34.4% in confirmed disability progression (CDP) over three months, and a 32.5% reduced risk of six-month CDP, compared with Aubagio.

Additionally, ofatumumab-treated patients showed fewer gadolinium-enhancing T1 lesions on magnetic resonance imaging compared with those treated with Aubagio, suggesting that ofatumumab suppresses inflammatory activity.⁵⁶

Ublituximab

Company: TG Therapeutics

- *Given via IV infusion*
- *Being studied in RMS*

Results from two simultaneous Phase III clinical trials testing the effectiveness of ublituximab for slowing disease progression in people with relapsing forms of MS (RMS) are expected to be released later in 2020.¹⁵

The ULTIMATE I and ULTIMATE II studies are randomized, double-blind, 2-year studies involving 1,094 adults with RMS. The study population reflects the typical real-world caseload of individuals with MS based on its history of relapse and existence of lesions shown via magnetic resonance imaging (MRI). Participants range in age from 18 to 55 years, and approximately two-thirds are women.^{58,21,15}

Participants have been receiving a one-hour IV infusion of ublituximab at 450 milligrams every 24 weeks plus a daily placebo tablet, or oral Aubagio at 14 milligrams daily plus a twice-yearly sham (placebo) IV infusion. Neither the researchers nor the participants know which of the two treatments is active and which is placebo. Improvements in annualized relapse rates, a commonly used measurement of disease activity, will be used to determine the effectiveness of ublituximab in slowing or preventing neurologic damage.⁵⁹

Similar to the disease-modifying therapies (DMTs) Ocrevus and Rituxan, ublituximab is a monoclonal antibody that targets the CD20 antigen on the surface of B lymphocytes, a

EXPERIMENTAL MEDICATIONS: MONOCLONAL ANTIBODIES

type of white blood cell. Lymphocytes can trigger an abnormal immune response that damages the protective sheath (myelin) that protects nerve cells in the brain and spinal cord. By binding to CD20, ublituximab is believed to initiate a process that destroys lymphocytes and slows neuronal damage.⁵⁹ Ublituximab employs antibody-dependent cellular cytotoxicity (ADCC), a type of immune reaction where target cells are coated with antibodies that attract white blood cells, which then kill the target cells.⁶⁰ Ublituximab can be administered less frequently (twice annually) than other DMTs, and can be infused in one hour.¹⁵

Ublituximab showed robust efficacy in a prior Phase II clinical trial that tested six different dosages and infusion durations in 48 individuals with RMS. Forty-five participants from the Phase II clinical trial were then enrolled in a subsequent open-label extension. Among the findings:

- B cells were depleted by a median of 99% at four weeks into the original Phase II study and stayed at reduced levels throughout the trial.
- Infusion-related reactions occurred in only five patients (11%) in the extension study, and all reactions were mild.
- An annualized relapse rate of 0.07 was observed, and 93% of study participants were relapse-free at Week 48.
- Gadolinium-enhancing T1 lesions were eliminated at the initial study's halfway point, and the volume of new or enlarging T2 lesions was reduced by 10% at study's end.^{15, 58}

Opicinumab

Company: Biogen

- *Given via IV infusion*
- *Being studied in RMS*

Researchers are investigating whether the monoclonal antibody opicinumab reverses neurologic damage and disability when added to existing therapy in select patients with relapsing forms of MS (RMS).

If the ongoing AFFINITY clinical trial shows a significant benefit for opicinumab as add-on therapy, the results could be the first step toward a breakthrough that could give physicians an option for restoring functional and neurologic loss in MS, rather than just slowing or preventing further decline. However, opicinumab did not show a meaningful benefit in a previous Phase II study, called SYNERGY, which examined the use of concomitant opicinumab with another disease-modifying therapy.⁶¹

MS can manifest when the myelin sheath, the protective fibers around nerve cells in the brain and spinal cord, is damaged by an abnormal autoimmune response. Opicinumab is formulated to promote myelin sheath repair by blocking the effects of LINGO-1, a protein that hinders development of myelin-generating cells called oligodendrocytes. It is hoped that allowing oligodendrocytes to proliferate will restore damaged myelin, offering the potential for opicinumab to prevent and possibly reverse disability.⁶² Opicinumab has been shown in animal studies to restore myelin, and investigators hope to replicate

EXPERIMENTAL MEDICATIONS: MONOCLONAL ANTIBODIES

that effect in humans.

In the Phase II SYNERGY trial, 418 adults with RMS received interferon beta-1a at 30 micrograms per week, plus IV opicinumab every four weeks or a placebo infusion. Opicinumab was dosed at 3, 10, 30, or 100 milligrams per kilogram (about 2.2 pounds) of body weight. After 72 weeks, disability was lessened in between 40% and 65% of those individuals who received opicinumab at any dosage. Similar benefits, however, were seen in 49% of the other group. The investigators found no overall dose-related benefit with opicinumab, but found an increased rate of discontinuation with the higher doses.⁶¹

However, a later analysis of the SYNERGY findings showed more-robust treatment responses in a subgroup of individuals whose first MS symptom came within the past 20 years. These patients also had magnetic resonance imaging (MRI) findings that indicated that some nerve fibers remained intact despite myelin damage, suggesting that more nerve fibers and myelin may have been preserved. A lower proportion of people in this subgroup showed confirmed disability worsening with the 10 mg/kg dosage of opicinumab, and more of these individuals showed positive effects on exploratory biomarkers of central nervous system repair. These findings prompted Biogen, the developer of opicinumab, to continue assessing the medication's potential effects on myelin reconstruction.

The AFFINITY trial is following 263 people with RMS who are being treated with interferon-based DMTs, Tecfidera, or Tysabri.

Participants will receive intravenous opicinumab at 750 mg or a placebo IV infusion every four weeks as an add-on to their current therapy for 72 weeks.⁶³ Several tests will be performed throughout the trial to measure treatment effect on participants' cognitive and physical function. Study completion is scheduled for May 2022.⁶³

Rituxan® (rituximab)

Company: Genentech/Roche

- *Given via IV infusion*
- *Being studied in RMS*

Rituxan is a monoclonal antibody that binds to a receptor, known as CD20, on the surface of B cells. These cells are then destroyed, and their levels in the circulation are decreased. Rituxan is approved for use in the treatment of lymphomas, leukemias, and autoimmune disorders. It is not approved by the FDA for use in MS, but many neurologists prescribe it for that purpose.

