

MS RESEARCH UPDATE



MSAA

MULTIPLE SCLEROSIS
ASSOCIATION OF AMERICA

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The logo features the letters 'MS' in a large, bold, black font on a yellow square background. 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 2019 edition of its *MS Research Update*. The *Update* provides important new data on approved and experimental treatments for MS, and is designed 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**. Questions to MSAA's Client Services department may also be emailed to MSquestions@mymsaa.org.

Additionally, please be aware that due to the timing of the national and international MS conferences, study data from 2019 conferences generally could not be included in the *Update*. Information in this publication includes data presented at the 2018 conferences, as well as any important updates that occurred in early 2019. Please visit MSAA's website at mymsaa.org for future summaries of 2019 conference highlights.



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CONTENTS

Introduction	2
--------------------	---

FDA-APPROVED MEDICATIONS

Recently Approved

Mayzent® (siponimod)	7
Mavenclad® (cladribine)	8

New Data on Previously Approved Medications

Ocrevus® (ocrelizumab)	10
Tecfidera® (dimethyl fumarate)	12
Tysabri® (natalizumab)	14
Gilenya® (fingolimod).....	15
Lemtrada® (alemtuzumab).....	17
Plegridy® (peginterferon beta-1a)	18
Aubagio® (teriflunomide)	19
Copaxone® (glatiramer acetate)	20
Betaseron® (interferon beta-1b)	22

EXPERIMENTAL MEDICATIONS

Monoclonal Antibodies

Rituxan® (rituximab)	24
Ofatumumab (also known as Arzerra®)	25
Opicinumab	26
Ublituximab (also known as TG-1101)	27
Temelimab (formerly GNbAC1)	27

New S1P Receptor Modulators

Ozanimod (formerly RPC1063)	29
Ponesimod	30

Administered Orally

Vumerity™ (diroximel fumarate)	32
Evobrutinib (M2951).....	33
Ibudilast (MN-166)	33
Simvastatin (Zocor® and others)	34

NEW DIRECTIONS IN MS RESEARCH

Diet and MS	36
Vitamin D	38
Biotin.....	39
Gut Microbiome	40
Lipoic Acid	41
Stem-Cell Therapy.....	42
Genetics	44
Biomarkers	45

Closing Notes	48
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CHART: Approved Disease-Modifying Therapies for MS	49
--	----

References	51
------------------	----



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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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The 2019 *MS Research Update* highlights new data and findings on:

- Experimental drugs currently under investigation for the long-term treatment of multiple sclerosis (MS)
- FDA-approved disease-modifying therapies (DMTs)
- 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

This 2019 edition of MSAA's *MS Research Update* is once again being printed as a stand-alone issue, reflecting the great wealth and wide scope of research progress in MS. Nonetheless, there is far too much ongoing research in MS therapeutics for all of it to be covered here. As a result, this update provides

a comprehensive overview, rather than an exhaustive compilation, of relevant research; not all study results could be included. The information presented is drawn from a variety of sources, including e-journal literature on MS and its management, a review of ongoing clinical trials, and papers presented 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 on each medication, keeping the length of information equal for each medication is not possible. Please understand that the different lengths of text should in no way be considered as favoritism toward any one product. Additionally, references have been cited only for the newer study results.

While medications for management of MS symptoms are not within the scope of this

report, information on the specific symptoms of MS and their treatment is available at mymsaa.org. On the website's homepage, please select "Symptoms" under "MS Information."

Providing these resources is central to 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 2019 *MS Research Update*, as well as other MSAA publications, are welcomed. These can be directed to the organization at **(800) 532-7667** or editor@mymsaa.org.

Overview of MS Research Progress

By any measure - the United States Food and Drug Administration (FDA) approval of new medications, Phase III trials under way, expanded knowledge of the causes and course of MS, emerging treatment strategies, and many others - the last 12 months have seen great strides in the effort to better understand and more effectively manage multiple sclerosis.

The FDA's approval of two new disease-modifying therapies (DMTs) - just days apart - gives a sense of the pace of progress. In late March 2019, the FDA approved Novartis' Mayzent® (siponimod) for use in adults experiencing relapsing forms of MS, including clinically isolated syndrome (CIS), relapsing-remitting disease, and - notably - active secondary-progressive disease. This FDA action made Mayzent, a sphingosine 1-phosphate (S1P) receptor inhibitor, the first oral drug to treat secondary-progressive MS with active disease.¹

While the DMT Novantrone® (mitoxantrone), given via IV infusion, has been approved since 2000 for reducing the neurologic disability and/or frequency of clinical relapses in adults with secondary-progressive MS, its use has been greatly limited due to its side-effect profile. Immediately following the approval of Mayzent, Mavenclad® (cladribine) was also approved for use in adults with relapsing forms of MS, including RRMS and active secondary-progressive disease. Mavenclad, which is a product of EMD Serono, is given in a two-course regimen, with the initial course separated from the second course by at least 43 weeks (about 10 months).^{2,3,4} Several other medications are making their way through late-stage clinical trials and the evaluation process. These include Vumerity™ (diroximel fumarate), a molecular "relative" of Biogen's Tecfidera® (dimethyl fumarate) that Biogen and Alkermes plc are developing. This agent will offer efficacy comparable to that of Tecfidera, but with fewer of the gastrointestinal effects that sometimes are associated with Tecfidera use. The companies have filed a New Drug Application (NDA) for Vumerity, and the FDA is expected to issue a decision on that application in late 2019.⁵

Meanwhile, Celgene has filed an NDA with the FDA for its oral S1P receptor inhibitor ozanimod, seeking approval for use of the medication in relapsing forms of MS.⁶ As the *MS Research Update* was going to press in early May, Celgene announced that a post hoc analysis of data from its Phase III RADIANCE Part B trial showed that ozanimod reduced brain volume loss across all age groups

INTRODUCTION

studied in adults with relapsing MS.⁷ Other agents in late stages of clinical development, including the monoclonal antibodies (mAbs) ofatumumab, ublituximab, opicinumab, and temelimab, as well as the S1P receptor modulator ponesimod and other agents, all have reported research findings over the past 12 months that are summarized in this publication.

Important research also is examining the optimal use and long-term efficacy and safety profiles of medications already approved by the FDA. For example, Biogen announced in January 2019 that it had enrolled the first patients in its Phase IIIb study evaluating the impact of extending the dosing of its DMT Tysabri® (natalizumab) from every four weeks to every six weeks.⁸ The two-year NOVA study, which ultimately will enroll 480 patients worldwide, was initiated after smaller studies indicated that extending the dosing interval for Tysabri significantly reduced the risk of progressive multifocal leukoencephalopathy (PML) without diminishing the efficacy of the agent. Caused by the JC virus, PML is a rare

but potentially life-threatening viral disease associated with the use of Tysabri and some other DMTs.

On a related note, a study published in the April 25, 2019 edition of *The New England Journal of Medicine* reported that pembrolizumab, a type of cancer therapy called a PD-1 inhibitor, was given to eight individuals diagnosed with PML (all with different underlying conditions). Improved laboratory measures of PML were seen in all eight patients. Five of these eight individuals experienced clinical improvement or stabilization of their PML, along with additional improvements in laboratory measures, including a reduction in JC viral load and an increase in anti-JC viral activity.^{9,10}

Two recurring themes mark much of the research into current FDA-approved DMTs. The first is that the sooner the therapy is initiated following the diagnosis of MS, the more effective the medication is likely to be. This point is highlighted in studies concerning Ocrevus® (ocrelizumab), Tysabri, and other agents, as reported in this *MS Research Update*.¹¹⁻¹⁹ The second theme is that long-term studies of various DMTs demonstrate the ongoing effectiveness and consistent safety profiles of the medications, as reported in the pages that follow in summaries of research into Tecfidera, Gilenya® (fingolimod), Lemtrada® (alemtuzumab), Plegridy® (peginterferon beta-1a), Aubagio® (teriflunomide), glatiramer acetate, Betaseron® (interferon beta-1b), and other agents.^{1,2,20-24}

As researchers are able to draw upon data encompassing several years of DMT use by thousands of people with MS, they also are



able to identify patterns and trends regarding the relative impact of various agents. One important study in this regard was published in the *Journal of the American Medical Association*, or *JAMA*, in January 2019. Researchers drew on multi-year data for 1,555 patients treated at 68 neurology centers in 21 countries to examine whether initial use of particular DMTs was associated with varying degrees of risk of moving from relapsing-remitting MS to secondary-progressive MS (SPMS).

The researchers concluded that initial treatment with Gilenya, Tysabri, or Lemtrada was associated with a lower risk of conversion to SPMS compared with initial use of interferon beta or glatiramer acetate.² “Comparative effectiveness” studies that examine how various agents perform relative to one another represents a growing area of scientific inquiry. Such studies are likely to help clinicians decide which medication is best suited to the needs of individual patients.

Of course, not all research yields positive findings. The path to progress can be a winding one with many a detour and dead end. The results of the MS-SMART trial represent a case in point. The study, sponsored by University College London, examined whether three established medications used to treat other conditions would be effective in the treatment of SPMS. The Phase II study enrolled 445 patients to receive 96 weeks of treatment with either amiloride (used to treat high blood pressure and congestive heart failure), fluoxetine (an antidepressant), riluzole (used to treat amyotrophic lateral sclerosis, also known as

ALS or “Lou Gehrig's disease”), or placebo. The primary outcome was the percentage of brain volume change as measured on MRI.³

Unfortunately, none of the medications tested slowed the brain atrophy that is a hallmark of SPMS. MS-SMART did, however, make many valuable contributions to the overall effort to improve outcomes in people with SPMS, which has posed a major challenge to clinicians for many years. The study's innovative design showed that it is feasible to assess several agents simultaneously, an important finding as neurologists and other physicians seek treatments for many conditions that historically have lacked effective therapies. The findings also enable researchers to re-focus their efforts on other potentially fruitful avenues of inquiry.

Beyond traditional medications, exciting research findings have been reported in recent months in promising areas such as stem-cell therapy, dietary strategies, and attempts to affect MS by altering the composition of the gut microbiome – a key component of the immune system. There also is important new information on the role of genetics in MS, the significance of biomarkers such as serum neurofilament light chains and the so-called “central vein sign,” and more. Highlights from those studies also are included in this 2019 *MS Research Update*.

Staying current with the latest findings on the medications, techniques, and avenues of inquiry in MS is challenging, and can be daunting... not only for patients and family members, but for clinicians as well. We hope this *MS Research Update* will be a helpful

resource for everyone working to improve the lives of people with MS.

Every study reported in this publication depended not only on the expertise of physicians, nurses, and other healthcare professionals, but also on the commitment of people with MS who made a decision to contribute to the effort to better understand, better manage, and one day conquer multiple sclerosis. If you have been part of that effort and have participated in the clinical trials or

have provided assistance to MS research in some other way, 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 contribute to MS research. The more diverse populations that enroll in clinical trials, the more meaningful are the results. 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 as 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

March 2019 saw the United States Food and Drug Administration (FDA) approve two more medications for use in multiple sclerosis (MS) – Mayzent® (siponimod) and Mavenclad® (cladribine). Information on those agents and the clinical trial data that helped secure their approval follow.

Mayzent® (siponimod)

Company: Novartis

- *Starting dose for most patients: 0.25 mg orally on Day 1, increasing in .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, including clinically isolated syndrome, relapsing-remitting disease, and active secondary-progressive disease, in adults.*

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. As a result of this binding, 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 therapeutic 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.¹ Gilenya is also an S1P-receptor modulator.

Mayzent is the first oral drug to treat secondary-progressive MS in adults experiencing active disease. This represents an important advance because up to 80% of patients with relapsing forms of MS will develop secondary-progressive MS (SPMS) at some point. As a side note, just a few days after the FDA approved Mayzent to treat SPMS, it approved Mavenclad® (cladribine) for this use, which is discussed in the following section. Mayzent is also approved for use in clinically isolated syndrome (CIS) and relapsing-remitting MS (RRMS), giving it a fairly broad range of indications relative to many other disease-modifying therapies (DMTs).²⁶

The FDA's approval of Mayzent followed positive findings from the Phase III EXPAND study, a randomized, double-blind, placebo-controlled study that compared the efficacy and safety of Mayzent with placebo in people with SPMS.^{1,22}

In EXPAND, 1,645 patients were randomized

FDA-APPROVED MEDICATIONS: RECENTLY APPROVED

in a 2:1 ratio to receive siponimod (n = 1099) or placebo (n = 546). At baseline, the participants had a mean age of 48 years and had been living with MS for approximately 16 years; more than half had a median Expanded Disability Status Scale (EDSS) score of 6.0 and relied on a walking aid. The trial's primary endpoint was time to three-month confirmed-disability progression (CDP). Mayzent reduced the risk of such progression by 21% compared to placebo in the overall study population, and cut the risk by 33% relative to placebo in those who had experienced relapse activity in the two years prior to screening. Both reductions were statistically significant. Further, Mayzent delayed the risk of six-month CDP by 26% versus placebo and reduced the annualized relapse rate (ARR) by 55%. Treatment with Mayzent also showed favorable outcomes in other measures of MS disease activity, including cognition, MRI disease activity, and brain volume loss. The most common adverse events were headache, high blood pressure, and an increase in liver enzyme levels.^{1,22}

The FDA-approved prescribing information for Mayzent advises clinicians to assess patients for specific cardiovascular, ophthalmic, and other conditions before starting them on Mayzent. It recommends obtaining an electrocardiogram (ECG) for all patients, and monitoring those with sinus bradycardia or certain other heart rate and rhythm conditions when they take their first dose of Mayzent. The medication is contraindicated for individuals who in the past six months experienced a myocardial infarction (heart attack) or certain other heart and cerebrovascular conditions, who have

various heart rhythm conditions, or whose genetic make-up, or phenotype, affects how their bodies metabolize certain drugs.²³

In other cases, a person's phenotype may require that the individual take a lower ongoing dose of the oral medication.²³ Phenotype is an individual's characteristics as determined by a combination of genetic and environmental factors.

The phenotype-related recommendations reflect a growing understanding of how genetics influence a specific person's response to a medication. Agents approved several years ago do not carry such requirements, because the science was not sufficiently advanced at that time to perform the in-depth genetic analyses that are possible today. Going forward, it is likely that many more medications will have phenotype-specific guidance regarding their use.

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, including relapsing-remitting disease, and active secondary-progressive disease, in adults.*

Mavenclad® (cladribine) has followed a long road to FDA approval for use in MS. Results from its Phase III CLARITY trial were announced in 2009. The trial showed that cladribine 3.5 mg/kg cut the annualized relapse rate (ARR) by 58% relative to placebo

over 96 weeks, and that cladribine also had a favorable effect on disability progression, lesion activity on MRI, and other measures of MS activity.²⁴ Clinical trial data also showed that 81% of patients receiving cladribine were free of relapses two years after treatment, compared with 63% of those in the placebo group.² However, the FDA questioned whether use of cladribine in MS might be associated with an increased risk for cancer, prompting a long-term effort by EMD Serono and its parent company, Merck, to assess the safety of the medication.

EMD Serono ultimately collected data representing 9,500 patient years of cladribine use from people who spent up to eight years in studies. The clinical program found malignancy rates with cladribine use that were low overall but higher than those seen with placebo – 0.27 events per 100 patient-years in patients receiving cladribine versus 0.13 events per patient years in the placebo group. The studies also found higher rates of herpes zoster infection and oral herpes in people receiving cladribine versus those in the placebo group.² In keeping with those findings, the prescribing information for Mavenclad includes a boxed warning that the medication may increase the risk of 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. The prescribing information also notes that, due to its safety profile, "use of Mavenclad is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug

indicated for treatment of MS."³ It should be noted that other disease-modifying therapies for MS approved by the FDA include language in their prescribing information concerning a potential increased risk of cancer. Beyond the malignancy concern, Mavenclad 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.

Clinicians considering treatment options for active SPMS or RRMS need to weigh those safety factors against the CLARITY results and follow-up data supporting the efficacy of Mavenclad, as well as the fact that the agent has a different mechanism of action than other MS medications and a short course of treatment. Mavenclad is an antimetabolite that reduces the number of lymphocytes (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 earlier this year. Mavenclad, which is given as tablets, has a two-course treatment regimen. Each course is, in turn, divided into two treatment cycles. In the first course, the drug is administered on Day 1 and then 23 to 27 days later. The second course involves giving tablets at least 43 weeks (approximately 10 months) after the last dose from the first course, and then 23 to 27 days later. After completing this two-course regimen, the medication is not given again.

Please note that not all of the approved treatments for MS have been included in this section. For a full listing, please see the chart on pages 49 to 51.

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 RMS and PPMS*

Ocrevus® (ocrelizumab) is an anti-CD20 monoclonal antibody. Humanized monoclonal antibodies are antibodies from non-human species whose protein sequences have been modified to increase their similarity to antibodies produced naturally in humans.

In 2017, the FDA approved Ocrevus for use in both relapsing forms of MS (RMS) and primary-progressive MS (PPMS). Approval was based largely on the results of three important studies announced in 2015. In relapsing MS, Ocrevus met both the primary and major secondary endpoints in the Phase III OPERA I and OPERA II studies. The OPERA studies had identical designs. The combined enrollment for both studies was 1,656 individuals with relapsing forms of MS.

In the OPERA studies, individuals received either 600 mg of Ocrevus via intravenous (IV) infusion every six months, or the approved 44 mcg dose of Rebif® (interferon beta-1a) via subcutaneous injection three times weekly. In

both studies, participants receiving Ocrevus had reductions in annualized relapse rates (ARRs) of 46 and 47 percent over a two-year period versus the interferon groups. Additionally, in the Ocrevus treatment groups, new MRI lesions were reduced by 94 and 95 percent, brain atrophy was decreased by 24 and 25 percent, and risk of progression of sustained clinical disability was decreased by 40 percent.

Recent data from an open-label extension of OPERA suggest that Ocrevus slows disease progression among patients with RMS who switched from another disease-modifying therapy. Patients who received Ocrevus or interferon beta-1a during the OPERA trial either continued or were switched to Ocrevus at the start of the trial's open-label extension phase. The mean ARR in the interferon-to-Ocrevus group fell from 0.20 in the year before the patients switched agents to 0.10, 0.08, and 0.07 in years 1, 2, and 3 of the open-label phase, respectively. Patients who continued Ocrevus maintained low mean ARRs throughout the latter stages of the core study and the extension phase.

Notably, the Ocrevus continuation group had a significantly lower proportion of patients with 24-week confirmed disability progression at all points of the open-label extension, suggesting that the interferon-to-Ocrevus group would have benefited from earlier Ocrevus initiation.²⁵

Rates of T1 enhancing lesions and new or

enlarging T2 lesion development were lower among the continuous Ocrevus group, compared with the interferon-to-Ocrevus group. Rates of brain atrophy likewise were significantly lower in the continuous Ocrevus group, again suggesting strong benefits of early Ocrevus initiation. Whole brain volume, cortical gray matter volume, and white matter volume were analyzed.²⁶

Recently released data also provide new details on the ORATORIO study, which assessed the effectiveness and safety of Ocrevus in people with PPMS. Prior to this study, no Phase III studies in PPMS had been successful. ORATORIO, which was published in 2015, was a double-blind, global, multi-center trial involving 732 people with PPMS. Participants were randomized to receive either placebo or Ocrevus, which was administered every six months in two 300 mg doses given two weeks apart. The primary endpoint of the study was time to onset of confirmed disability progression, defined as an increase in EDSS sustained for at least 12 weeks.

The ORATORIO study met its primary endpoint, showing that treatment with Ocrevus significantly reduced the progression of sustained clinical disability by 24 percent compared with placebo. Walking speed, as measured by the timed 25-foot walk, was improved by 29 percent. Hyperintense T2 lesions on MRI actually were reduced among patients taking Ocrevus, and brain-volume loss as viewed on MRI was reduced by 17.5 percent. The incidence of adverse events associated with Ocrevus in ORATORIO was similar to placebo; the most

common adverse events were mild-to-moderate infusion-related reactions.

New data from the ORATORIO open-label extension suggest that starting Ocrevus therapy sooner than later in the course of MS may slow disability progression. Seventy-two percent of patients who participated in the double-blind portion of the ORATORIO trial entered the study's open-label extension phase between 156 and 240 weeks after the core trial started. Depending on which study arm they had been in during the double-blind phase, participants were either switched to Ocrevus from placebo or continued Ocrevus through the extension phase. During the extension period, researchers assessed the prevalence of disability progression at 24 weeks by means of Expanded Disability Status Scale (EDSS) and 9-hole peg test scores.

Throughout the core trial, Ocrevus had reduced the risk of EDSS-scored disability progression by 25 percent and peg test-scored disability progression by 45 percent. In the open-label extension, overall confirmed disability at 24 weeks was significantly less prevalent in the continuous Ocrevus group, compared with the placebo-to-Ocrevus group.⁹

Researchers also recently released pooled safety data from seven Phase III trials and a Phase II trial that followed a total of 3,811 Ocrevus-treated individuals with MS. The researchers reported that per 100 patient years of use (a measurement of medication benefits and risk based on study participation) the rates of adverse events were: any adverse events, 242; serious

adverse events, 7.23; infections, 74.5; serious infections, 2.00; malignancies, 0.45. They noted that those statistics are consistent with the adverse event rates reported among patients with PPMS and RRMS who have been taking Ocrevus outside of clinical trials in the time since the medication was approved for use.²⁷

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 FDA’s 2013 approval of Tecfidera® (dimethyl fumarate) for use in RMS followed completion of two randomized, double-blind, placebo-controlled trials in which the medication reduced the annualized relapse rate (ARR) by 44 percent to 53 percent relative to placebo. Tecfidera also had a favorable impact on disability progression and MRI measures of MS activity, compared to placebo, in those studies.²⁸

The exact means by which Tecfidera, or dimethyl fumarate, exerts its therapeutic effects in MS is not known. The agent 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.²⁸

In 2017, the prescribing information for Tecfidera was amended to include direction

to obtain a complete blood cell count and to measure liver enzymes and other values before initiating the medication. Additionally, 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.²⁸

Data from the ongoing ENDORSE extension study suggest that Tecfidera helps preserve function over time in RMS. ENDORSE is a long-term study that follows people who were newly diagnosed with RMS and had participated in a Phase III study of Tecfidera versus placebo. In the first study, participants received either Tecfidera 240 mg twice daily or placebo for two years. They then had the opportunity to enter ENDORSE. Those who had received Tecfidera in the earlier study continued on that medication, while those who had received placebo were switched to Tecfidera.

Adjusted mean ARRs in the placebo-to-Tecfidera group fell from 0.25 during the two-year placebo period to 0.09 in seven years of Tecfidera treatment, representing a 64-percent decrease. Additionally, between 90 and 93 percent of patients in both groups maintained Expanded Disability Status Scale (EDSS) scores of 3.5 or less, suggesting that Tecfidera helps patients maintain function long-term.¹¹

A Swedish MS registry identified two very different paths for its 2,010 participants who reported taking Tecfidera. One-quarter discontinued the drug within the first year, and almost half stopped the medicine eventually. Of those who discontinued

treatment, 53 percent cited adverse effects as their reason for stopping, while 29 percent cited lack of effect. However, the 918 patients who took Tecfidera continuously for two years or longer showed significant improvements in mean scores of several tests used to measure physical, psychological, and cognitive function in MS. The EDSS, Multiple Sclerosis Severity Scale, Symbol Digit Modalities Test, Multiple Sclerosis Impact Scale, and Visual Analog Scale were among the tests used.²⁹

Another recent study, this one from Italy, looked at risk factors for the development of lymphopenia among people using Tecfidera. Lymphopenia, a common side effect of disease-modifying therapies, is marked by a shortage of lymphocytes, a type of white blood cell that helps the body fight infection. Data from the Italian researchers suggest that older age and treatment duration may be risk factors for Tecfidera-induced lymphopenia.

A total of 147 individuals with RMS were divided into two groups – those with lymphopenia and those with normal lymphocyte counts – and then were divided again into four groups based on the age at which they started Tecfidera. Patients aged 50 years or older were found to have developed lymphopenia an average 15.5 months after starting Tecfidera. As patient age decreased, the interval between Tecfidera initiation and lymphopenia diagnosis increased, suggesting an age-related correlation. The researchers hypothesized that gradual deterioration of the immune system with aging might increase an older patient's risk of Tecfidera-induced lymphopenia, and that low

baseline lymphocyte counts and longer treatment with Tecfidera might further increase that risk.³⁰

Tecfidera® (delayed-release dimethyl fumarate) altered the gut microbiome in relapsing-remitting MS (RRMS) patients who took the oral disease modifying therapy (DMT) over 12 weeks.³¹ The gut microbiome is a mix of bacteria and other microbes found in the gastrointestinal (GI) tract. In recent years, the gut microbiome has been recognized as a key component of the body's immune system. In particular, research suggests that the composition of the microbiome, in terms of the presence and number of various microbes, may affect the course of MS.

In a study of 36 patients with RMS, 17 types of microbes were significantly altered in MS patients compared with 165 healthy controls. Notably, people with MS had lower levels of *Faecalibacterium* compared to the healthy controls. A total of 27 of the study participants received Tecfidera, while nine received an injectable DMT. At two weeks, subjects receiving Tecfidera reported a worsening of GI symptoms compared to baseline, but this impact on symptoms was not seen at 12 weeks. Meanwhile, at 12 weeks, the Tecfidera patients had an increased abundance of *Faecalibacterium*. Similar changes were not seen in the participants receiving an injectable DMT.

Researchers continue to investigate the role of the gut microbiome in MS. As that effort continues, this study comparing patients taking different DMTs adds to the understanding of the interaction between MS

medications and the composition of the microbiome. As the investigators note, “It could therefore be speculated that direct effects on the gut microbiome are part of the therapeutic actions” of Tecfidera.

Tysabri® (natalizumab)

Company: Biogen

- *300 mg given via IV infusion*
- *Approved in 2004 for RMS*

This monoclonal antibody acts against a molecule involved in the activation and function of lymphocytes, which are immune-system cells produced to fight infection and disease. It also acts against the passage of lymphocytes into the central nervous system (CNS). The CNS consists of the brain, spinal cord, and optic nerves.

The FDA approved Tysabri in 2004 on the basis of the Phase III AFFIRM trial, in which Tysabri reduced the risk of progression of disability by 42 percent to 54 percent, and reduced the annual rate of relapse by two-thirds. 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.³²

Since then, researchers have been

exploring ways to minimize the risk of PML associated with Tysabri use. In one retrospective study, investigators reviewed four years’ of clinical and MRI data from individuals with RMS at six MS treatment centers in Italy to see if extended-interval dosing of Tysabri reduces PML risk without diminishing the medication’s efficacy. In the United States, the standard dosing of Tysabri is 300 mg infused intravenously over the course of one hour, every four weeks.³³ In this Italian study, patients either received Tysabri every 35 days (standard-interval dosing group), received it at longer intervals stretching up to 56 days (extended-interval dosing group), or started with 35-day dosing and then were switched to extended-interval dosing. A total of 532 participants were included in the first-year analysis, and approximately half of those individuals (270) were still being followed at four years. None of the participants developed PML.

During the first year of treatment, 84.9 percent of patients (421) in the standard-dosing group (had no evidence of MS disease activity, compared with 73.6 percent of patients (111) receiving extended-interval dosing. That difference in disease-free prevalence between groups narrowed at Years 2 and 3, however, and the prevalence was virtually the same at Year 4. These findings suggest that the differences in Tysabri treatment effectiveness between standard and extended-interval dosing dissipate with treatment duration.³⁴

Meanwhile, data from a retrospective, multicenter cohort study in France describe a drop in Tysabri-related PML associated with

the physicians' ability to identify at-risk patients.

The researchers focused on 6,318 people in a French MS patient database who had been treated with Tysabri during a 10-year period. There were 45 cases of PML among those 6,318 patients. After adjusting for patient age and sex, and using statistical analysis to estimate yearly incidence rates, the researchers found a much higher incidence in PML from 2007 to 2013 compared with subsequent years. They note that since 2012, physicians have had information on factors that increase a patient's risk for developing PML. Those risk factors include testing positive for anti-JC virus antibodies, having previously used an immunosuppressive medication, and having received Tysabri for two years or longer. The investigators surmise that, armed with this knowledge, physicians in recent years have had a greater ability to determine whether a patient is a good candidate for Tysabri or would be better suited to receive another DMT. In support of this conclusion, they note that starting in 2013, estimated PML incidence has decreased by 23 percent each year. ^{35, 36}

Meanwhile, new data on long-term use of Tysabri suggest that the sooner the agent is started, the longer function can be preserved. In a nationwide, prospective cohort study, researchers identified 2,306 individuals with RMS from neurology clinics across Sweden who had been diagnosed with MS after January 1, 1995 and had been receiving Tysabri for at least one year. Researchers divided the patients into two groups – those

who began Tysabri within three years of MS onset, and those who started treatment more than three years after onset – and then measured rates of cognitive and physical decline. The patients were also compared with three sets of similar patients: those who had been diagnosed before 1995, who were treated with interferon beta-1a or glatiramer acetate injections, or who received no treatment.

During a median six-year follow-up period, patients who started Tysabri later showed more rapid increases in Expanded Disability Status Scale scores (indicating worsening of disease) and declines in Symbol Digit Modality Test scores (indicating worsening of cognitive function), compared with patients who started the medication sooner. However, disease progression in both Tysabri groups was slower than that seen in the groups of patients with pre-1995 onset, interferon or glatiramer acetate treatment, or no treatment.¹⁰

Gilenya® (fingolimod)

Company: Novartis

- *0.5 mg capsule given orally once per day*
- *Approved in 2010 for RMS*

Gilenya® (fingolimod) was the first S1P-receptor modulator approved for the treatment of MS. Mayzent® (siponimod), which was approved by the FDA earlier this year for treatment of RMS, secondary-progressive MS, and clinically isolated syndrome, also belongs to this class of

immune-modulatory drugs. 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 the CNS and enhance the repair of damaged nerves within the brain and spinal cord.

Recent data suggest that Gilenya has a positive long-term effect on patients with RMS. The Immunomodulation and Multiple Sclerosis Epidemiology Study 2 in Sweden followed 1,617 patients who had received Gilenya for MS. Of that group, 91 percent had RMS, and 70 percent had been treated with interferons, glatiramer acetate, natalizumab, dimethyl fumarate, or teriflunomide before switching to Gilenya. Seventy-six percent (1,230 people) had taken Gilenya for at least one year at study cutoff, and the average treatment duration was 34 months (two months short of three years).