A recent analysis of electronic medical records found no increased risk of cancer with several disease-modifying therapies (DMTs), including Rituxan. The impact of DMTs on cancer incidence is a concern because the medications suppress the immune system to counteract the abnormal inflammatory immune response that harms the nervous system in MS. This immunosuppression, however, can increase the risk of cancer.⁶⁴

A total of 4,340 people with MS who received Rituxan were identified from the Kaiser Permanente Southern California health

EXPERIMENTAL MEDICATIONS: MONOCLONAL ANTIBODIES

system's electronic records and the Swedish National Cancer Registry. Seven women (0.2%) had breast cancer, translating to a breast cancer rate of 1.2 per 1,000 person years. Breast cancer rates were similar among women taking other DMTs, and in a comparison group of women without MS, suggesting a low risk of cancer with these medications.⁶⁵

Temelimab

Company: GeNeuro

- *Given via IV infusion*
- *Being studied in SPMS and PPMS*
- *Studies are postponed due to the COVID-19 pandemic*

A Phase II clinical trial to assess the efficacy of temelimab in progressive, non-relapsing forms of MS has been put on hold so that investigators can instead focus on developing solutions against COVID-19. Trial organizers also expressed concern about exposing individuals with MS to increased risk of viral infection during the pandemic.

The one-year clinical trial, when initiated, will test the efficacy of temelimab in slowing disability progression in severe, progressive forms of MS.¹ Temelimab, a monoclonal antibody, is formulated to slow disease progression by targeting a human endogenous retrovirus (HERV), a protein that is either replicated from a host cell, is caused by a germ, or is hereditary.

The HERV protein activates immune cells that cause inflammation in the brain and destruction of the protective sheath (myelin) surrounding the nerve cells in the brain and spinal cord. The protein also inhibits development of myelin-generating cells called oligodendrocytes. It is hoped that neutralizing HERV will halt both the abnormal inflammatory immune response and neurologic deterioration and disease progression. This treatment approach is unlike that of currently approved DMTs.⁶⁶

Temelimab showed efficacy in a previous Phase II clinical trial, called ANGEL-MS. The study enrolled 219 individuals with relapsing-remitting MS who had completed an earlier 48-week, Phase IIb trial, CHANGE-MS. Participants in ANGEL-MS were followed for up to 48 weeks, or 96 weeks after the start of CHANGE-MS. At study's end, those who received monthly infusions of temelimab at 18 milligrams per kilogram (or approximately 2.2 pounds) of body weight showed lower volume of T1 hypointense lesions, which indicate severe damage to the central nervous system (CNS), compared with the placebo-treated group from CHANGE-MS.

No clinically relevant effect was seen on measures of CNS inflammation, however.⁶⁷ In the previous CHANGE-MS trial, the 18 mg/kg dose was significantly more effective in slowing lesion development and CNS damage than two lower doses of the medication.⁶⁶ Temelimab overall was well tolerated, and no dose-related safety issues were reported.⁶⁷

EXPERIMENTAL MEDICATIONS: S1P RECEPTOR MODULATORS

About S1P Receptor Modulators

Sphingosine-1-phosphate receptor (S1P) modulators confine certain immune cells in the lymph nodes so that they cannot reach the central nervous system (CNS) and contribute to the formation of the lesions that are hallmarks of MS. Two FDA-approved disease-modifying therapies (DMTs), Gilenya® and Mayzent®, work in this manner, and other S1P receptor modulators are being evaluated for a possible role in treating MS. The company developing one of those investigational medications, ponesimod, recently asked the FDA and the European regulators to authorize use of its medication in relapsing forms of MS based on the results of the following study.⁸

Ponesimod

Company: Janssen/Johnson & Johnson

- *Oral medication being studied at 20 mg/day*
- *Being studied in RMS*

Janssen/Johnson & Johnson has applied to the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) for approval of its selective sphingosine-1-phosphate receptor 1 (S1P1) immunomodulator ponesimod for treating adults with relapsing forms of MS (RMS).

The applications for approval are supported by data from a multicenter, double-blind, Phase III clinical trial (OPTIMUM), in which ponesimod outperformed another disease-modifying therapy, Aubagio, in a head-to-head comparison among 1,133 adults with relapsing MS.¹⁰ Participants received ponesimod 20 mg or Aubagio 14 mg once daily for approximately two years. Ponesimod was started at 2 mg daily, then increased gradually to 20 mg daily to prevent effects on heart rate that can result with S1P receptor modulators.⁹

After two years, the annualized relapse rate was 30% lower in the ponesimod group (0.2) compared with individuals who received Aubagio (0.29). Also, the number of combined unique active lesions (gadolinium-enhancing T1 and new or enlarging T2 lesions) detected by magnetic resonance imaging was 56% lower in the ponesimod group, compared with those receiving Aubagio.¹⁰

Additionally, scores on the Fatigue Symptoms and Impacts Questionnaire - Relapsing Multiple Sclerosis (FSIQ-RMS) - a 20-item patient survey that measures MS-related fatigue symptoms and their impact on quality of life - were a mean of 3.57 points lower in the ponesimod group.¹⁰ This finding suggests that ponesimod may alleviate fatigue, an often-debilitating symptom that affects roughly 80% of people with MS.

Ponesimod also displayed the same level of tolerability shown in previous clinical trials. The most common treatment-related adverse effects were colds, headache, upper respiratory tract infections, and an increase in alanine amino transferase, an enzyme that at elevated levels could signal liver dysfunction.¹⁰

Evobrutinib

Company: EMD Serono

- *Oral medication being studied at 75 mg once and twice daily*
- *Being studied in RMS*

Two simultaneous Phase III clinical trials – EVOLUTION RMS 1 and EVOLUTION RMS 2 – will be testing the efficacy of the oral investigational medication evobrutinib for delaying neurologic and functional decline in people with relapsing forms of MS (RMS).

In a previous Phase II trial, evobrutinib reduced the total cumulative number of T1 gadolinium-enhancing (Gd+) lesions compared with placebo. The reduction in Gd+ T1 lesions was seen at 12 weeks and maintained through 48 weeks with evobrutinib 75 mg once or twice daily. Reductions in relapse rates were also observed at week 24 and were maintained through 48 weeks.¹⁶

Evobrutinib is a highly selective inhibitor of Bruton's tyrosine kinase (BTK), a non-receptor enzyme. BTK contributes to the development and function of B lymphocytes, a type of white blood cell that can attack and destroy the neuroprotective myelin sheath that surrounds nerve cells in the brain and spinal cord. Evobrutinib is formulated to inhibit the primary B cell actions that lead to abnormal immune responses and, ultimately, neurodegeneration. It is hoped that through this mechanism of action, neurologic and functional decline will be delayed or even prevented.¹⁶

In another Phase II clinical trial, evobrutinib at different dosages did not appreciably reduce total B cells or immunoglobulin levels. This finding suggests that BTK inhibition, which is often employed to treat certain cancers, may not kill enough myelin-damaging cells and proteins to effectively combat MS.³⁷ Still, however, the preliminary findings that point to evobrutinib's effect on lesions and relapses give investigators reason to hope.

EVOLUTION RMS 1 and 2 are two-year, randomized, double-blind studies comparing twice-daily evobrutinib with interferon beta-1a (given intramuscularly once weekly). Researchers in both studies will record changes in annualized relapse rates, time to first occurrence of 12- and 24-week confirmed disability progression, and total number of lesions based on magnetic resonance imaging readings.¹⁶ Study completion for evaluation of primary results is expected sometime in 2023.⁶⁸

Ibudilast (also known as MN-166)

Company: MediciNova

- *Oral medication being studied at up to 100 mg (50 mg twice daily)*
- *Being studied in RMS*

An upcoming Phase III clinical trial will examine whether ibudilast effectively slows disease progression in more-severe, non-relapsing MS. Ibudilast is a small molecule (specifically, a macrophage migration inhibitory factor [MIF] inhibitor and phosphodiesterase [PDE] -4 and -10 inhibitor)

EXPERIMENTAL MEDICATIONS: ADMINISTERED ORALLY

that suppresses pro-inflammatory molecules and promotes nerve-growth factors.⁶⁹

In a Phase IIb trial, this oral medication, also known as MN-166, slowed brain-volume loss and reduced the risk of confirmed disability progression (CDP) by 46% relative to placebo among individuals with secondary-progressive MS (SPMS).^{69,2}

Ibudilast suppresses the pro-inflammatory cytokines that can cause neurologic damage in MS and supports the nurturing of nerve cells. It also prevents glial cells, which help regenerate the protective myelin sheath around nerve cells in the brain and spinal cord, from becoming overactive and triggering inflammation that can damage myelin.^{69,2} For the Phase III trial, researchers will measure time to CDP across three months, a marker of long-term disability in MS, as measured with the Expanded Disability Status Scale.⁶⁹

Meanwhile, MediciNova, the biopharmaceutical company developing ibudilast, announced in April 2020 that it will also study the medication for use in acute respiratory distress syndrome (ARDS) caused by COVID-19.²

CNM-Au8

Company: Clene Nanomedicine

- *Oral medication being studied at up to 30 mg per day*
- *Being studied in RMS*

Researchers are investigating the efficacy and safety of the oral suspension medication CNM-Au8 for repairing central nervous

system damage in people with relapsing forms of MS (RMS) who experience visual impairment.

A Phase II clinical trial is under way, with full results expected in mid-2021. Preliminary results showed a median improvement in visual function among 34 patients across 36 weeks, based on performance on the Low Contrast Letter Acuity (LCLA), a vision test for individuals with MS. Physical and cognitive function also improved, based on several patient surveys commonly used to measure MS-related functional decline.

Preliminary results also indicate that CNM-Au8 is safe and well tolerated. All reported adverse events (AEs) were mild in severity, with headache, upper respiratory infection, and sore throat being the most commonly reported AEs with either the 15 mg per day or 30 mg per day dosage, according to the company developing the medication.^{70,71}

CNM-Au8 consists of nanocrystalline gold particles formulated to promote normal cellular function while decreasing abnormal, destructive activity. It is hoped that this treatment approach will not only prevent further damage to myelin (the protective sheath surrounding neurons), but will repair previously damaged myelin and, in the process, restore lost function in MS.⁷⁰

In preclinical studies, CNM-Au8 prolonged survival of nerve cells in the central nervous system and showed effectiveness in regenerating myelin. CNM-Au8 also showed safety and tolerability in Phase I studies that involved healthy volunteers. Clene Nanomedicine, the biopharmaceutical company developing

EXPERIMENTAL MEDICATIONS: ADMINISTERED ORALLY

CNM-Au8, has received FDA approval to conduct clinical studies of this experimental medication for reversing remyelination failure in patients with MS.⁷⁰

MD1003

Company: MedDay Pharmaceuticals

- Oral medication being studied at up to 300 mg per day
- Being studied in SPMS and PPMS

The oral biotin-based medication MD1003 did not significantly affect disability progression in patients with secondary- or primary-progressive MS (SPMS, PPMS) in a pivotal Phase III clinical trial, according to the company developing MD1003. Those results run counter to a previous small pilot study, which showed evidence that biotin at high doses might slow disability and progression in MS.⁷²

Biotin is a B-group vitamin (vitamin B7)

commonly found in over-the-counter supplements. Biotin activates enzymes involved in energy production and development of myelin, the protective sheath around the nerve cells of the brain and spinal cord. Researchers are examining whether high-dose biotin can promote myelin repair by activating an enzyme involved in myelin synthesis and by enhancing energy production in damaged nerves.