Relapse rates were expressed in “patient years,” a method of calculating study participation over a set period to more accurately measure a medication's risks and benefits. Based on this calculation, relapse rates fell significantly among Gilenya-treated patients, from 281 per 1,000 patient years before Gilenya treatment to 87 per 1,000 patient years during treatment. However, nearly half the study group (803 patients) discontinued Gilenya at some point, with

most patients citing lack of effect or adverse effects as reasons. Still, the researchers viewed Gilenya as “a generally well-tolerated drug that reduces the clinical activity in MS patients.”¹²

Meanwhile, LONGTERMS, an open-label, single-arm extension study, evaluated the long-term effects of Gilenya 0.5 mg in people with RMS who had taken the medication for at least five years and who continued to receive it for up to 10 years. The annualized relapse rate (ARR) in this study declined with longer use of Gilenya, from 0.26 after one year of use to 0.14 after 10 years. Seventy-eight percent of participants remained free of confirmed six-month disability progression through five years of treatment. Changes in brain volume remained stable for five years and 10 years after Gilenya initiation.³⁷

In a retrospective claims database analysis in the United States, investigators followed 1,599 people with MS for three years after they started Gilenya. Annualized relapse rates were calculated over one year before patients started the medication, and during each year of the three-year follow-up period. Among the Gilenya initiators, 1,158 (72 percent) were still taking the medication at the start of Year 2, and 937 (59 percent) were still on Gilenya at Year 3. Median time on Gilenya treatment was 33 months.

The mean baseline ARR of 0.51 recorded during the pre-initiation period fell more than 50 percent after Gilenya initiation, and that reduction was sustained over three years for the individuals who were still taking Gilenya.³⁸

Lemtrada® (alemtuzumab)

Company: Genzyme

- *Intravenous infusion over four hours for two treatment courses: First course: 12 mg/day on five consecutive days; Second course: 12 mg/day on three consecutive days 12 months after the first treatment course*
- *Approved for RMS in 2014*

Lemtrada® (alemtuzumab) is a monoclonal antibody. Its exact mechanism of action is unknown, but it is believed to involve binding to a cell surface antigen found on key immune-system cells, including T and B lymphocytes, leading to the depletion of these cells and other effects on the inflammatory process. Because Lemtrada can cause serious autoimmune conditions and infusion reactions, and can increase the risk for some cancers, its use is typically reserved for individuals who have not responded adequately to two or more other disease-modifying therapies.

Lemtrada was approved for use in RMS on the basis of the Phase III CARE MS I and CARE MS II trials; both studies compared the medication with subcutaneous interferon beta-1a over two years of treatment. Now, new data indicate that Lemtrada's effects on slowing MS disease progression are maintained with long-term use.

A total of 290 individuals with RMS who completed two courses of Lemtrada in the CARE-MS I trial entered a four-year extension study. They then were evaluated for an additional two years as part of a second

extension study, called TOPAZ. In all, patients were evaluated for eight years after they started Lemtrada. During both the initial CARE-MS I extension study and TOPAZ, participants could receive additional courses of Lemtrada or another disease-modifying therapy at the investigators' discretion, but more than half (56 percent) received no additional treatment during TOPAZ.

At the eight-year evaluation mark, the annualized relapse rate was 0.14, and 88 percent of the participants were relapse-free. Expanded Disability Status Scale (EDSS) scores were stable or improved from the core baseline for 78 percent of patients; 71 percent were free of six-month confirmed disability worsening; 41 percent achieved six-month confirmed disability improvement; and 60 percent had no evidence of disease activity. In addition, 87 percent had no new T1-enhancing lesions, and 67 percent had no new or enlarging T2-hyperintense lesions.¹³

Similarly, people with RMS who received interferon beta-1a therapy during the core CARE-MS II trial and who then were switched to Lemtrada for the CARE-MS II extension period and TOPAZ, showed significant improvements six years after switching to Lemtrada. The annualized relapse rate for the 117 individuals in this group was 0.19, and EDSS scores were stable or improved from CARE-MS II baseline in 68 percent of the participants. Similar to the CARE MS I findings, reductions in evidence of disease activity on MRI, as measured by assessment of T1-enhancing lesions, and new or enlarging T2-hyperintense lesions, were reported.³⁹

CARE-MS I researchers also found that Lemtrada reduced levels of serum neurofilament light chain (sNfL), a biomarker of neuro-axonal damage in MS that can measure response to a disease-modifying therapy. Researchers analyzed more than 1,500 sNfL samples from 329 patients who had active MS at baseline and who then were treated with Lemtrada. Median sNfL levels fell significantly, from 31.6 pg/mL at baseline to 17.2 pg/mL six months after Lemtrada treatment, and between 13.0 and 13.9 pg/mL two years after therapy. During the same period, MRI disease activity and brain volume loss also decreased in these patients. The researchers plan to analyze more than 7,000 sNfL samples across seven years to obtain a more-detailed picture of how sNfL reduction may slow MS disease progression.⁴⁰

In another trial, researchers in the United Kingdom and Ireland found positive results in individuals with RMS who switched from Tysabri® (natalizumab) to Lemtrada. Of the 79 participants in the trial, 51 were followed for more than two years after initial Lemtrada infusions, and independent blinded MRI analysis was performed in 20 patients. Data were analyzed in five phases: pre-Tysabri treatment, Tysabri treatment, the medication switch period, Lemtrada treatment, and post-Lemtrada treatment.

Mean annualized relapse rates fell from 2.3 before Tysabri treatment to: 0.8 during Tysabri treatment; 0.4 during Lemtrada treatment; and 0.5 after the last Lemtrada treatment.⁴¹

Plegridy® (peginterferon beta-1a)

Company: Biogen

- *Dose: 125 mcg every 14 days, self-administered subcutaneously (starting at 63 mcg at Day 1, then increasing to 94 mcg on Day 15 and to 125 mcg on Day 29)*
- *Approved for RMS in 2014*

Plegridy® (peginterferon beta-1a) is a synthetic version of the human interferon beta. Interferon beta slows progression of MS by balancing the expression of pro- and anti-inflammatory substances in the brain and preventing some inflammatory neurons from crossing into the brain. This reduces neuron inflammation and is believed to increase production of nerve growth factor.

Plegridy gained FDA approval in 2014 for relapsing forms of MS (RMS). The pivotal double-blind study followed 1,012 individuals with RMS who had a baseline Expanded Disability Status Scale (EDSS) score of 5.0 or less and who had experienced at least two relapses within the previous three years and at least one relapse in the previous year. The participants were randomized to Plegridy 125 mcg or placebo once every 14 days. Neurological evaluations were performed at baseline, every 12 weeks, and during a suspected relapse. Brain MRI evaluations were done at baseline, week 24, and week 48.

At 48 weeks, the mean number of T1-enhancing lesions was significantly lower in the Plegridy group than among placebo-treated patients (0.2 versus 1.4), as was the

mean number of T2 new or enlarging-hyperintense lesions (3.6 versus 10.9). Relapse rates also were significantly reduced among individuals receiving Plegridy, compared with placebo.⁴²

New Phase IV (post-approval) data suggest Plegridy slows MS-related disability with long-term use. Researchers studied 963 patients who received at least one dose of the medication. The individuals were split into two groups: newly diagnosed (242) and non-newly diagnosed (721). More than 80 percent of the participants with either newly diagnosed or long-standing RMS remained relapse-free for up to two years.

Nearly one-third of the individuals in both groups discontinued Plegridy at some point after initiation. Adverse events and lack of effect were the most commonly cited reasons for discontinuation, and influenza-like illness and injection-site irritation were the most commonly reported adverse effects.¹⁴

Aubagio® (teriflunomide)

Company: Genzyme

- *Oral; 7 mg or 14 mg once daily*
- *Approved for RMS in 2012*

As with many other disease-modifying therapies (DMTs) for 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

Aubagio secured FDA approval for use in RMS following positive results from four randomized, controlled, double-blind clinical trials. In the first study, 1,088 patients were randomized in a 1:1:1 ratio to receive Aubagio 7 mg, Aubagio 14 mg, or placebo, and were followed for up to 26 months. Individuals receiving Aubagio had a statistically significant reduction in the annual relapse rate (ARR) - the study's primary endpoint - compared to those receiving placebo. The second study followed 1,165 patients for up to 40 months, also randomizing them in a 1:1:1 ratio to receive Aubagio 7 mg, Aubagio 14 mg, or placebo, and specifying ARR as the primary endpoint. Both doses of Aubagio again showed statistically significant advantages over placebo in terms of a lower relapse rate and on other measures of efficacy.⁴³

The third study followed a similar design in terms of randomization and endpoint but focused on people who had experienced a first clinical event consistent with acute demyelination (damage to protective nerve fibers in the brain) occurring within 90 days of randomization. After following these individuals for up to 108 weeks (two years and four weeks), the study found that significantly higher proportions of Aubagio-treated patients remained free of relapse, compared with those receiving placebo. The fourth study examined MRI characteristics of 179 individuals with RMS. The mean number

of active lesions per MRI scan of the brain during the 36-week treatment period was lower in people treated with Aubagio 7 mg (1.06) and Aubagio 14 mg (0.98) than with placebo (2.69). The difference was statistically significant for both.⁴³

New data show low ARRs in patients who previously received no DMT or who switched to Aubagio from another DMT. A post-hoc analysis of data from a Phase II study and from the Phase III TEMSO, TOWER, and TENERE studies identified 2,643 patients who received Aubagio 14 mg/d or placebo and had received another DMT or no therapy before switching to Aubagio or placebo. The participants were divided into three groups: those who discontinued another DMT six months before randomization (348), those who stopped another therapy six months to two years before randomization (412), and those who received no prior DMT (1,883). ARRs ranged from 0.33 to 0.53 for the three groups, and the mean rates were all significantly lower than those for placebo.⁴⁴

Meanwhile, a separate post-hoc analysis showed that long-term Aubagio use reduced brain-volume loss. Researchers identified individuals who had received Aubagio 14 mg/d (214) or placebo (197) during the Phase III TOPIC study, which measured the efficacy of Aubagio in people with a first clinical episode suggestive of MS. The investigators used an automated brain-measurement system to calculate brain-volume loss at six-month intervals over two years. At endpoint, an overall 43-percent reduction in whole-brain-volume loss was reported with Aubagio use, and the median

percentage of brain-volume loss was significantly lower in the Aubagio-treatment group compared with the placebo group. Median reductions in whole-brain-volume loss at six, 12, and 18 months were 87 percent, 29 percent, and 36 percent, respectively, in the Aubagio-treatment group.¹⁵

Copaxone® (glatiramer acetate)

Company: Teva Pharmaceuticals

- *Dose: 20 mg/mL daily or 40 mg/mL three times weekly, self-administered subcutaneously*
- *Approved for RMS in 1996*

Copaxone® (glatiramer acetate) is a synthetic protein that simulates myelin basic protein, a component of the myelin that insulates nerve fibers in the brain and spinal cord. Though its mechanism of action is not completely understood, this medication appears to work by blocking myelin-damaging T cells. The Copaxone brand of glatiramer acetate was approved in 1996, and generic formulations have since become available.

Copaxone gained FDA approval for the treatment of RRMS based on five placebo-controlled studies. In the first two studies, a total of 301 individuals with RRMS with at least two exacerbations in the two years preceding the study were randomized 1:1 to Copaxone 20 mg/mL daily or placebo. In both studies, relapse rates and frequency were reduced in the Copaxone groups, but the sample sizes in both studies were small. In

the third study, 481 individuals who had experienced demyelination (damage to protective fibers around nerves in the brain) within the previous 90 days and who showed lesions on MRI received Copaxone 20 mg/mL daily or placebo. After a maximum three-year follow-up period, time to a second exacerbation was significantly delayed in the Copaxone group compared with placebo.⁴⁵

In the fourth study, 239 individuals who had suffered at least two exacerbations in two years and showed at least one enhancing lesion on MRI at screening were randomized to double-blind administration of Copaxone or placebo for nine months. During that period, all study participants underwent monthly MRI scans. At study's end, the median cumulative number of T1-enhancing lesions was significantly lower in the Copaxone group compared with placebo (11 versus 17). In the fifth study, 1,404 people with RMS received Copaxone 40 mg/mL (943) or placebo (461) three times weekly for one year. At study's end, the Copaxone group had experienced fewer confirmed relapses and showed significantly fewer cumulative new or enlarging T2 lesions and cumulative T1-enhancing lesions, compared with placebo.⁴⁵

New data from an analysis of disease-modifying therapies point to the long-term effectiveness of glatiramer acetate in delaying disability and preserving function in MS. Researchers in the United Kingdom compared 755 individuals with RRMS who had received glatiramer acetate with 898 similar patients who received no treatment. Participants were evaluated at least once with the Expanded Disability Status Scale (EDSS)

after baseline. After a mean follow-up period of 7.12 years, individuals who had received glatiramer acetate showed a 16.5-percent reduction in disability progression and 25-percent reduction in loss of function, compared with the untreated group.¹⁶

Meanwhile, findings on the effects of DMTs on pregnancy and breast feeding suggest that neither glatiramer acetate nor interferon beta cause significant developmental delays in children who may have been exposed to either medication via breast milk. The researchers note that both interferon and glatiramer acetate are large molecules that are unlikely to enter breast milk, but that the specific effects on child development from using these disease-modifying therapies during breast feeding have not been studied.

Drawing on information in a German pregnancy database, researchers reviewed data on 76 pregnancies in 72 women who had received either glatiramer acetate or interferon beta for MS. The mothers provided information on both their disease activity and their children's development by completing a questionnaire after delivery. Forty-seven women stopped treatment during pregnancy and resumed treatment after delivery, and 18 women continued treatment through the entire pregnancy. At ages 1 and 2 years, the children's body lengths were within normal ranges for their ages. Four percent of mothers reported that their children were experiencing developmental delays in motor skills, but the percentage was similar to the prevalence of early motor skill delays in the general population.⁴⁶

Finally, an extended-release formulation of glatiramer acetate is under development. The experimental long-acting formulation, called “GA Depot,” consists of extended-release microspheres of glatiramer acetate released over approximately one month. GA Depot would be dosed once every 28 days, which researchers hypothesize may improve patient adherence to the treatment regimen, and thus, may also improve outcomes.

Recently released Phase IIa data suggest that GA Depot is well tolerated and efficacious. Eleven individuals with RRMS who participated in a one-year core efficacy study of GA Depot also completed a 48-week extension study. The patients received GA Depot 40 mg once every 28 days during the extension. No adverse effects other than mild injection-site reactions were reported. Mean EDSS scores did not change significantly from the core-study baseline, and 81.8 percent of participants showed no evidence of disease activity (NEDA) when the extension study ended.⁴⁷

Betaseron® (interferon beta-1b)

Company: Bayer

- *Dose: 25 mg (1 mL) self-administered subcutaneously (starting at 0.0625 mg (0.25 mL), then increasing over six weeks to 25 mg)*

- *Approved in 1993 for RMS*

Betaseron® (interferon beta-1b) is the first disease-modifying therapy (DMT) to receive FDA approval for the long-term treatment of MS. It is a synthetic version of the human interferon beta. Interferon beta balances the

expression of pro- and anti-inflammatory agents in the brain and restricts the flow of inflammatory neurons through the blood-brain barrier. This slows MS disease progression by reducing neuron inflammation, and is believed to increase production of nerve growth factor.

Betaseron secured FDA approval for relapsing forms of MS (RMS) after a double-blind, placebo-controlled study. The 372 patients with RMS in the study had a baseline mean Expanded Disability Status Scale (EDSS) of 5.5, indicative of severe disability that impedes daily activities. Participants also were required to have had at least two exacerbations in the two years before the trial, but with no exacerbations in the preceding month. The patients were randomized at a nearly 1:1:1 ratio to Betaseron 0.25 or 0.05 mg or placebo, self-administered subcutaneously every other day for two years.

At endpoint, the mean annual exacerbation rate was 0.9 among patients who received Betaseron 0.25 mg, compared with 1.14 in the Betaseron 0.05 mg group and 1.31 with placebo. An exacerbation was defined as the appearance of a new clinical sign/symptom or the clinical worsening of a previous sign/symptom that had been stable for at least 30 days. The exacerbation had to persist for at least 24 hours to be considered as a true relapse.⁴⁸

New data support early initiation and long-term use of Betaseron in individuals who develop a clinically isolated syndrome (CIS). A CIS is a preliminary episode of nerve inflammation or damage that may develop into clinically definite MS (CDMS) sometime

FDA-APPROVED MEDICATIONS: NEW DATA ON PREVIOUSLY APPROVED MEDICATIONS

in the future. A recently reported study followed 468 individuals who received Betaseron or placebo, either immediately after or within two years of a CIS episode. Participants in the placebo group were switched to Betaseron after two years, or were switched immediately after they developed CDMS.