MD1003, formulated as a capsule taken three times daily, is a highly concentrated formulation of biotin. The dosages being tested in clinical trials (100 to 300 milligrams daily) are several thousand times the recommended daily intake of biotin. The Food and Drug Administration (FDA) sets the recommended daily allowance for biotin at 0.3 milligrams per day.⁷³

MedDay Pharmaceuticals, the company developing MD1003, says it will continue to evaluate the data and confer with regulators in assessing potential next steps.⁷²

MRI

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NEW DIRECTIONS IN MS RESEARCH

Introduction

While the development of new disease-modifying therapies (DMTs) remains a major focus of multiple sclerosis research, considerable attention is also being devoted to other avenues of inquiry. These include stem cell therapy, the role of diet and vitamin supplementation in the onset and management of MS, the impact of genetics, and the significance of various biomarkers in tracking disease onset, progression, and response to therapy. (Examples of biomarkers include substances in the blood or cerebrospinal fluid, as well as findings on imaging). This section of the *2020 MS Research Update* reports on several interesting studies addressing these topics.

Stem Cell Therapies

Researchers around the world continue to explore the role of stem cells in treating multiple sclerosis (MS).

Most stem cell research in MS focuses on autologous hematopoietic stem cell transplantation, or aHSCT. The term “autologous” means that the cells are taken from the patient’s own body. Hematopoietic stem cells have the ability to generate new immune cells and blood cells.

The goal of stem cell transplantation in MS is to “re-boot” the immune system so that it stops the mounting inflammatory responses harmful to the brain and spinal cord. Physicians pursue this goal through a sophisticated process that typically begins with giving a patient several days of chemotherapy. This treatment prompts the bone marrow to produce stem cells and release them into the blood. Blood containing these stem cells is then drawn from a vein and stored.

Next, the patient is given another set of chemotherapy drugs to suppress or even entirely wipe out his or her immune system.

The patient is carefully monitored during and after this phase of treatment to guard against infection and other risks associated with reduced immunity. The stem cells taken from the patient’s blood earlier are then transplanted back into the patient by intravenous infusion.

These stem cells begin to re-build the body’s immune function over the course of a few months, with the hope being that the newly constituted immune system will “tolerate” the brain and spinal cord rather than generate an inflammatory response, which leads to the myelin sheath damage and outward symptoms that are the hallmark of MS. The transplantation process typically involves a prolonged hospital stay.

Just a few weeks before the COVID-19 pandemic came to dominate his every waking moment, Anthony S. Fauci, MD, announced that the government’s National Institutes of Health (NIH) had launched a clinical trial to test aHSCT against the best available biologic therapies for severe forms of relapsing MS.⁷⁴ In announcing the trial in early January, Dr. Fauci said, “aHSCT has the potential to halt the progress of relapsing MS, eliminate the need

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for a person to take life-long medication, and allow the body to partially regain function. However, we need to be certain that the benefits of this form of treatment outweigh its serious risks.”

The NIH noted that prior studies have suggested that aHSCT may be an effective and durable treatment for people with MS, but the therapy has never been formally compared head-to-head with relatively newer, so-called “third-line” MS medications, which the government agency noted are highly effective but can have harsh side effects. Treatment with aHSCT also carries the risks of serious side effects, and even death.

Given these risks and benefits, the NIH continued, investigators will seek to determine whether aHSCT is an appropriate treatment option for people with severe forms of relapsing MS who would otherwise receive one of the best available third-line biologic drugs. The trial is sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), the division of the NIH that Dr. Fauci leads.

The trial is called BEAT-MS (BEst Available Therapy versus autologous hematopoietic stem cell transplant for Multiple Sclerosis). It is being conducted by the NIAID-funded Immune Tolerance Network (ITN) in collaboration with the Blood and Marrow Transplant Clinical Trials network (BMT CTN). The BMT CTN is funded by the National Heart, Lung, and Blood Institute and the National Cancer Institute, both components of NIH. The trial is being led by Jeffrey A. Cohen, MD, a professor of neurology at the Cleveland Clinic

Lerner College of Medicine and the director of the Experimental Therapeutics Program in the Mellen Center for Multiple Sclerosis Treatment and Research at the Cleveland Clinic.

BEAT-MS will enroll 156 adults ages 18 to 55 years at 19 sites in the United States and the United Kingdom. Participants will be randomly assigned to receive either aHSCT or one of the best available high-efficacy biologic drugs, and will be followed for six years. The neurologists who periodically examine the participants and assess their level of disability will not know which type of treatment they were assigned.

The main outcome investigators will measure is how much time elapses between a participant’s assignment to a treatment strategy and MS relapse or death from any cause, if either of these occur, during the first three years of the follow-up period. The researchers will also examine the mechanisms of action of the two treatment strategies and will compare the newly developing immune systems of participants who receive aHSCT with the immunologic features of study participants who receive the best available biologic drugs. In addition, investigators will compare the effects of the two treatment strategies on other measures of disease activity and severity, cost-effectiveness in terms of health care costs and individual productivity, and participants’ quality of life.⁷⁴

At the September 2019 annual meeting of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) in Stockholm, Sweden, several other teams of

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researchers reported on their experience with stem cell transplantation. One of the largest stem cell transplantation studies reported atECTRIMS yielded disappointing results in terms of its primary endpoint, but offered some potentially encouraging news nonetheless.

The Phase II MESEMS trial was a multi-center, international study that included 144 people with MS. The trial was double-blinded, meaning that neither the physician nor patient knew whether or when the patient was receiving transplanted stem cells or placebo. The study also had a “cross-over” design, meaning that one group of participants received transplanted stem cells at the start of the trial, was observed for 24 weeks, and then received placebo for 24 weeks.

Participants in the other group received placebo for 24 weeks and then underwent transplantation, after which they were observed for 24 weeks. The purpose of this “cross-over” approach is to see how all patients do on six months of placebo and during the six months after transplantation. The patients were treated with their own mesenchymal stem cells. Mesenchymal stem cells are adult cells derived from bone marrow that have the ability to develop into many kinds, but not every kind, of human cell.

The primary endpoint of the MESEMS trial was reduction in the number of gadolinium-enhancing lesions on imaging compared to placebo. On this foremost measure, there was not a statistically significant difference between stem cell transplantation and placebo. However, the results of a secondary

endpoint, annualized relapse rate (ARR), were more promising. Although the study did not show statistical significance based on the criteria specified at the outset of the trial, stem cell transplantation showed a 36% reduction in the ARR relative to placebo. While the results have to be interpreted with caution because they did not achieve statistical significance, one of the study’s investigators termed them a “strong signal.”⁷⁵

The results of the MESEMS trial reinforce the fact that while medical research inexorably moves forward, it rarely does so in a perfectly straight line, or at the pace and with the near-term results that clinicians and patients would wish.

Investigators from Uppsala University Hospital in Sweden reported that 93% of people with MS who underwent aHSCT at their institution, between 2004 and early 2019, had no disease progression over an average 3.9 years of follow-up. Further, 87% of the 81 people studied had no relapses during that follow-up period, and 74% had no new lesions appear on MRI.⁷⁶ The study included 56 women and 25 men, and 95% of the participants had relapsing forms of MS. Their median age at transplantation was 29 years, and the average disease duration prior to the procedure was six years. Study participants had received a median of two MS therapies prior to aHSCT. Roughly three-quarters of these individuals received a low-intensity chemotherapy regimen prior to transplantation, while the remainder received an intermediate intensity-conditioning regimen.

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The group's annualized relapse rate (ARR) declined from 2.2 in the year preceding transplant to 0.0022 afterwards. Further, 63% of participants saw an improvement in their Expanded Disability Status Scale (EDSS) scores. Another 35% of those taking part in the study had an unchanged EDSS score, while 2% worsened. No patients died during the follow-up period.⁷⁶

A study examining outcomes in 30 people with relapsing forms of MS who underwent stem cell transplantation in Norway, between 2015 and early 2018, reported similarly favorable results. The study's primary outcome measure was the percentage of people who achieved "No Evidence of Disease Activity-3" (NEDA-3), which was defined as no clinical relapse, no MRI activity, and no Expanded Disability Status Scale (EDSS) progression post-transplant.⁷⁷

Eighty-three percent of the participants achieved this NEDA-3 status. Additionally, 43% had a sustained improvement in their EDSS score, 33% were working full-time after transplantation as compared to only 3% beforehand, and no patients received disease-modifying treatment after stem cell transplant.

While no individuals in the study died, and no serious treatment-related complications were reported, 17% of those treated were diagnosed with autoimmune thyroid disease following transplantation, and 43% of the women in the study reported not having a menstrual period for more than 12 months after transplant.⁷⁷

Meanwhile, investigators in Hamburg, Germany used a prospective case-control

approach to compare outcomes between aHSCT and the disease-modifying therapy (DMT) Lemtrada® (alemtuzumab) in 40 people with highly inflammatory MS. Nineteen of the patients received aHSCT. Of the people in that group, 12 had relapsing forms of MS, while seven had progressive MS. Five of the 21 individuals receiving Lemtrada had an underlying chronic disease.

The two groups were similar in terms of gender, age, EDSS score, number of prior therapies, and other factors. Disease duration, however, was longer in the Lemtrada group, while relapse activity in the two years prior to treatment initiation was lower.

The study's primary outcome measure was no evidence of disease activity (NEDA), meaning no clinical relapse, no MRI activity, and no Expanded Disability Status Scale (EDSS) progression. Average follow-up time was just under five years for the stem cell transplant group and just over two years for the individuals receiving Lemtrada. The researchers reported that significantly more patients receiving stem cell transplants achieved the goal of NEDA compared to people treated with Lemtrada, although no difference was seen in confirmed disease progression, as measured by EDSS scores, between the two groups.⁷⁸

Diet and MS

A diet consisting primarily of vegetables, whole grains, berries, poultry, fish, and olive oil was associated with larger thalamic volume - a measure of brain health and function - in a

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study examining how eating habits correlated with MRI findings in 185 people with MS.

Study participants were an average age of 34 years, and on average, had been diagnosed with MS a little more than two years before study entry. Two-thirds were female, and the participants' median Expanded Disability Status Scale (EDSS) was 1.0, indicating that most study subjects had no disability and only minimal symptoms in one functional area.

The participants underwent MRI assessment and completed a detailed questionnaire about their eating habits. They were then divided into four groups based on their reported dietary practices. Investigators examined how various MRI parameters differed across groups once adjustments had been made for patient demographics and markers of fitness.

The researchers found that people who followed the Mediterranean-DASH Intervention for Neurodegenerative Delay, or MIND, diet, which emphasizes the food described at the start of this section, tended to have larger thalamic volume than people in other groups. The thalamus is a grey-matter area of the brain that processes and relays sensory information, while also helping to regulate sleep and wakefulness.

Study findings showed that dairy intake was associated with smaller T2-weighted lesions and greater cortical thickness, while higher intake of polyunsaturated fatty acids, such as omega-3, was associated with increased microstructural integrity in normal-appearing white matter.

The researchers concluded that their findings showing an association between dietary factors and MRI metrics in people in the early stages of MS warranted similar studies in MS patients with longer disease duration.⁷⁹

People in Italy embraced the so-called "Mediterranean diet" long before that heart-healthy style of eating gained popularity, and its name, in America. So what better place than Italy to assess the impact that the diet – which emphasizes vegetables, fruits, whole grains, fish and poultry, with moderate use of dairy and limited red meat – has on MS?

Italian researchers recently enrolled 301 people with MS in a study to look at how diet, smoking, body mass index (BMI), waist-hip ratio (WHR), and other factors affect the course of MS. Two-thirds of the patients were women. Study participants' average age was 43 years. Their median Expanded Disability Status Scale (EDSS) score was 2, indicating that most had minimal disability.

Based on their responses to extensive diet questionnaires, the participants were divided into two groups. The first group (64.8% of all subjects) was composed of people who were totally adherent to a Mediterranean diet. The second group consisted of people deemed to be "sufficiently" adherent to the diet, meaning that they followed it less often than people in the other group.