Fifteen years after initial randomization, 261 of the initially enrolled patients completed a comprehensive clinical and MRI examination, and information was available on six additional study enrollees who had died. Risk of relapse in the early-treatment group (individuals who received Betaseron from the start) was 18.9 percent lower than that of the placebo/delayed-treatment group. Also, the risk of conversion to CDMS was 30.5 percent lower in the immediate-treatment group versus the delayed-treatment group.¹⁷

Meanwhile, another team of researchers

sought to determine whether extended beta interferon therapy, such as with Betaseron, increases survival in MS. Researchers followed 5,989 patients registered at two MS clinics in British Columbia and France who were diagnosed with RMS and treated with beta interferon. The patients had never received an immunosuppressant or DMT before the study period. A maximum of 18 years of data were reviewed for each person, and most of the 742 individuals who died during the study were matched with controls from the two databases.

After a series of mathematical analyses, the researchers found that treatment with beta interferon for three years or more was associated with increased survival in patients with RMS. However, the investigators did not find an association with extended survival for beta interferon treatment that lasted between six months and three years.¹⁸



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MSAA's MRI Access Fund is made possible with support from Biogen and Sanofi Genzyme.

About Monoclonal Antibodies

Monoclonal antibodies are derived from cells that are identical (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 be directed specifically toward 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 already are approved for MS. Several other monoclonal antibodies have shown promise in MS, and five of these are reviewed in this section.

Rituxan® (rituximab)

Company: Genentech/Roche

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

Rituxan is a monoclonal antibody that binds to a receptor on the surface of B cells. These cells are then destroyed, and their levels in the circulation are decreased. It is approved for use in the treatment of lymphomas, leukemias, and autoimmune disorders.

Serious adverse events have been reported in Rituxan-treated patients with other diseases, including rare cases of progressive multifocal leukoencephalopathy (PML), the same viral infection of the brain that has been seen with a small percentage of patients taking some approved DMTs. While no PML has been diagnosed in MS patients taking Rituxan, the number of individuals with

MS treated with Rituxan is relatively small to date.

New data from the University of Colorado assessed the safety profile and effectiveness of Rituxan in patients with MS. Researchers at the university's Rocky Mountain MS Center followed 125 individuals with either relapsing-remitting, primary-progressive, or secondary-progressive MS. The mean follow-up period was 40.6 months, and participants received an average of six infusions or 4,954 mg of Rituxan.

Rituxan was found to be effective overall, with just 32 of the 125 participants experiencing a clinical relapse, enhancing lesion, or T2 lesion during the follow-up period. Infections occurred in 34 of the participants and resulted in either emergency room or hospital treatment. Sixty people suffered a mild-to moderate infusion reaction during the first or second infusion; 57 individuals had abnormally low counts of the

infection-fighting IgM or IgG antibodies, and nine of the participants had a deficit of certain white blood cells. Two people were diagnosed with malignant cancer after they started Rituxan, but it is unclear whether the drug was a factor.⁴⁹

Meanwhile, a review of Kaiser Permanente and Swedish data found that all-cause death rates among people with MS receiving Rituxan are lower compared with those of MS patients receiving other disease-modifying therapies. The researchers analyzed data on 1,246 individuals with MS from a Kaiser Permanente Southern California database, and 1,252 patients from a chart-validated subset of a Swedish MS registry. Most of these individuals had received initial Rituxan infusions of 1,000 mg and subsequent infusions of 500 mg.

Seventeen deaths were reported from the two databases, but none occurred within two weeks of the last Rituxan infusion. Causes of death included suicide, cardiovascular disease, and complications from an MS-related disability (such as a fall or pneumonia). No deaths from infusion, systemic inflammatory response syndrome, or drug-induced acute coronary syndrome were reported. Similar complications have been reported among patients with cancer who received doses of Rituxan higher than 1,000 mg. The findings suggest that Rituxan at 500 mg or 1,000 mg is a safe option for individuals with MS.⁵⁰

Meanwhile, retrospective data suggest Rituxan is also effective in pediatric-onset MS. Researchers at Texas Children's Hospital reviewed MRI scans of 17 patients aged 13 to

22 years. These teens and young adults had been diagnosed with MS nine months to nine years before the MRI, and had been treated with Rituxan for a duration of between nine and 46 months. Sixteen patients were relapse-free while receiving Rituxan, while one developed optic neuritis.

Based on the MRI results, 14 of the 17 patients had no T2 or contrast-enhancing lesions and showed no evidence of disease activity. Expanded Disability Status Scale scores also remained stable, with a mean score of 0.5, suggesting near-normal function.⁵¹

Ofatumumab (also known as Arzerra®)

Company: Novartis

- *Given via IV infusion and also studied via subcutaneous injection*
- *Being studied in RMS*

Like Rituxan and Ocrevus, ofatumumab is an anti-CD20 monoclonal antibody. It has the potential advantage of being a human monoclonal antibody (versus antibodies from non-human species that have been modified). Ofatumumab has a unique target on the CD20 molecule and is approved for certain forms of leukemia.

Two simultaneous Phase III clinical trials - ASCLEPIOS I and ASCLEPIOS II - are comparing ofatumumab to teriflunomide in patients with RMS. Investigators in both trials are following patients aged 18 to 55 years with a baseline Expanded Disability Status Scale (EDSS) score of 0 to 5.5 at screening.

EXPERIMENTAL MEDICATIONS: MONOCLONAL ANTIBODIES

An EDSS score of less than 4.0 represents moderate disability, while a score between 4 and 5.5 indicates more severe MS-related disability that could interfere with daily activities.

Participants in both trials will receive either subcutaneous ofatumumab at three weekly 20-mg doses for two weeks followed by one 20-mg injection every four weeks, or oral teriflunomide 14 mg daily. The primary endpoint for both trials is the annual rate relapse. Secondary endpoints include MRI-related outcomes and confirmed disability worsening at three and six months. The 1,884 people enrolled in the two studies represent a typical RMS population (more than 65 percent female and 90 percent Caucasian). Sixty percent of the participants had received another disease-modifying therapy prior to entering the studies, and 40 percent showed enhancing lesions on MRI at screening. The trials are scheduled for completion around May 2019.⁵²⁻⁵⁴

Opicinumab

Company: Biogen

- *750 mg given via intravenous (IV) infusion*
- *Being studied in RMS and SPMS*

Opicinumab is a human monoclonal antibody that targets LINGO-1, a protein that suppresses the redevelopment of axons (brain cells that send functional information throughout the body) and re-formation of myelin sheaths (fibers that protect the axons). Axons and myelin sheaths are lost or damaged in patients with MS, leading to loss

of physical and cognitive function. By blocking LINGO-1, opicinumab is formulated to promote regeneration of axons and myelin.⁵⁵

The Phase II, double-blind AFFINITY study is assessing the effectiveness of opicinumab as an add-on therapy in people with relapsing or secondary-progressive forms of MS (RMS or SPMS). Approximately 240 individuals treated with an interferon beta medication, dimethyl fumarate (Tecfidera), or natalizumab (Tysabri) will receive IV opicinumab 750 mg or placebo every four weeks for 72 weeks.

Researchers will measure overall disability improvement or worsening, as well as specific measures of physical and cognitive function. Participants entering the study have had MS for 20 years or less, and have moderate to severe disability, preserved brain function, stable disease status, and at least one relapse between four months and two years before the study.⁵⁵ The estimated completion date for the study is May 2022.⁵⁶

A previous Phase II trial evaluated four doses of opicinumab as an adjunct to interferon beta therapy in an MS patient group with similar characteristics. Patients who received 10 mg of opicinumab per kilogram of body weight each month saw a 65.6 percent improvement in MS disability, while those who received 30 mg/kg every four weeks improved by 68.8 percent. However, individuals who received lower and higher doses (3 mg/kg or 100 mg/kg) did not see significant improvement compared with those in the placebo group. In all, 334 participants completed the study.⁵⁷

Ublituximab (also known as TG-1101)

Company: TG Therapeutics

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

Like Ocrevus, Rituxan, and ofatumumab, ublituximab targets the CD20 molecule to deplete B cells. Its developer, TG Therapeutics, is evaluating the monoclonal antibody for use in treating both hematological malignancies and relapsing forms of MS (RMS). One area of inquiry in MS is whether the activity of ublituximab will enable it to be administered in lower doses and shorter infusion times than currently available anti-CD20 agents.⁵⁸

Findings from a Phase II multi-center, placebo-controlled study suggest that ublituximab reduces MS disease activity, suppresses relapses, and can be safely infused in approximately one hour. Forty-eight individuals with RMS received an initial infusion of ublituximab, subsequent infusions 15 days and 24 weeks later, and then were followed for 48 weeks. Infusion times ranged between one and four hours.

Median depletion of B cells exceeded 99 percent at Week 4, and that level of depletion was maintained at Weeks 24 and 48. No enhancing lesions were seen at Weeks 24 and 48, and T2-lesion volume was decreased by 10.6 percent at Week 48, compared with baseline. Also, none of the patients who could be evaluated showed sustained disability progression. Mild to moderate infusion reactions were reported, but the

incidence did not increase with faster infusion.^{58,59}

Two parallel, placebo-controlled, Phase III trials of ublituximab are also in progress. The global, multicenter ULTIMATE I and ULTIMATE 2 studies are comparing ublituximab with teriflunomide in people with RMS. The primary endpoint for both studies is annualized relapse rate after 96 weeks of treatment.⁶⁰

Temelimab (formerly GNbAC1)

Company: GeNeuro SA

- *Intravenous (IV) medication in monthly 6-mg, 12-mg, or 18-mg/kg doses*
- *Being studied in RMS*

Temelimab (GNbAC1) targets a human endogenous retrovirus (HERV) believed to play a role in the development of MS. This treatment approach, or mechanism of action, differs from those of currently approved medications. HERVs are genetic elements that are either hereditary, replicated from a host cell, or result from a germ. The viral envelope protein encoded by one HERV has been found in active MS lesions. Temelimab, a monoclonal antibody, is formulated to neutralize this protein and, thus, it is hoped, block harmful inflammation and facilitate restoration of the myelin sheath that coats nerve fibers and that is damaged in MS. The agent is also being studied in Type 1 diabetes and other autoimmune disease.⁶¹

In the Phase IIb CHANGE-MS trial, MRI findings were used to assess the impact of temelimab on MS lesions in the central

EXPERIMENTAL MEDICATIONS: MONOCLONAL ANTIBODIES

nervous system. A total of 270 people with relapsing forms of MS were randomized in a near 1:1:1:1 ratio to receive monthly IV infusions of temelimab in doses of 6, 12, or 18 mg per kilogram of body weight or placebo for 24 weeks. After week 24, participants in the placebo group were randomized to receive one of the three temelimab doses for a second 24-week period. Individuals who had been receiving temelimab during the first 24-week period kept receiving their original doses for the second period.

After 48 weeks, temelimab use was associated with significant reductions in both central nervous system deterioration and development of T1-enhancing hyperintense lesions measuring at least 3 millimeters in diameter. These improvements were more substantial among those who had received temelimab for 48 weeks, compared with those who started with placebo, underscoring the potential effectiveness of temelimab as a long-term treatment. In most measures, benefits were dose-dependent: The higher the dose, the more substantial the benefit.⁶² Temelimab has also shown ongoing benefit over the longer term. The

ANGEL-MS study was designed to examine the safety and efficacy of the medication over roughly two years of treatment. Individuals who had participated in the CHANGE-MS trial were offered the opportunity to continue receiving treatment in ANGEL-MS. Ninety-four percent of eligible patients (219) opted to enter the trial; each received the same dose of temelimab that he or she had been receiving at the conclusion of CHANGE-MS. Although the study was ended early when one of the companies involved in developing temelimab ended its partnership with the other company involved, 154 patients received temelimab for at least 96 weeks.

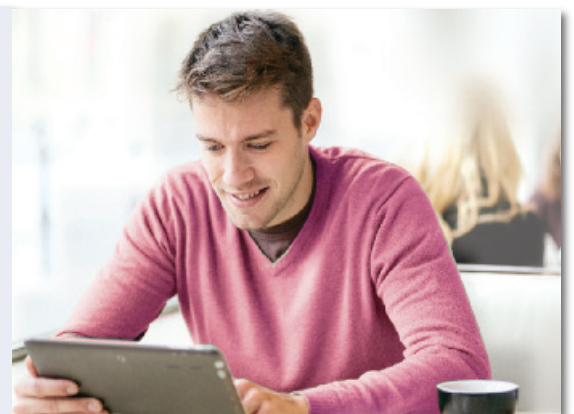
Data from this study found that the medication had a positive effect of reducing brain atrophy, maintaining the integrity of myelin, and measures of impact on slowing MS progression, with the 18 mg/kg dose having the greatest benefit. GeNeuro, the Swiss company developing temelimab, notes that because the protein temelimab targets “has no known physiological function,” temelimab was anticipated to have a good safety profile, with no effect on the patient’s immune system, which has been shown in clinical trials conducted thus far.⁶³

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About S1P Receptor Modulators

Several investigational oral agents currently under study work in a manner similar to Gilenya® and Mayzent® in that they also trap immune cells in the lymph nodes so that they cannot get into the CNS to create lesions. Researchers recently reported new data on two of these S1P receptor modulators, ozanimod and ponesimod.

Ozanimod (formerly RPC1063)

Company: Celgene

- Oral medication studied at several doses
- Being studied in RMS

Ozanimod (RPC1063) is a selective modulator of two types of S1P receptors: S1P1 and S1P5. The once-daily pill was studied in a trial called RADIANCE, where the experimental medicine was compared at two different doses with placebo. A total of 258 individuals with relapsing forms of MS (RMS) were studied in this trial, which began with a seven-day gradual titration of ozanimod up to the full investigational dose. (Titration refers to starting with a lower dose and gradually increasing until the full dose is reached. This helps reduce the risk of side effects when starting a new medication.) The double-blind study ran for 24 weeks, followed by a year-long safety-extension period.

At the end of the initial 24-week treatment period, individuals in both groups taking ozanimod showed an 86-percent decrease in the cumulative number of gadolinium-enhanced lesions compared to the placebo group. The relapse rates also decreased in the treatment groups compared with placebo, with a 31-percent decrease in the

0.5-mg group and a 53-percent decrease in the 1-mg group.

The most common side effects reported were nasopharyngitis (the common cold) and headache. However, both of these events were reported more commonly by placebo-treated individuals than by ozanimod-treated participants. Notably, none of the subjects receiving ozanimod experienced serious cardiac events, infections, or episodes of macular edema (a buildup of fluid in the retina that can cause vision loss. It can occur in rare cases with use of Gilenya).⁶⁴

In 2016, the 72-week extension data of the RADIANCE trial were released. These data showed a continued reduction in relapses and gadolinium-enhancing lesions for those individuals who remained on ozanimod, with efficacy results favoring the 1-mg dose over the lower 0.5-mg dose. No new safety or tolerability issues were identified during this blinded extension phase of the trial.