Perhaps surprisingly, the investigators did not find an association between greater adherence to the Mediterranean diet and measures of MS disease severity, such as EDSS score or Fatigue Severity Scale (FFS)

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score. Rather, they found that people with higher BMI had worse EDSS and FFS scores. Similarly, they found a direct and statistically significant relationship between waist-hip ratio and higher (meaning worse) EDSS and FFS values. Not surprisingly, higher smoking intensity was associated with higher EDSS scores, while people who were more physically active had less impairment as measured on the EDSS and reported less fatigue.⁸⁰

Gut Microbiome

The gut microbiome - the milieu of bacteria found in the digestive tract - is a major component of the immune system, and has emerged in recent years as a focus of MS research. Investigators are exploring how the overall mix of bacteria and different levels of specific types of bacteria may affect the risk for MS and the course of disease. Other researchers are examining whether altering the composition of the microbiome can help reduce relapses, slow MS progression, or otherwise improve outcomes.

One recent study suggests that increasing levels of a fatty acid that typically is reduced in people with MS can affect immune function. It also suggests that in conjunction with disease-modifying therapies (DMTs), it may reduce relapses.⁸¹

Propionic acid (PA) is a short-chain fatty acid (SFCA). PA and other fatty acids are produced when bacteria in the gut microbiome process indigestible dietary fibers. Reduced levels of PA, as is seen in MS, are associated with alterations in the

composition of the gut microbiome.

Investigators in Germany, Denmark, and Israel recently assessed blood and stool samples from people with MS and healthy controls. They found that the MS patients had reduced amounts of PA and of SCFA-producing bacteria compared to the controls. The people with MS also had reduced amounts of regulatory T (Treg) cells, which play an important role in maintaining immune system function. In MS, Treg cells often are decreased, while two types of pro-inflammatory, autoreactive cells - T helper (Th) 1 and 17 - are increased. Researchers believe that this imbalance contributes to the inflammation and neurodegeneration seen in MS.

The investigators then had 91 people with MS and 24 healthy controls take 1,000 mg per day of PA. After 14 days of taking PA, people with MS saw their Treg cell amounts increase by 30%, while the controls had a 25% increase in their Treg cells. Several people in the initial phase of the study continued on PA for 90 days, as did a separate group of newly diagnosed people with MS who had not initiated any disease-modifying therapy (DMT). Both groups of people with MS saw their Th1 and Th17 cell counts decrease after 14 days and 90 days of PA supplementation. The researchers noted that along with increases in Treg cell amounts, this helped to improve the balance between immune-system modulating Treg cells and inflammatory, reactive Th cells.

To assess the clinical implications of these immune system changes, the investigators

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studied annual relapse rates in 97 study participants with MS. All of the patients had taken PA continuously for at least one year, and had data on prior relapse rates, with the data in some cases going back six years. The participants were stratified, or categorized, based on their baseline annualized relapse rate (ARR), Expanded Disability Status Scale (EDSS) score, and current MS therapy.

The researchers found that 41.2% of patients improved on PA, 47.4% remained stable, and 11.3% had an increase in their ARR. Overall, the annualized relapse rate decreased from 0.24 at baseline to 0.008 after one year or more of PA supplementation, and that difference was statistically significant. Additionally, EDSS scores generally were stable in the patients taking PA. While no severe adverse events were reported, <5% of participants in the long-term group reported mild adverse events, including nausea, flatulence, and abdominal swelling.

The investigators concluded, "PA supplementation had a beneficial effect on immunological, neurodegenerative, and clinical parameters in MS patients, including relapse rate and disability progression. The results of our proof-of-concept study reveal not only that purified PA supplementation is a safe add-on to existing immune-modulating drugs but also confirm that one mode of action of this supplemental treatment is because of stimulation of Treg cells."⁸¹ These intriguing results are, as the authors note, generated by a proof-of-concept study, which by its nature calls for validation through a larger trial. With their findings, the

investigators have identified several important areas for further research.

Meanwhile, a study from Spain suggests that elevated levels of one family of bacteria, *Lactobacillaceae*, in the gut microbiome are associated with a greater number of relapses in people with MS. Investigators drew that conclusion after studying 16 people with relapsing-remitting MS and 15 healthy controls. The researchers used sophisticated genetic sequencing to identify the types and levels of bacteria found in each person's microbiome. They also followed the study participants over a period of 24 months, tracking how often the people with MS had relapses and new or newly enlarged gadolinium-enhancing lesions seen on MRI during that follow-up period.

Investigators found that the healthy controls had more types of bacteria in their microbiome than did the people with MS. Further, in the study subjects with MS, an association was found between increased levels of *Lactobacillaceae* - particularly the genus *Lactobacillus* and the genus *Lachnoclostridium* - and new relapses, new lesions on MRI, or both. Eighty-one percent of study participants with MS were on a disease-modifying therapy (DMT) when they entered the study.⁸²

Another recent study found that one alteration in the gut microbiome seen in early MS appears to be consistent across different ethnic groups. Researchers performed genetic analysis and sequencing on the bacteria in fecal samples from 15 Caucasian, 16 Hispanic, and 14 African-American people with MS, as

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well as 44 healthy controls matched by ethnicity. They also conducted genomic sequencing involving 24 people with MS – all of whom were newly diagnosed, not on a DMT, and not taking steroids – plus 24 controls.

The researchers found that individuals with MS in all three ethnic groups had an increased abundance of the genus *Clostridium* in their microbiome relative to controls from the same ethnic groups. The genomic analysis identified specific species within the *Clostridium* genus that were significantly enriched in the people with MS. Identifying a type of bacteria that has an increased abundance in MS patients across ethnic groups, provides investigators with a valuable target for further research, potentially benefiting a wide range of people.⁸³

Vitamin D

Lower-than-normal blood levels of 25-hydroxyvitamin D (25(OH)D) are associated with elevated risk for MS and greater disease activity. However, research has yielded conflicting results on how vitamin D3 supplementation affects disease activity in MS. Additionally, no consensus has been reached on the optimal supplemental dose to give or the blood level of Vitamin D3 to target.

Against that backdrop of uncertainty, researchers in Slovenia investigated the safety and efficacy of administering relatively high doses of vitamin D3 to people with relapsing forms of MS. In particular, they focused on the impact of vitamin D3 supplementation in the winter months, when sunlight exposure is reduced. This timing is significant because the

body's production of vitamin D depends in part on the skin's absorption of sunlight.

The researchers randomized 78 people with relapsing-remitting MS to receive either 1,000 international units (IU) per day or 4,000 IU/day of Vitamin D3 supplementation. A dose of 1,000 IU/day is considered a standard dose, and 4,000 IU/day is designated as the higher dose. Neither the study participants nor their clinicians knew who was receiving which dose.

At the outset of the study, patients in the two groups had similar average blood levels of 25(OH)D: 59.53 nmol/l in the standard group and 55.19 nmol/l in the higher-dose group. The two groups were also similar in other ways. After four months of daily Vitamin D3 supplementation, average blood levels of 25(OH)D were 74.97 nmol/l in the standard-dose group and 104.92 nmol/l in the higher-dose group.

At the end of the four-month treatment period, people in both groups had better average walking time as measured by the Timed 25-Foot Walk. No side effects of therapy were reported in either group. Similarly, measures of kidney function and calcium levels were normal, and not significantly changed, in both groups. However, when asked to use a visual scale to assess their health, people in the higher-dose group gave themselves higher scores than did the people in the standard-dose group.

Those findings prompted the researchers to conclude that higher-dose vitamin D3 supplementation is safe and effective, and should be employed, particularly in winter time.⁸⁴

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Meanwhile, a study by Dutch researchers found that longer treatment with an even higher dose of vitamin D3 did not have a meaningful impact on one key biomarker of MS disease activity.

The investigators examined whether 14,000 IU/day of vitamin D3 taken for 48 weeks would lower blood levels of neurofilament light chain (NfL) in people with MS who already were taking an interferon-based disease-modifying therapy (DMT). Elevated levels of NfL in the blood are associated with MS disease activity.

The study involved 40 people with relapsing-remitting MS. All received interferon therapy, while 24 also received Vitamin D3 and the remaining 16 instead received a placebo. After 48 weeks, blood levels of 25-hydroxyvitamin D were roughly four times higher in the treatment group than in the placebo group, as would be expected, but serum NfL levels were almost exactly the same - at a median level of 25.4 pg/mL in the treatment group and 25.3 pg/mL in the placebo group. While this does not mean that Vitamin D3 supplementation may not have a role to play in the overall management of MS, the study findings failed to show a connection between increased Vitamin D levels and a key biomarker of disease activity.⁸⁵

Biomarkers

Researchers and clinicians continue to look for ways to speed the diagnosis of MS in patients with suspicious symptoms, monitor the course of the disease, and assess response to treatment. Biomarkers play a

major role in those efforts. While findings on MRI studies are the biomarkers most frequently employed and best known to patients, recent research has examined how substances in the blood and cerebrospinal fluid (CSF) may also yield important information. To follow are two studies that examine such findings.

Neurofilament light chain (NfL) is a protein that serves as a biomarker of damage to axons, the parts of a nerve cell that carry messages from the brain to other parts of the body. Recent research has shown that blood levels of NfL are elevated in people with MS. Based on this finding, researchers are investigating additional ways in which NfL levels may reveal evidence of disease course and severity, response to treatment, and other aspects of MS.

One team of investigators recently decided to explore whether serum (blood) levels of NfL are elevated well before a person experiences symptoms of MS. They noted that unrecognized demyelinating events, in which the myelin sheath that covers and protects nerve is damaged, can occur prior to the clinical onset of MS. They added, "Identification of these events at the time of occurrence would have implications for early diagnosis and treatment, as well as the search of causal factors for the disease."

To see if serum NfL could aid in identifying those events, the researchers conducted a case-controlled study involving active-duty United States military personnel who had serum samples stored in the Department of Defense Serum Repository. They selected 60

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people with MS, each of whom either had two serum samples collected before MS onset or with one sample collected before and one after onset of MS. They then matched each of those people with a “control” – a person of the same age, sex, race, ethnicity, and dates of sample collection.

Their analysis found that people who went on to develop MS symptoms had higher serum NfL than their matched controls a median of six years before the clinical onset of the disease. Further, the differences in NfL levels became greater as time to symptom onset became shorter. Meanwhile, for people with MS, the arrival of MS symptoms was marked by a significant increase in serum NfL levels.

The researchers said their findings show that MS has a “prodromal” phase, meaning a build-up to obvious symptoms, which lasts several years. They also noted that the elevated blood NfL levels identified during this period indicate that damage to the nervous system is occurring long before symptoms are apparent.⁸⁶

While NfL is a topic of intense interest to MS researchers, other potential biomarkers are also being evaluated. For example, a group of Canadian investigators recently reported that plasma levels of a protein known as interleukin-1 receptor antagonist (IL-1RA) can help identify the transition from relapsing-remitting MS (RRMS) to secondary-progressive MS (SPMS).

The researchers analyzed plasma levels of the protein in 110 people with RRMS, 17 people with SPMS, and another 17 people

who – based on neurological assessment and Expanded Disability Status Scale (EDSS) scores – were transitioning from RRMS to SPMS. They found that the average level of IL-1RA was markedly higher in patients transitioning to secondary-progressive MS. The mean level was 857.4 pg/ml in the transitioning group, as compared to 299.8 pg/ml in the RRMS group and 156.2 ng/ml in people with SPMS.

Further, plasma levels of IL-1RA were correlated with EDSS scores in people with RRMS and those transitioning to SPMS. Plasma levels of the protein did not, however, correlate with patient age, disease duration, or use of disease-modifying therapy (DMT). A lack of correlation with those patient characteristics actually may enhance the utility of using IL-1RA to identify or confirm transition to SPMS by eliminating “background noise,” or confounding factors that would need to be taken into consideration.

While further research into the protein’s potential role in monitoring disease course is needed, the investigators noted that, “Our results demonstrate that IL-1RA is a novel exploratory biomarker that both correlates with EDSS and may suggest when a patient is either in a transitional clinical phase or has fully converted to SPMS.”⁸⁷

Genetics

Researchers continue to unravel the genetic basis of MS, identifying genetic variants associated with increased risk for multiple sclerosis and exploring how complex interactions between genetics and

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environmental factors affect disease onset and course. The summarized studies to follow highlight representative findings from these investigations.