Celgene, the company that is developing ozanimod, has submitted a New Drug Application asking the United States Food and Drug Administration to approve ozanimod for the treatment of RMS. Celgene has also submitted a Marketing Authorization Application to the European Medicines Agency for the same indication. Pivotal data

EXPERIMENTAL MEDICATIONS: NEW S1P RECEPTOR MODULATORS

from RADIANCE and from another Phase III study, SUNBEAM, were included in both applications.^{5,65}

More recently, SUNBEAM and RADIANCE data showed dose-dependent improvements in relapse frequency and MRI-measured disease activity in individuals with early or advanced RMS. A total of 2,659 patients, including 1,267 with advanced RMS, received either daily ozanimod 0.5 mg or 1 mg or weekly interferon beta-1a injections (30 mcg) for one to two years. The median time since MS diagnosis was 0.5 years for the early RMS group and 5.7 years for the advanced RMS group.

After one year, the mean number of T1-enhancing lesions and T2 new and enlarging lesions were lower among participants who received the higher ozanimod dose versus the lower dose, but both groups had significantly fewer lesions than the participants who were treated with interferon. Ozanimod improved all measures of disease activity among both the early and advanced RMS groups.⁶⁶

Overall relapse rates were 42 percent and 26 percent lower among the ozanimod 1 mg and 0.5 mg groups, respectively, compared with interferon-treated group. Relapses that required hospitalization or treatment with steroids decreased by 43 percent and 26 percent in the ozanimod 1 mg and 0.5 mg groups, respectively. The incidence of acute relapses was 20 percent to 35 percent lower among ozanimod-treated patients compared with interferon.⁶⁷

Ozanimod also was shown in the SUNBEAM trial to prevent or delay cognitive

deficits. MS can slow "processing speed" (the time needed to perform a mental task). Slowed processing speed can make executive functions such as paying attention and making decisions more difficult, and can impair the quality of life for individuals with MS.

More than 1,300 people who received ozanimod 1 mg or 0.5 mg or intramuscular interferon beta-1a were studied in an analysis in which researchers administered the Symbol Digit Modalities Test (SDMT), which measures cognitive impairment, at baseline, six months, and one year. Improvements in SDMT scores of 4 points or greater were more common among the participants in both ozanimod-treatment groups than among those treated with interferon. A 4-point SDMT increase signifies clinically meaningful improvement in processing speed, and these improvements were seen six months and one year after baseline testing among individuals receiving ozanimod.⁶⁸

Ponesimod

Company: Actelion

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

Ponesimod is another selective S1P1 receptor modulator that completed a Phase II trial; results were reported in 2012. In this study, 462 people with RMS were randomized to placebo or 10 mg, 20 mg, or 40 mg of ponesimod. Reductions in annualized relapse rate and reductions in

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new lesions were seen for all treatment groups versus placebo. However, the 40-mg dose was associated with an increase in adverse events. Two randomized, double-blind, phase III trials involving the 20-mg dose are now under way.

The POINT study is examining ponesimod as adjunctive therapy to Tecfidera® (dimethyl fumarate). Investigators are following approximately 600 individuals with RRMS who had been taking Tecfidera for at least six months at screening. The participants, all of whom are being randomized at a 1:1 ratio to add-on ponesimod 20 mg/d or placebo for 60 weeks, showed clinical or MRI evidence of disease activity within 12 to 15 months of screening. Major endpoints will include annual relapse rate, clinical and MRI disease

activity, and measures of the safety and tolerability of ponesimod. Study completion is scheduled for March 2020.^{69,70}

Meanwhile, the ongoing OPTIMUM (Oral Ponesimod Versus Teriflunomide in Relapsing MULTiple Sclerosis) trial is comparing ponesimod and teriflunomide (Aubagio®) in patients with RMS. A total of 1,133 participants have been randomized to ponesimod 20 mg/d or teriflunomide 14 mg/d over 108 weeks. Investigators are measuring annualized relapse rate, changes in fatigue symptoms, cumulative number of T1 enhancing or T2 lesions on MRI, and prevalence of patients who report confirmed disability at 12 and 24 weeks. The trial is scheduled for completion in May 2019.⁷¹

Vumerity™ (diroximel fumarate)

Company: Alkermes plc and Biogen Inc.

- *Oral medication being studied at 462 mg twice daily*
- *Being studied in RMS*

Diroximel fumarate is in the same class of MS therapy as Biogen's Tecfidera® (dimethyl fumarate), but is believed to cause fewer gastrointestinal (GI) side effects – such as diarrhea, nausea, vomiting, and abdominal pain – than Tecfidera. The exact mechanism of action by which diroximel fumarate exerts 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.⁴

The FDA in February accepted a New Drug Application (NDA) from Biogen and Ireland-based Alkermes plc, seeking approval of diroximel fumarate for treatment of relapsing forms of MS (RMS). The FDA, which under federal law has six to 10 months to rule on an NDA, is expected to decide in late 2019 whether to approve the agent for RMS.⁴

The ongoing open-label EVOLVE-MS-1 trial is assessing the safety/tolerability and efficacy of diroximel fumarate over 96 weeks in 503 individuals with RMS. Those study subjects include both newly diagnosed

patients (people who were diagnosed with MS less than one year before study entry and who have not had a prior disease-modifying therapy [DMT]) and those with more long-standing RMS. All participants in the Phase III trial receive diroximel fumarate 462 mg twice daily.

Interim results from the Phase III study were reported at the American Academy of Neurology's 2019 Annual Meeting, held in Philadelphia in May. Data covering 48 weeks of treatment showed that relapse rates fell approximately 80 percent among the entire study group relative to baseline. In addition, the number of gadolinium-enhancing lesions seen on MRI was reduced by 77% from baseline for the entire group and by 96% from baseline for the individuals who were newly diagnosed.⁷²

Meanwhile, the five-week EVOLVE-MS-2 study, which is comparing the GI tolerability of diroximel fumarate with that of its kindred medication, dimethyl fumarate (Tecfidera), was scheduled for completion in June 2019.⁷³ During this Phase III, double-blind trial, approximately 420 patients with RMS are being randomized in a 1:1 ratio to receive twice-daily doses of diroximel fumarate 462 mg or dimethyl fumarate 240 mg. Investigators are measuring the incidence, intensity, onset, duration, and functional impact of medication-related nausea, vomiting, upper or lower abdominal pain, and diarrhea. Their goal is to show that diroximel fumarate is better tolerated than dimethyl fumarate while offering comparable efficacy.⁷⁴

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Evobrutinib (M2951)

Company: Merck

- *Oral medication being studied at 25 mg daily, 75 mg daily, and 75 mg twice daily*
- *Being studied in RMS and SPMS*

B cells, which help the body fight infection, have become an increasingly prominent focus of MS research. That's because when B cells become overabundant, they activate the T lymphocytes (T cells) known to cause the central nervous system inflammation that damages brain cells and their protective fiber (myelin) in MS. Bruton's tyrosine kinase (BTK) inhibitors, currently approved to treat certain B-cell cancers, impede B-cell proliferation by blocking an enzyme that contributes to B-cell development.⁷⁵

Evobrutinib is a BTK inhibitor under development for relapsing and secondary-progressive forms of MS (RMS and SPMS). This investigational medication demonstrated efficacy in a recent 48-week, Phase II, double-blind trial. A total of 243 participants with RMS or SPMS were assigned to one of five arms for the first 24 weeks of the study: evobrutinib 25 mg daily, 75 mg daily, or 75 mg twice daily; open-label dimethyl fumarate (Tecfidera®) 240 mg twice daily; or placebo.

At 24 weeks, the average total number of T1-enhancing lesions on MRI was significantly lower among patients in the groups receiving 75 mg of evobrutinib daily or twice daily (1.69 with daily dosing and 1.39 with twice-daily dosing) than among participants receiving placebo (4.07). Relapse rates were also lower among individuals who received evobrutinib

75 mg once or twice daily compared with placebo, but the difference was not statistically significant. Asymptomatic liver enzyme elevations were reported with evobrutinib 75 mg twice daily, but were considerably less common in other groups.⁷⁶

Upon completing the trial's first 24-week period, participants then entered the second 24-week phase, during which patients in the placebo group were switched to evobrutinib 25 mg once daily. In all, 227 subjects completed both 24-week phases of the 48-week trial.

During the second study phase, T1-enhancing lesions still were significantly less common among both the evobrutinib 75 mg daily and 75 mg twice daily treatment groups at weeks 12, 16, 20, and 24, compared with the original placebo group now receiving 25 mg of evobrutinib daily. Researchers said that these findings suggest that evobrutinib may be effective as a long-term disease-modifying therapy.⁷⁶

Ibudilast (MN-166)

Company: Medicinova

- *Oral medication being studied at up to 100 mg/day (50 mg twice daily)*
- *Being studied in PPMS and SPMS*

Ibudilast is a small-molecule targeted treatment that works on several sites in the brain to prevent macrophages, a type of immune cell, from migrating. This action suppresses production of cytokines, which are inflammatory molecules, and promotes regeneration of brain cells and the protective

EXPERIMENTAL MEDICATIONS: ADMINISTERED ORALLY

fiber that surrounds them. This treatment approach, or mechanism of action, differs from those of currently approved MS medications.⁷⁷

The efficacy and safety of ibudilast in people with progressive forms of MS was assessed in the randomized, placebo-controlled Phase IIb SPRINT-MS trial. That 96-week study included 134 people with primary-progressive MS (PPMS) and 121 individuals with secondary-progressive MS (SPMS). Participants were randomized in a 1:1 ratio to receive ibudilast 100 mg daily or placebo. Based on MRI analyses, the study found that ibudilast reduced the rate of progression of whole brain atrophy (or shrinkage) by 48 percent compared to placebo, while being well tolerated and showing other benefits.⁷⁷

Further analyses of the SPRINT-MS data sought to determine whether response to ibudilast differed among people with primary-progressive MS, secondary-progressive MS without relapse, and secondary-progressive MS with relapse. After assessing the data, investigators reported that the overall effect of ibudilast on progression of brain atrophy in patients with progressive forms of MS appeared to result mainly from its impact on people with primary - rather than secondary - progressive MS.⁷⁸

Subgroup analysis also found that - relative to placebo - the risk of confirmed disability progression was 46 percent lower among individuals with SPMS without relapse who received ibudilast, and 29 percent lower among treatment-group individuals with PPMS. That benefit, however, was not seen

among those with SPMS who had suffered a relapse.⁷⁹ These findings underscore the value of looking at the impact of medications in very specific patient populations in order to tailor treatments as closely as possible to a patient's situation.

Simvastatin (Zocor® and others)

Company: Medicinova

- *Oral medication being studied at 80 mg daily*
- *Being studied in SPMS*

HMG-CoA reductase inhibitors, commonly known as statins, long have been a mainstay of lipid control in the United States. One of these agents has shown promise in early clinical trials as a potential disease-modifying therapy for secondary-progressive MS (SPMS).

Results from the Phase II MS-STAT study in the United Kingdom suggest that simvastatin, which is available in the United States generically and under brand names such as Zocor and FloLipid, may slow disease and disability progression in SPMS. A total of 140 individuals with SPMS were randomized to receive simvastatin 80 mg daily (twice the recommended high-end dosage for lipid control) or placebo for two years. MRI scans performed at each patient visit showed slower rates of brain deterioration among individuals who received simvastatin compared with the placebo-treated group.⁸⁰

Expanded Disability Status Scale (EDSS) scores, a common measurement of disability progression in MS, also increased more slowly

among simvastatin-treated participants, compared with placebo. For anyone not familiar, the higher the EDSS score, the greater the severity of MS-related disability.⁸⁰

The mechanism by which simvastatin exerts a therapeutic effect on MS is unclear. Researchers, however, believe that the medication's actions in reducing "bad" cholesterol and preserving brain function in MS are independent of each other.⁸⁰

Researchers hope to learn more about the

potential role of simvastatin in treating SPMS from the upcoming Phase III MS-STAT2 clinical trial. An estimated 1,180 individuals with SPMS from throughout the United Kingdom and Ireland will be randomized to receive simvastatin 40 mg daily for one month followed by 80 mg for 35 months, or placebo. Participants' physical and cognitive function will be tested every six months during the three-year study. Results are expected late summer 2023.^{81,82}

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Diet and MS

People with multiple sclerosis long have sought to improve their health and stabilize the course of their MS through diet. While the impact of specific eating plans and foods on MS itself continues to be investigated (as discussed below), clinicians emphasize the importance of following sound nutritional approaches generally to improve overall health, reduce risk for common comorbid conditions such as high blood pressure and diabetes, and to support energy levels and immune function.

Turning to studies looking at specific issues related to MS and diet, one recent analysis involving 277 people with MS found that the better you eat, the better you think – and move. In this study, the participants had an average age of 48.2 years and an average body mass index (BMI) of 28.2, which is in the overweight range. More than three-quarters were women.

All participants completed the MS Performance Test (MSPT) assessment of neurologic function and a questionnaire on how often they ate 153 different food items. Investigators used the Healthy Eating Index-2010, a measure of dietary quality, to assign each participant a score from 0 (poorest quality diet) to 100 (highest quality diet). Based on those scores, researchers placed people into four quartiles, or groups, with one group composed of people with the highest-quality diets, one made up of people with the worst-quality diets, and the other two groups for people with intermediate degrees of lower- or higher-quality diets. Next, the

researchers drew on the MSPT results to see how performance in various aspects of neurologic function differed from group to group.⁸³

The analysis found that people in the highest quartile of dietary quality had significantly faster cognitive processing speeds and 25-foot walking speeds than those in the lowest quartile, and marginally faster manual dexterity speeds. They also were at significantly lower risk of moderate disability. The study's authors concluded, "High dietary quality was associated with lesser disease severity using measures of disability, mobility, and cognitive function." They added that ongoing studies would be important to determine if high-quality diets are associated with slower rates of disease and disability progression.⁸³

Ketogenic diets (KD), which are high-fat, low-carbohydrate eating plans, have attracted significant interest from people with MS. Proponents of these diets point to indications that this approach to food intake reduces inflammation and oxidative stress. A recent study examined the ability of people with MS to follow a ketogenic diet over time, as well as how that diet affected conditions that commonly accompany MS.⁸⁴

The study involved 20 individuals with stable relapsing multiple sclerosis (RMS). A dietitian provided study participants with in-person education on how to adhere to a modified ketogenic diet, such as the Atkins diet. Daily urine testing then was employed to check levels of ketone – markers of adherence to the diet. Researchers also collected data on patient-reported fatigue and depression, while

laboratory testing at the start of the study (before people began their ketogenic diets) and at six months assessed insulin resistance, liver function, electrolytes, and other markers of health. Brain magnetic resonance imaging was also performed at baseline and at six months.

None of the study participants showed clinical or imaging signs of disease worsening while on the diet. Meanwhile, improvements were seen in fatigue and depression scores ($p=0.03$), as were reductions in body mass index (BMI). Insulin resistance was significantly reduced at three months.

While data were still being collected when these initial results were released, the findings to date prompted researchers to conclude that for people with RMS, a ketogenic diet “appears to be safe, feasible, and well-tolerated,” while offering a number of health benefits.⁸⁴

Another recent study showed that high consumption of monounsaturated fatty acids (MUFAs) - which are found in olive oil, avocados, nuts, and other foods - may limit the negative impact of MS on gray matter in the brain.⁸⁵

Researchers used baseline data from the NYC RESERVE cohort, an ongoing study evaluating risk factors and protective factors for disability in people who have been diagnosed with MS in the past five years. They analyzed information on 140 people with MS. Ninety of those study subjects were women. The average age of the overall group was 34.7 years, and the average time from diagnosis of MS was 2.2 years.

The investigators divided the study

participants into three groups based on whether the people had reported low, medium, or high intake of fatty acids when completing a food-frequency questionnaire. The researchers then used MRI to measure participants’ cortical thickness (CT) and normalized grey matter (nGM) in the brain. Reduced cortical thickness reflects atrophy, which is a shrinking or loss of brain cells.

The study found that cortical thickness was lower among patients with low MUFA intake than in patients with medium or high intake. Results were similar for normalized grey matter. By contrast, the researchers did not find significant links between saturated or polyunsaturated FA intake and cortical thickness or amount of normalized gray matter.