A team of Spanish investigators concluded that environmental factors play a larger role than genetic predisposition in development of MS. They reached this conclusion after examining the relative contributions of the two types of risk factors in a study that involved 150 people with MS and 150 healthy controls.

In terms of environmental factors, the researchers focused on latitude, smoking status, and Vitamin D deficiency. They included study subjects from three different latitudes within Spain and surveyed those participants on their smoking history. Interestingly, they used skin tone as a marker for Vitamin D status, employing a medical classification system that relates skin tone to levels of Vitamin D, which influences skin tone. In examining genetic factors, they focused on the *HLA-DRB1*15:01* allele, a genetic variation linked to elevated risk for MS.

The researchers then used sophisticated statistical processes to identify the significance of various risk factors and combinations of risk factors. Looking at individual factors, they found that having light brown skin rather than clear skin and being a smoker versus a non-smoker were associated with greater risk for developing MS than was having the *HLA-DRB1*15:01* allele versus not having that genetic variation.

However, the genetic factor had more influence on MS risk than whether a person was female or male (nonetheless, compared

to men, women had roughly twice the risk for MS). In looking at combinations of risk factors, they found that smokers with light brown skin were 1.5 times more likely than those with light brown skin and the *HLA-DRB1*15:01* allele to develop MS. However, both groups were at far greater risk for MS than people without any of the risk factors studied. The investigators concluded, "Our study suggests that the confluence of several environmental factors contributes to MS developments to a greater extent than the greatest genetic risk factor known today."⁸⁸

Why do relapses tend to peak in spring (at least in the northern hemisphere), and occur least often in autumn? Similarly, why are new focal lesions more frequently identified in the spring and summer than in autumn or winter? While those questions remain unanswered, researchers and clinicians have proposed causes including seasonal fluctuations in Vitamin D levels related to sun exposure and the waxing and waning of viral infections over the course of the year. More recently, a team of international investigators explored whether genetics play a role in these patterns.

The researchers analyzed data on 731 people with MS who participate in a long-term study at the Brigham and Women's Hospital in Boston. They looked for the presence or absence of 9 single nucleotide polymorphisms (SNPs), or types of genetic variations. Seven of those SNPs previously have been linked to increased risk for MS and are positionally or functionally linked to so-called "seasonal genes," meaning genes whose expression varies by season. The two

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other SNPs that were assessed are linked to Vitamin D metabolism or function.

The investigators then used a statistical method called a Wald test to see whether there were significant differences in when relapse peak occurred among patients with different genotypes for the various SNPs being studied. They found that participants who carried an MS-risk allele (an alternative form of a gene resulting from mutation) for the SNP known as rs2248137 had a significant shift in time of relapse peak compared to other patients who did not have that allele. Interestingly, this SNP affects an enzyme involved in Vitamin D metabolism, further focusing attention on that vitamin - and the genetic factors influencing Vitamin D levels - in seasonal patterns of disease activity.⁸⁹

Certain genetic variations long have been associated with increased susceptibility to MS, but do specific genes or genetic mutations also influence disease severity? Researchers sought to answer that question by drawing on data from three large, randomized controlled trials sponsored by the biopharmaceutical company Biogen.

The investigators focused on two measures of disease severity - levels of serum neurofilament light (sNfL), a protein found in the blood that is elevated in people with MS and other neurologic diseases - and percent brain volume change (PBVC). For sNfL, they examined data on 500 patients with secondary-progressive MS and 474 study participants with relapsing MS. Their assessment of percent brain volume change (PBVC) involved data on

1,796 people with MS.

The researchers performed genome-wide association studies (GWAS) to identify loci, or areas, on different chromosomes associated with increased sNfL levels and decreasing brain volume over time. The investigators found loci on chromosomes 17 and 18 that were associated with elevated sNfL. The overall analysis found no genome-wide significant "hits" for brain atrophy, but did identify three significant hits, on chromosomes 2 and 5, in the secondary-progressive MS group. "Thus far," they wrote, "we have not found overlap in signal between MS susceptibility, sNfL, and brain atrophy."

Having identified genetic regions potentially associated with those two measures of MS progression, the researchers now are working to validate their results by examining data on 1,056 patients, for sNfL, and 1,555 people with MS, for PBVC, who participated in large clinical trials sponsored by another biopharmaceutical company, Roche.⁹⁰

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CLOSING NOTES

This 2020 edition of the *MS Research Update* highlights a representative selection of some of the most important studies shaping the care of people with MS. The dozens of clinical trials showcased here are but the proverbial “tip of the iceberg.” Thousands of researchers in hundreds of clinics and laboratories around the world are exploring questions and possibilities that offer considerable hope for progress.

Of course, this global research effort is taking place against the backdrop of the COVID-19 pandemic. The coronavirus outbreak poses particular challenges and concerns for people with MS in terms of uncertainty regarding disease susceptibility and severity, among other issues. While some MS-related research initiatives have been halted due to the COVID-19 crisis, other investigators are exploring whether MS therapies may help speed recovery from the viral infection. Above all else, the terrible toll of COVID-19 has underscored the importance of research into the causes and treatment of both acute and chronic conditions.

As people with MS continue to be proactive partners in their care, their participation in clinical trials has enabled the development of several new DMTs, including three approved by the FDA in the past several months and others now being assessed by the FDA or in late stages of investigation.

The challenges and complexities that 2020 has presented thus far are, in the end, no match for the resilience of people with MS and the dedication of their clinicians. That is why MSAA is proud to provide patients and clinicians alike with this edition of its annual *MS Research Update*. We hope that it will be a valuable resource for all who are committed to enhancing the lives and health of people with MS. We also hope that you will turn to MSAA throughout the year for the latest information in this exciting time of frequent, significant advances in the treatment of MS. For information about opportunities to participate in clinical trials, please visit mymsaa.org/clinicaltrials. For more information about MS, its treatments, and MSAA’s programs and services, please contact MSAA at **(800) 532-7667**, or visit mymsaa.org.

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