The researchers concluded that their findings suggest that “MUFA intake may serve a protective role in MS patients, limiting the impact of MS-related lesions on cerebral gray matter, which may have important implications later in the disease.”⁸⁵

Turning to another question regarding nutrition and multiple sclerosis, a recent study of 479 people recently diagnosed with MS found no indication that mineral intake was an important factor in their developing the condition.⁸⁶ Researchers drew on more than 170,000 food-frequency questionnaires completed by participants in the Nurses’ Health Study (which ran from 1984 to 2002) and the Nurses’ Health Study II (1991 to 2007), focusing especially on the information provided by 479 participants who were diagnosed with MS during follow-up. They found no association between MS risk and the

NEW DIRECTIONS IN MS RESEARCH: NEW THERAPEUTIC APPROACHES

amount of potassium, magnesium, calcium, phosphorus, iron, zinc, manganese, or copper in participants' diets.⁸⁶ While negative studies such as this one do not yield guidance on whether patients should increase or decrease their intake of certain foods, they nonetheless are valuable in helping investigators set research priorities.

Vitamin D

Perhaps no nutrient has been the subject of more MS-related research than Vitamin D. This focus arose in part from the observation that the prevalence of MS is higher in northern latitudes, where exposure to the sun - which facilitates the body's production of vitamin D - is limited. As more and more research demonstrated the immune-related benefits of Vitamin D, efforts to determine whether the nutrient protects against MS intensified.

One of the latest studies pursuing these questions comes from Sweden, where investigators analyzed blood samples from 666 people who later developed relapsing MS and from 666 healthy controls matched to the people with MS in terms of age, sex, and other factors. All of the blood samples from MS patients were collected before the people developed symptoms and before they reached 40 years of age.⁸⁷

An analysis of Vitamin D levels in participants' blood samples found that those with the highest concentrations of Vitamin D had a significantly lower risk of developing MS compared with people with lower concentrations. This effect was more pronounced in younger adults than in older

adults. The researchers noted, "This study lends further support to the hypothesis that vitamin D may be protective against MS."⁸⁷

Further support for the protective benefits of Vitamin D comes from extended follow-up of 278 people with clinically isolated syndrome (CIS), a common precursor to MS.⁸⁸ A recently reported study examined long-term cognitive status in CIS patients who had participated in the BENEFIT (Betaferon/ Betaseron in Newly Emerging Multiple Sclerosis for Initial Treatment) clinical trial, and who had undergone 11 years of follow-up. After assessing a number of potential factors, researchers found that higher levels of 25-OH Vitamin D, a biomarker for Vitamin D concentrations, predicted better cognitive function. Smoking, meanwhile, predicted worse cognitive function over the long term.⁸⁸

Another study examined whether adding a high-dose Vitamin D supplement to interferon beta-1b therapy would affect the number of central nervous system (CNS) lesions found on MRI in people with relapsing multiple sclerosis (RMS).⁸⁹ The randomized, double-blind trial involved 53 people. Twenty-eight of those patients received 20,400 IU of cholecalciferol, a Vitamin D supplement, every other day for 18 months, while 25 participants received of 400 IU cholecalciferol, also given every other day for 18 months. The primary endpoint of the study was the cumulative number of new hyper-intense T2 lesions after 18 months compared to baseline. Secondary endpoints were safety, T2-lesion volume, disability progression, and annualized relapse rate, or ARR.

At the study's completion, researchers analyzed data on 38 patients who fulfilled the protocol for the trial. Twenty-one of those people were in the high-dose arm; 17 were in the low-dose arm. Serum levels of 25-OH-Vitamin D increased in both groups over 18 months, more than tripling from 18 ng/ml to 65 ng/ml in the high-dose group and rising from 16 ng/ml to 24 ng/ml in the low-dose group. However, the change in cumulative number of new lesions over 18 months was not significantly different between the study arms. The median T2-lesion count in the high-dose arm rose from 42 at baseline to 46 in the high-dose arm, while that number rose from 64 to 70 in the low-dose arm. Meanwhile, 44 adverse events were recorded in the high-dose arm versus 34 in the low-dose arm. Importantly, however, no serious adverse events related to Vitamin D were recorded.

In examining the study findings, researchers concluded, "High-dose supplementation increased serum 25-OH-Vitamin D to sufficient levels with no positive effect on the cumulative number of new T2 lesions. Supplementation with high dose Vitamin D (20,400 IU) as an add-on therapy to IFN β is safe and tolerable in RRMS patients."⁸⁹

The study and its results examined an important question - whether the protective benefit against developing MS seen with higher blood levels of Vitamin D could be translated into an effective strategy for reducing the number of CNS lesions in people who already have MS. While the results were disappointing, they underscore the complexity of the MS disease process and

add significantly to investigators' knowledge base.

Biotin

Biotin is another vitamin being studied in MS, particularly in progressive forms of the condition. In particular, recent and ongoing studies have focused on MD1003, which is a pharmaceutical-grade version of the B-complex vitamin.

In MS-SPI, the first trial of MD1003 in progressive MS, study participants taking the vitamin had a significant sustained improvement in disability. Based on those results, researchers now are conducting a Phase III trial called SP12.⁹⁰ A total of 660 individuals with either primary- and secondary-progressive MS have been enrolled in the trial, which is fully recruited and underway now.

The study participants have been randomized on a 1:1 basis to receive either MD1003 at 300 mg/day or placebo. The study's primary endpoint is a composite of a decrease in Expanded Disability Status Scale (EDSS) score and/or improved timed 25-foot walk of 20 percent or more from baseline to Month 12, confirmed at Month 15. The study will also assess changes in brain volume, cognitive measures, quality of life scores, and other metrics. Final results are expected by late 2019.⁹⁰

While the SP12 study moves toward completion, researchers from a French MS Center recently reported their experience in treating people with progressive MS with 300 mg a day of MD1003.⁹¹ From January 2016 to

May 2018, the investigators had treated 220 patients with MD1003, and had acquired 12 months' worth of data on 91 of those individuals.

After one year of treatment with MD1003, 23 percent of patients for whom data were available had experienced improvement in their EDSS score, and a separate 23 percent experienced a 20 percent or greater improvement in the time it took them to walk 25 feet. Eleven percent had experienced a clinically defined relapse or had a gadolinium-enhancing T1 lesion on MRI. The investigators, who reported that MD1003 was well-tolerated, concluded that, "This real-world study supports the growing body of evidence that MD1003 is an effective and safe treatment for PMS."⁹¹

Gut Microbiome

The gut microbiome is the milieu of bacteria and other microbes found in the gastrointestinal (GI) tract. It is a major component of the body's immune system, and a growing body of evidence suggests that the presence and number of various microbes in the microbiome may affect the course of MS.

In one recent study, Italian investigators explored whether changes in the mix of microbes that make up the microbiome were associated with the onset of MS as indicated by an initial episode of demyelination. The researchers examined stool and blood samples from 18 recently diagnosed MS patients and 18 healthy volunteers who were matched for age, sex, diet, and lifestyle.

Using DNA analysis and other

sophisticated tests, those investigators determined that at the onset of MS, the gut microbiomes of patients were markedly different from those of healthy volunteers. People with MS had fewer different types of microbes than healthy volunteers, and a reduced presence of butyrate-producing bacteria that are believed to have an impact on various immune system cells. They concluded, "Our data indicate that gut microbial dysbiosis [an imbalance of the bacteria in the gut] exist at the onset of MS and could be associated with the autoimmune response in the periphery, highlighting the importance of gut microbiome in the etiology of MS."⁹²

Another study found that a toxin potentially associated with the formation of central nervous system (CNS) lesions was present in the gut microbiome of 21% of people with MS studied, but in none of the healthy volunteers studied. Researchers used sophisticated tests to identify the presence and genetic characteristics of *Clostridium perfringens epsilon* toxin in fecal samples from people with MS and matched healthy volunteers. They noted that the toxin is an attractive candidate for new lesion formation because it targets both CNS endothelial cells and oligodendrocytes/myelin.⁹³

Based on the fact that one in five people with MS had a specific type of the toxin in their gut microbiome, while it was absent from all of the healthy volunteers participating in the study, the researchers concluded, "Colonization of the gut by *C. perfringens* type B is statistically associated with MS. While two epsilon toxin-producing *C. perfringens* strains (type B and type D) exist in nature, thus far we

have identified only type B strains from MS subjects.”⁹³

Meanwhile, another group of investigators is exploring whether borrowing an unusual technique from their infectious disease colleagues may help change the gut microbiome of people with MS. Positive results in terms of altering the microbiome’s composition would set the stage for pursuing the larger questions of whether those changes affect the course of MS.⁹⁴

The technique is called fecal microbial transplantation, or FMT. It involves using a rectal enema to transfer fecal material from a healthy person into the GI system of someone with MS to see if this intervention changes the mix of microbes present in the gut of the MS patient. Infectious disease specialists have employed FMT to treat people suffering from colitis due to infection with *Clostridium difficile*, a bacterium that can cause severe diarrhea and other complications.

The single-site, randomized, open-label study will randomize 40 people with MS into two groups of 20 subjects each. Participants in the early-intervention group will receive FMT by rectal enema, while the other group will receive standard MS treatment for the first six months of the study. Thereafter, the early-intervention group no longer will receive FMT, while the second group will begin a six-month course of FMT. The study’s primary outcome will be the level of cytokines – inflammatory molecules – in the peripheral blood. Ten healthy volunteers will serve as a reference control group for cytokine levels. Secondary outcomes are blood DNA bacteria and gut permeability. MRI scans of the head also will

be obtained as a means of assessing safety.

At the time that investigators presented an update on their research, 16 patients had been enrolled in the study. The participants had experienced MS symptoms for an average of 18 years, and 11 of the 16 were using a disease-modifying therapy. Six of the participants had begun receiving fecal microbial transplants, with a total of 24 interventions performed in those patients. No serious adverse events had been reported.

The investigators stated, “This proof of concept, first in humans, independent pilot study will shed light on the relationships between gut bacteria and MS. We aim to explore FMT feasibility in MS and its possible impact on disease inflammation. Moreover, we hope that these study results can guide future large-scale researches.”⁹⁴

Lipoic Acid

Lipoic acid is a naturally occurring compound that has antioxidant properties and also has an impact on the function of the mitochondria, the so-call “energy plants” of cells. A Phase II trial involving 118 participants is examining whether daily oral intake of lipoic acid can reduce the impact that progressive MS has on brain atrophy and patients’ mobility.⁹⁵

Fifty-nine study participants will take 1,200 mg of lipoic acid by mouth every day for two years. The other 59 participants will take a placebo. The primary outcome measure will be the change from baseline to Year 2 in the time it takes subjects to walk 25 feet. Other endpoints include change in brain volume

NEW DIRECTIONS IN MS RESEARCH: NEW THERAPEUTIC APPROACHES

from baseline to Year 2 as measured by MRI, and change from baseline to Year 2 in number of falls and in distance covered in a two-minute timed walk. Safety measures will also be assessed. The estimated completion date for the study is April 2021.⁹⁵

The Phase II study under way now follows a smaller, single-center randomized trial of lipoic acid that yielded favorable results in people with secondary-progressive MS. In that double-blind study, 27 people took 1,200 mg of lipoic acid daily for two years, while 24 participants took placebo on the same schedule. After two years, people in the lipoic acid group had a 68% reduction in the annualized percent change in brain volume – a measure of brain atrophy, or shrinkage – compared to the placebo group. More gastrointestinal upset but fewer falls occurred among the people taking lipoic acid relative to those receiving placebo, and there was one case of unexpected renal failure and a separate case of serious kidney injury in the lipoic acid group.⁹⁶

Other studies are assessing the impact of lipoic acid on blood glucose, diabetes, and complications of diabetes.

Stem-Cell Therapy

In a preliminary study, researchers found that a stem-cell transplant process using a relatively mild version of chemotherapy was more effective than disease-modifying therapies (DMTs) in slowing the progression of relapsing-remitting multiple sclerosis (RRMS).

In preparing participants for stem-cell transplantation, physicians generally

administer high-dose chemotherapy, radiation, or both to kill cells in the bone marrow so that the transplanted stem cells can then “re-set” the body’s immune system. This “myeloablative conditioning” can cause severe side effects. In an attempt to enable patients to benefit from stem-cell transplants while facing fewer side effects, researchers have experimented with myeloablative-conditioning approaches that use less-toxic chemotherapy regimens. These approaches usually are referred to as “mini-transplant” strategies.

An international team of researchers recently pursued such a strategy in a study that involved 110 individuals with RRMS who had experienced at least two relapses while receiving a DMT in the prior year. These participants were randomized to either switch to another DMT believed to be more effective than their initial therapy or to undergo hematopoietic stem-cell transplantation (HSCT). Hematopoietic stem cells are immature blood cells that can grow into white blood cells, which fight infection; red blood cells, which carry oxygen; or platelets, which aid in the clotting process. The 55 patients in the HSCT group received 200 mg/kg of cyclophosphamide, a chemotherapy that suppresses the immune system; and anti-thymocyte globulin, which is used to prevent the body from rejecting transplanted cells. This regimen is milder than the chemotherapy that traditionally has been used in HSCT patients.

While some participants left the trial, 98 were evaluated at one year and 23 were evaluated each year for five years. The average

follow-up period was 2.8 years. As measured by Expanded Disability Status Scale (EDSS) scores, three patients in the HSCT group had disease progression, as compared with 34 patients in the DMT group. The median time to progression could not be measured in the HSCT group because there were too few events to allow for a calculation. In the DMT group, the median time to progression was 24 months. During the first year, the average EDSS score in the HSCT group improved from 3.38 to 2.26 (a lower score reflects less disability), and worsened from 3.31 to 3.89 in the DMT group.

No deaths occurred among the participants in the study, and no individuals who received HSCT developed serious (Grade 4) adverse events in other organ systems or tissues.⁹⁷ The researchers conducting the trial noted that it was a preliminary study, and that further research is needed to replicate its favorable findings and assess long-term outcomes and safety.

As researchers have explored the viability of stem-cell transplantation as a therapy in MS and other conditions, the side effects associated with traditional myeloablative conditioning have been a significant concern. If subsequent trials confirm this preliminary study's findings that patients can receive a milder form of chemotherapy while enjoying significant reduction in disease progression with HSCT, it will constitute a major step forward in the effort to make stem-cell transplantation a mainstream treatment for RRMS.

Another study examined the effectiveness and safety of HSCT as initial treatment for

RRMS in individuals experiencing "aggressive" disease. The study involved 20 patients from five centers in Europe and North America. The individuals' median age at diagnosis was 33 years, and their median pre-treatment EDSS score was 6.5, indicating significant disability. None had received any standard DMTs for more than three months before undergoing a chemotherapy conditioning regimen and autologous HSCT (AHSCT). "Autologous" refers to using each patient's own stem cells, which had been removed prior to the conditioning regimen and then transplanted back into each of the patients.

After a median follow-up period of 30 months, median EDSS score was 2.0 (as compared with 6.5 prior to treatment). No participants experienced a clinical relapse following AHSCT. Three of the study subjects had new T2 lesions at their first follow-up MRI, but no new or enhancing lesions were seen on subsequent scans. Researchers reported that participants had routine side effects associated with AHSCT, but no treatment-related deaths.

The investigators concluded, "AHSCT was safe and highly effective in inducing rapid and sustained remission in this cohort and was associated with a significant improvement in patients' level of disability. This demonstrates the potential role of AHSCT as first line therapy in 'aggressive' MS."⁹⁸

Meanwhile, another study is examining the effectiveness and safety of a therapy that would use patients' own stem cells to treat progressive MS. In December 2018, the FDA approved an application from BrainStorm Cell Therapeutics to conduct a Phase II clinical trial

NEW DIRECTIONS IN MS RESEARCH: NEW THERAPEUTIC APPROACHES

of NurOwn® mesenchymal stem cell-neurotrophic factors (MSC-NTF) cells.⁹⁹ The trial has an estimated primary completion date of February 2020 and full completion date of September 2020.¹⁰⁰

The trial will involve 20 people with progressive MS, and will be conducted at multiple locations.¹⁰⁰ Participants' mesenchymal stem cells will be removed from their bone marrow via insertion of a hollow needle. Those cells then will be converted into MSC-NTF cells by growing them under patented conditions that cause the cells to secrete high levels of neurotrophic factors, molecules that support the development and differentiation of neurons.⁹⁹ The MSC-NTF cells will be re-introduced into the patients' bodies through three intrathecal cell transplantations over 16 weeks.¹⁰⁰

Autologous (meaning from the patient's own body) MSC-NTF cells can deliver neurotrophic factors and other immune-modulating molecules "directly to the site of damage to elicit a desired biological effect and ultimately slow or stabilize disease," BrainStorm Cell Therapeutics explained in outlining the rationale for the treatment.⁹⁹

Participants will be followed for 28 weeks after the start of treatment. Researchers will monitor these individuals for adverse events and will assess change from baseline to 28 weeks post-treatment in patients' 25-foot walking speed. Sixteen weeks after treatment, researchers will analyze participants' cerebrospinal fluid (CSF) to determine how many patients had changes in neurotrophic factors in their CSF.¹⁰⁰

Genetics

The last decade has seen an increased focus on the role of genetics in multiple sclerosis (MS). The process by which genetics interact with other health factors and environmental influences in driving the development and course of MS is not fully understood. However, researchers have identified more than 230 common genetic variants tied to increased risk for MS.¹⁰¹ New insights are emerging on a regular basis, as reflected in the three studies summarized below.

The International Multiple Sclerosis Genetics Consortium brings together investigators from around the world to conduct large-scale research projects drawing on information from tens of thousands of people. One such initiative recently analyzed data from more than 68,000 people with MS and healthy subjects; the analysis found that up to 5% of the risk for MS heritability can be explained by low-frequency (or seldom occurring) variations in gene coding sequence.

The research identified four novel genes – PRF1, HDAC7, PRKRA, and NLRP8 – that drive the risk for MS, independent of more common variants. The investigators noted that their research was important because it demonstrates the value of looking beyond common variants in seeking the genetic basis of MS risk, because identification of these novel genes will help scientists better explore the mechanisms by which MS develops. Additionally, all four novel genes that they identified serve immunologic purposes,

reinforcing the central role of immunologic dysfunction in the origination of MS.¹⁰¹

Clinicians long have noted that people with MS who are overweight often have greater disease activity and more disability than individuals with MS who maintain a healthy weight. To explore the reasons for this difference, a team of researchers evaluated 54 people with relapsing-remitting MS who were not receiving disease-modifying therapy (DMT). Twenty-seven of the subjects had a high BMI, meaning that they were overweight or obese, while the other 27 had a normal BMI. People in the two groups had a similar degree of disability at baseline.

At the two-year follow-up, however, the high-BMI group had an increased lesion load on MRI, increased disease activity, and worsened disability relative to those with a normal BMI. Genetic analyses performed on people in both groups found that a process called ceramide-induced DNA methylation contributed to the worse outcomes in the high-BMI group by increasing the number of monocytes, a type of white blood cell, in their blood. Ceramides are waxy lipid molecules, while DNA methylation is the process by which methyl groups are added to the DNA molecule. Methylation can interfere with the way DNA conveys its genetic “instructions.”¹⁰²

While the researchers continue to pursue this avenue of inquiry in animal models and with sophisticated genetic analyses, their findings are a reminder that while our genes influence our health, our health – in terms of body weight, physical activity, and the like – can also influence genetic processes.

Another important area of research

examines how different genetic loci – fixed positions on chromosomes, such as the location of a gene – associated with increased risk for MS affect particular populations. A group of researchers recently performed a genomic association study involving almost 4,000 Italians – 1,727 with MS and 2,258 healthy controls. To increase the statistical power of their analysis, they examined their findings in the context of data on roughly 40,000 Americans of European ancestry – half of whom had MS and half of whom did not.

After further genetic analyses, they identified 203 loci on chromosome 17 associated with increased risk for MS among Italian people with MS. They now plan to look more closely at the impact of those loci and at how they may play a causative role in development of MS.¹⁰³ With gene therapy making promising strides in the treatment of cancer and other life-threatening diseases, the hope is that this enhanced understanding of the specific genetic contributors to MS risk may one day translate into effective interventions.

Biomarkers

A biomarker is a finding on an imaging study or from an analysis of blood or other substances or tissues from a patient’s body that can help clinicians assess the patient’s health. Biomarkers are used to make diagnoses, assess any changes in the status of a condition, and evaluate how an individual is responding to a treatment, among other purposes. Two biomarkers – one involving MRI studies and the other involving a blood test –

NEW DIRECTIONS IN MS RESEARCH: NEW THERAPEUTIC APPROACHES

have emerged in recent years as having considerable potential value in guiding the management of MS.

The first is called the central vein sign, or CVS. This term refers to the identification of a central vein in brain lesions on MRI. A recent multi-center study examined how useful the finding of a central vein sign on high-powered 3 Tesla (3T) MRI was in distinguishing MS from other conditions. The study involved 606 subjects, including 236 with relapsing-remitting MS, 142 with various types of cerebral small-vessel disease, 117 with clinically isolated syndromes (CIS) suggestive of MS, 25 with systemic lupus erythematosus, 29 with migraine, 20 with diabetes, and 37 with other conditions.

Clinicians examined the images of 4,447 lesions without knowing the associated diagnosis. The median proportion of lesions with a positive CVS identified was 50% among patients with CIS or RRMS, and was 0% among patients who did not have MS. The researchers also found that the ability to identify RRMS or CIS was greater with the use of specific imaging techniques and when the individual had at least three lesions with a central vein evident on imaging.¹⁰⁴

Another, smaller study found that the CVS can help improve the diagnosis of MS in people who have some signs of MS but who also have atypical findings, or “red flags,” that cast doubt on whether they actually have MS or some other condition. The prospective study was conducted at three centers in Europe, and included 17 people. Eight had clinical signs that were “red flags”; another eight had laboratory findings that raised

concerns about the correct diagnosis; and one had imaging findings that created uncertainty.

Each patient underwent a single-standardized 3T MRI protocol, with two independent raters evaluating the images obtained to look for a CVS. Meanwhile, expert clinicians who did not know the results of the CVS assessment conducted a thorough evaluation of the patients and then made a diagnosis. Twelve of the 17 participants were diagnosed with MS, while the remaining five received alternative diagnoses. More than half of the lesions in those diagnosed with MS had the CVS, while less than 50% of the lesions in those who received other diagnoses had the sign. The investigators said this finding was “preliminary evidence that the CVS detected on 3T FLAIR images can accurately predict MS diagnosis in patients suspected to have MS, but with atypical clinical, laboratory, and imaging features.”¹⁰⁵

The CVS also has shown promise in the diagnosis of MS in children and adolescents. Investigators analyzed 232 lesions found on the imaging of 26 individuals with pediatric-onset multiple sclerosis (POMS). All of the participants had at least one lesion containing a central vein, while 21 of the 26 patients had two lesions with CVS, and 17 (65%) had three or more lesions with a central vein. The researchers said that their findings suggest “a high potential of the CVS to improve POMS diagnosis.”¹⁰⁵

Other investigators are focusing on how blood levels of a protein called neurofilament light chain (NfL) can predict brain atrophy and response to treatment in MS. NfL is a

“scaffolding protein” that helps give form to neurons. When axons, or nerve fibers, are damaged, NfL is released and can be found in the cerebrospinal fluid (CSF) and peripheral blood. However, since obtaining CSF requires a lumbar puncture procedure, investigators have focused on understanding the significance of NfL levels, which are more easily obtained from blood samples.

One study involving 85 people with relapsing forms of MS, 42 with progressive MS, and 20 with CIS, examined how serum NfL levels correlated with MRI measures of brain atrophy and disability progression. The researchers found the baseline serum NfL predicted brain-volume change, atrophied lesion volume as measured by T2 MRI imaging, and absolute change in lesion volume as measured by T1 MRI. After five years of follow-up, participants who had baseline serum NfL of 30 pg/ml or more had significantly higher atrophied lesion volume on T2 MRI imaging as well as a higher percentage of brain-volume change, compared to study participants with serum NfL levels of less than 30 pg/ml.¹⁰⁶

Another study drew on data from Phase III trials of two DMTs to analyze the impact of serum NfL in secondary-progressive MS (SPMS) versus primary-progressive MS (PPMS). The retrospective analysis involved 1,452 people with SPMS and 378 with PPMS. Baseline serum NfL levels were categorized as low (<30 pg/ml), medium (30 pg/ml to 60/pg/ml), or high (>60 pg/ml). Researchers found that baseline serum NfL levels were higher in people with SPMS than in those with PPMS. In both forms of progressive MS, serum

NfL levels were higher in those with gadolinium-enhancing lesions on MRI at baseline relative to those without such lesions. Similarly, in both PPMS and SPMS, high serum NfL at baseline was associated with a greater percentage of brain-volume loss at Month 12 and Month 24. The researchers concluded, “In both SPMS and PPMS patients, NfL may serve as a prognostic marker of brain atrophy.”¹⁰⁷

Serum NfL levels may also be useful in measuring response to therapy, according to researchers who drew on data from the Swiss MS Cohort Study. These investigators examined baseline and annual follow-up NfL levels on more than 230 patients who were taking disease-modifying therapies (DMTs). They found that serum NfL levels increased with age, with worsening disability as measured by the Expanded Disability Status Scale (EDSS) score, and by history of relapse in the past 120 days. Conversely, blood levels of NfL decreased with time on DMT at a rate of 3.2 percent per year, with the rate of decrease varying among different DMTs. The investigators concluded that by following the change in serum NfL levels over time, this provides another means of monitoring how a patient is responding to treatment.¹⁰⁸



CLOSING NOTES

The 2019 edition of the *MS Research Update* is a powerful testament to the progress that has been made in understanding the potential causes of multiple sclerosis and in developing therapies to effectively treat the condition. The studies reported in this update examine everything from intricate biochemical processes occurring at the molecular level to long-term treatment outcomes in international registries with records on tens of thousands of patients. Squarely in between what can be seen with an electron microscope and what patterns can be discerned from Big Data analytics stands the ultimate focus all of this research - the individual patient.

Regardless of which questions clinical researchers and basic-science investigators set their sights on, their shared vision is to develop treatments and apply knowledge so that people with MS can live healthier, fuller, and richer lives. Recent months have seen several important advances toward that goal, as evidenced by this publication's reports on newly approved therapies, other agents under consideration by the FDA, and still more in late stages of clinical development. Other research is better defining the role of diet and nutrition in enhancing the health of people with multiple sclerosis, while scientists also are steadily mapping the complex interactions that give rise to MS and identifying biomarkers that can speed its diagnosis and predicts its course.

In short, while MS remains a formidable foe, there never has been more cause for hope, nor more opportunity to confront and,



hopefully, control multiple sclerosis - which brings us back to the individual patient. People with MS are the unsung heroes of the advances reported in this *MS Research Update*. Without their participation in clinical trials, without their willingness to act on the findings of those trials, and without their commitment to being proactive partners in their care, all of the efforts documented here would be for naught.

Because knowledge truly is power, staying informed of recent developments in MS is a prerequisite to taking a proactive approach. That is why MSAA is proud to provide this 2019 edition of its annual *MS Research Update*. We hope that you will find it of interest and value. 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 or www.clinicaltrials.gov. For more information about MS, its treatments, and MSAA's programs and services, please contact MSAA at **(800) 532-7667**, or visit mymsaa.org.

SELF-INJECTED MEDICATIONS

NAME	TYPE OF MEDICATION	HOW ADMINISTERED AND SIDE EFFECTS
Avonex® (interferon beta-1a)	immune system modulator with antiviral properties	30 micrograms taken via weekly intramuscular injection; side effects include flu-like symptoms and headache, as well as blood count and liver test abnormalities; side effects are manageable and usually temporary
Betaseron® (interferon beta-1b)	immune system modulator with antiviral properties	250 micrograms taken via subcutaneous injection every other day; side effects include flu-like symptoms, headache, and injection-site reactions, as well as blood count and liver test abnormalities; side effects are manageable and usually temporary
Copaxone® (glatiramer acetate)	synthetic chain of four amino acids found in myelin; it is an immune system modulator that blocks attacks on myelin	20 (daily) or 40 (three times weekly) milligrams taken via subcutaneous injection; side effects include injection-site reaction as well as an occasional systemic reaction, usually lasting only a few minutes with no long-term effects
Extavia® (interferon beta-1b)	immune system modulator with antiviral properties	250 micrograms taken via subcutaneous injection every other day; side effects include flu-like symptoms, headache, and injection-site reactions, as well as blood count and liver test abnormalities; side effects are manageable and usually temporary
Generic Glatiramer Acetate Injection (glatiramer acetate)	synthetic chain of four amino acids found in myelin; it is an immune system modulator that blocks attacks on myelin	20 (daily) or 40 (three times weekly) milligrams taken via subcutaneous injection; side effects include injection-site reaction as well as an occasional systemic reaction, usually lasting only a few minutes with no long-term effects
Glatopa® (glatiramer acetate)	synthetic chain of four amino acids found in myelin; it is an immune system modulator that blocks attacks on myelin	20 (daily) or 40 (three times weekly) milligrams taken via subcutaneous injection; side effects include injection-site reaction as well as an occasional systemic reaction, usually lasting only a few minutes with no long-term effects
Plegridy® (interferon beta-1a)	immune system modulator with antiviral properties	125 micrograms taken via subcutaneous injection once every two weeks; side effects include flu-like symptoms, headache, and injection-site reactions, as well as blood count and liver test abnormalities; side effects are manageable and usually temporary
Rebif® (interferon beta-1a)	immune system modulator with antiviral properties	44 micrograms taken via subcutaneous injection three times weekly; side effects include flu-like symptoms, headache, and injection-site reactions, as well as blood count and liver test abnormalities; side effects are manageable and usually temporary

APPROVED DISEASE-MODIFYING THERAPIES FOR MS

ORAL MEDICATIONS

NAME	TYPE OF MEDICATION	HOW ADMINISTERED AND SIDE EFFECTS
Aubagio® (teriflunomide)	immunomodulator affecting the production of T and B cells; may also inhibit nerve degeneration	7 or 14 milligram tablet taken orally, once per day; side effects include headache, elevated liver enzymes, thinning hair, diarrhea, nausea, neutropenia (a condition causing a reduction of certain white blood cells), and paresthesia (tingling, burning, and numbness); adverse events include severe liver injury and birth defects if pregnant
Gilenya® (fingolimod)	S1P-receptor modulator, which blocks potentially damaging T cells from leaving lymph nodes	0.5 milligram capsule taken orally once per day; side effects include headache, flu, cough, diarrhea, back pain, and abnormal liver tests; adverse events include transient heart-rate reduction and AV block, swelling behind the eye, and possibly PML*, a viral brain infection
Mavenclad® (cladribine)	Selectively targets and depletes the immune system's B cells and T cells, followed by a 'reconstitution,' as new B cells and T cells are produced	Two annual courses are given orally for a maximum of 20 days over two years; no treatment is needed for Years 3 and 4. The most common adverse reactions include upper respiratory tract infections, headache, and decreased lymphocyte counts. Potential adverse events include lymphopenia, a condition that causes abnormally low counts of white blood cells, and herpes zoster infection. Mavenclad has an increased risk of malignancy (cancer) and fetal harm.
Mayzent® (siponimod)	Its primary actions are at the S1P1 and the S1P5 receptors, blocking the movement of lymph cells from lymph nodes; it has a relatively short half-life compared to similar medications, meaning that it does not stay in the body as long	After starting at a low dose, the recommended maintenance dosage is 2 mg taken orally once daily starting on Day 6. Headache, high blood pressure, and changes in liver function tests were the most common adverse reactions. Serious adverse events include a decrease in white blood cells, heart rate, and rhythm abnormalities, as well as hypertension, swelling of the macula of the eye, varicella zoster reactivation, and convulsions. Women who could become pregnant should use contraception to avoid potential risk of fetal harm.
Tecfidera® (dimethyl fumarate)	immunomodulator with anti-inflammatory properties; may have neuroprotective effects, potentially protecting the nerves and myelin covering	240-milligram tablet taken twice daily; side effects include flushing, gastrointestinal events, reduced white blood cell count, and elevated liver enzymes; adverse events include respiratory infection, chronic itching, rash, gastric-lining inflammation, and possibly PML*, a viral brain infection

**Progressive multifocal leukoencephalopathy (PML), a potentially fatal, viral infection of the brain, can develop in some individuals taking Tysabri. Risk factors include the presence of anti-JCV antibodies, taking Tysabri for two years or more, and prior immunosuppressant treatment. Currently, PML has occurred in a few patients taking Gilenya, Tecfidera, or Ocrevus; some of these cases are still under investigation.*

INFUSED MEDICATIONS

NAME	TYPE OF MEDICATION	HOW ADMINISTERED AND SIDE EFFECTS
Lemtrada® (alemtuzumab)	humanized monoclonal antibody that rapidly depletes or suppresses immune system cells (T and B cells), which can damage the myelin and nerves of the CNS	Five-day course of 12 mgs daily via intravenous (IV) infusion and followed one year later by a second three-day course; side effects include rash, itching, headache, fever, nasopharyngitis, nausea, diarrhea and vomiting, insomnia, numbness, dizziness, pain, and flushing; adverse events include infusion reactions, infection, autoimmune diseases, potentially severe bleeding disorder (ITP), and malignancies
Novantrone® (mitoxantrone)	antineoplastic agent; immune system modulator and suppressor	IV infusion once every three months (for two to three years); side effects include nausea, thinning hair, loss of menstrual periods, bladder infections, and mouth sores; seldom prescribed for MS due to the potential for heart damage and leukemia
Ocrevus™ (ocrelizumab)	humanized monoclonal antibody designed to selectively target CD20-positive B cells, a type of immune cell important to the MS-disease process.	600-milligram dose given via IV every six months; initial dose given in two 300-milligram doses; side effects include potentially serious infusion reactions, infections (respiratory and skin infections most common); adverse events include cancer and possibly PML*, a viral brain infection
Tysabri® (natalizumab)	humanized monoclonal antibody; inhibits adhesion molecules; thought to prevent damaging immune cells from crossing the blood-brain barrier	300 mg dose given via IV infusion every four weeks; side effects include headache, fatigue, depression, joint pain, abdominal discomfort, and infection; serious adverse events include infection (including pneumonia), and the potential for PML*, a viral brain infection

*Progressive multifocal leukoencephalopathy (PML), a potentially fatal, viral infection of the brain, can develop in some individuals taking Tysabri. Risk factors include the presence of anti-JCV antibodies, taking Tysabri for two years or more, and prior immunosuppressant treatment. Currently, PML has occurred in a few patients taking Gilenya, Tecfidera, or Ocrevus; some of these cases are still under investigation.

REFERENCES

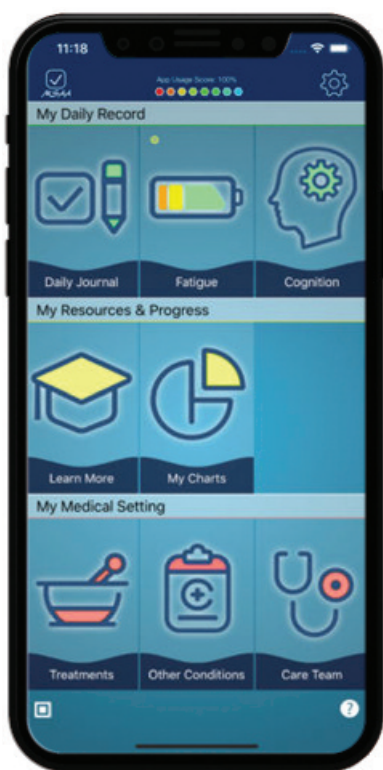
- Novartis press release, March 27, 2019. "Novartis receives FDA approval for Mayzent® (siponimod), the first oral drug to treat secondary progressive MS with active disease." <https://www.novartis.com/news/media-releases/novartis-receives-fda-approval-mayzent-siponimod-first-oral-drug-treat-secondary-progressive-ms-active-disease>
- EMD Serono press release, March 29, 2019. "FDA approves MAVENCLAD® (Cladribine) Tablets as first and only short-course oral treatment for relapsing-remitting and active secondary progressive multiple sclerosis." <https://www.prnewswire.com/news-releases/fda-approves-mavenclad-cladribine-tablets-as-first-and-only-short-course-oral-treatment-for-relapsing-remitting-and-active-secondary-progressive-multiple-sclerosis-300821333.html>
- Mavenclad (cladribine) prescribing information. April 2019. EMD Serono, Inc. Rockland, MA.
- Biogen press release, February 25, 2019. "Alkermes and Biogen announce U.S. Food and Drug Administration acceptance of dioximel fumarate New Drug Application for multiple sclerosis." <http://investors.biogen.com/news-releases/news-releasedetails/alkermes-and-biogen-announce-us-food-and-drug-administration>
- Celgene press release, March 25, 2019. "Celgene Submits Application to FDA for Ozanimod for the Treatment of Relapsing Forms of Multiple Sclerosis." <https://ir.celgene.com/press-releases/press-releasedetails/2019/Celgene-Submits-Application-to-FDA-for-Ozanimod-for-the-Treatment-of-Relapsing-Forms-of-Multiple-Sclerosis/default.aspx>
- Celgene press release, May 7, 2019. "Analysis showed oral ozanimod1 reduced brain volume loss across all age subgroups in adults with relapsing multiple sclerosis." <https://ir.celgene.com/press-releases/pressrelease-details/2019/Analysis-Showed-Oral-Ozanimod-Reduced-Brain-Volume-Loss-Across-All-Age-Subgroups-in-Adults-with-Relapsing-Multiple-Sclerosis/default.aspx>
- Biogen Inc. press release, January 3, 2019. "First patient enrolled in Biogen's Phase 3B study to evaluate extended interval dosing (EID) with natalizumab in multiple sclerosis." <http://investors.biogen.com/newsreleases/news-release-details/first-patient-enrolled-biogens-phase-3b-study-evaluate-extended>
- Cortese I, Muranski P, Enose-Akahata Y, et al. "Pembrolizumab treatment for progressive multifocal leukoencephalopathy." *N Engl J Med.* 2019;380:1597-605.

REFERENCES

- 9 Wolinsky JS, et al. ECTRIMS 2018. [Abstract P910]
- 10 Manouchehrinia A, et al. ECTRIMS 2018. [Abstract P881]
- 11 Gold R, et al. ECTRIMS 2018. [Abstract P920]
- 12 Fält A, et al. ECTRIMS 2018. [Abstract P1228]
- 13 Comi G, et al. ECTRIMS 2018. [Abstract P1235]
- 14 Salvetti M, et al. ECTRIMS 2018. [Abstract P1236]
- 15 Zivadinov R, et al. ECTRIMS 2018. [Abstract P870]
- 16 Al-Izki S, et al. ECTRIMS 2018. [Abstract P1275]
- 17 Kappos L, et al. ECTRIMS 2018. [Abstract P1748]
- 18 Kingwell E, et al. "Multiple sclerosis: effect of beta interferon treatment on survival." *Brain*. 2019; March 18. doi:10.1093/brain/awz055. [Epub ahead of print]
- 19 Brown JW, Coles A, Horakova D, et al. "Association of initial disease-modifying therapy with later conversion to secondary progressive multiple sclerosis." *JAMA*. 2019;321(2):175-187.
- 20 Chataway J. ECTRIMS 2018. [Abstract 324]
- 21 Tavares A, Barrett O, Alagille D, et al. "Brain distribution of MS565, an imaging analogue of siponimod (BAF312), in non-human primates." (P1.168) *Neurology*. 2014;82(10):suppl. P1.168.
- 22 Kappos L, Bar-Or A, Cree BAC, et al. "Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study." *Lancet*. 2018 391:1263-1273.
- 23 Mayzent (siponimod) prescribing information. March 2019. Novartis Pharmaceuticals Corporation. East Hanover, NJ.
- 24 Giovannoni G, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med*. 2010. 362:416-426.
- 25 Hauser SL, et al. ECTRIMS 2018. [Abstract P590]
- 26 Arnold DL, et al. ECTRIMS 2018. [Abstract P588]
- 27 Hauser SL, et al. ECTRIMS 2018. [Abstract P1229]
- 28 Tecfidera (dimethyl fumarate) prescribing information. December 2017. Biogen Inc. Cambridge, MA.
- 29 Safer Demibuker S, et al. ECTRIMS 2018. [Abstract P1234]
- 30 Mancinelli CR, et al. ECTRIMS 2018. [Abstract P931]
- 31 Storm-Larsen C, et al. ECTRIMS 2018. [Abstract P960]
- 32 Bloomgren G, et al. "Risk of natalizumab-associated progressive multifocal leukoencephalopathy." *N Engl J Med*. 2012;366:1870-1880.
- 33 Tysabri (natalizumab) prescribing information. April 2018. Biogen Inc. Cambridge, MA.
- 34 Ruggieri S, et al. ECTRIMS 2018. [Abstract P1770]
- 35 Vukusic S, et al. ECTRIMS 2018. [Abstract P1746]
- 36 Tysabrihcp.com. "Tysabri safety: a well-established profile." https://www.tysabrihcp.com/en_us/home/efficacy-safety/pmlrisk.html
- 37 Kappos L, et al. ECTRIMS 2018. [Abstract P916]
- 38 Fox E, et al. "Real-world durability of relapse rate reduction in patients with multiple sclerosis receiving fingolimod for up to 3 years: a retrospective US claims database analysis." *J Neuro Sci*. 2019;398:163-170.
- 39 Oreja-Guevara C, et al. ECTRIMS 2018. [P1239]
- 40 Kuhle J, et al. ECTRIMS 2018. [Abstract P1747]
- 41 Gallagher P. ECTRIMS 2018. [Abstract 264]
- 42 Plegridy (peginterferon beta-1a) prescribing information. July 2016. Biogen Inc. Cambridge, MA.
- 43 Aubagio (teriflunomide) prescribing information. November 2016. Genzyme Corporation. Cambridge, MA.
- 44 Comi G, et al. ECTRIMS 2018. [Abstract P1205]
- 45 Copaxone (glatiramer acetate) prescribing information. September 2018. Teva Pharmaceuticals USA, Inc. North Wales, PA.
- 46 Hellwig K, et al. ECTRIMS 2018. [Abstract P1004]
- 47 Flechter S, et al. ECTRIMS 2018. [Abstract P1777]
- 48 Betaseron (interferon beta-1b) prescribing information. August 2018. Bayer HealthCare Pharmaceuticals Inc. Whippany, NJ.
- 49 Vollmer B, et al. ECTRIMS 2018. [Abstract P1237]
- 50 Langer-Gould A, et al. ECTRIMS 2018. [Abstract 88]
- 51 Shukla NM, Lotze T. ACTRIMS 2019. [Abstract P047]
- 52 Kappos L, et al. ECTRIMS 2018. [Abstract P965]
- 53 Novartis press release, October 10, 2018. "Breadth of data at ECTRIMS underpins Novartis' relentless commitment to decoding the science of multiple sclerosis (MS) and decreasing the patient burden." <https://www.novartis.com/news/media-releases/breadth-data-ectrims-underpins-novartis-relentless-commitment-decoding-science-multiple-sclerosis-ms-and-decreasing-patient-burden>
- 54 ClinicalTrials.gov Identifier: NCT02792218.
- 55 Zhu B, et al. ECTRIMS 2018. [Abstract EP1619]
- 56 ClinicalTrials.gov Identifier: NCT03222973.
- 57 Mellion M, et al. "Efficacy results from the Phase 2b SYNERGY study: treatment of disabling multiple sclerosis with the anti-LINGO-1 monoclonal antibody opicinumab." (S33.004) *Neurology*. 2017;88(16Suppl).
- 58 Fox E. ECTRIMS 2017. [Abstract P793]; Fox E. ECTRIMS 2018. [Abstract 229]
- 59 TG Therapeutics press release, March 1, 2019. "TG Therapeutics, Inc. announces final Phase 2 multiple sclerosis data presentation at the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Annual Meeting." <http://ir.tgtherapeutics.com/news-releases/news-release-details/tg-therapeutics-inc-announces-final-phase-2-multiple-sclerosis-1>
- 60 TG Therapeutics press release, August 7, 2018. "TG Therapeutics announces completion of target enrollment in the ULTIMATE Phase 3 trials in multiple sclerosis." <http://ir.tgtherapeutics.com/news-releases/news-release-details/tg-therapeutics-announces-completion-target-enrollment-ultimate>

- 61** GeNeuro SA press release, January 21, 2019. "GeNeuro Announces Positive Results from Temelimab (GNbAC1) Phase 1 High-dose Clinical Trial." <https://www.businesswire.com/news/home/20190121005367/en/GeNeuro-Announces-Positive-Results-Temelimab-GNbAC1-Phase>
- 62** Hartung H. ECTRIMS 2018. [Abstract 143]
- 63** GeNeuro SA press release, March 12, 2019. "GeNeuro's ANGEL-MS Phase 2b extension study confirms and extends the neuroprotective effects of temelimab in MS." <https://www.geneuro.com/data/news/GeNeuro-PR-ANGEL-MS-EN-VF.pdf>
- 64** Cohen JA, et al. "Safety and efficacy of the selective sphingosine 1-phosphate receptor modulator ozanimod in relapsing multiple sclerosis (RADIANCE): a randomised, placebo-controlled, phase 2 trial." *Lancet Neurol.* 2016;15(4):373-381.
- 65** Celgene press release, March 8, 2019. "Celgene Submits Application to EMA for Ozanimod for the Treatment of Relapsing-Remitting Multiple Sclerosis." <https://ir.celgene.com/press-releases/press-releasedetails/2019/Celgene-Submits-Application-to-EMA-for-Ozanimod-for-the-Treatment-of-Relapsing-Remitting-Multiple-Sclerosis/default.aspx>
- 66** Comi G, et al. ECTRIMS 2018. [Abstract P1191]
- 67** Comi G, et al. ECTRIMS 2018. [Abstract P869]
- 68** Deluca J, et al. ECTRIMS 2018. [Abstract P556]
- 69** ClinicalTrials.gov identifier: NCT02907177.
- 70** Kappos L, et al. ECTRIMS 2018. [Abstract P568]
- 71** ClinicalTrials.gov identifier: NCT02425644.
- 72** Arnold DL, et al. AAN 2019. [Abstract P3.2-060]
- 73** ClinicalTrials.gov Identifier: NCT03093324.
- 74** Naismith R, et al. ECTRIMS 2017. [Abstract P708]
- 75** Lehmann-Horn K, et al. "Targeting B cells in the treatment of multiple sclerosis: recent advances and remaining challenges." *Ther Adv Neurol Disord.* 2013;6(3):161-173.
- 76** Montalban X. ECTRIMS 2018. [Abstract P322]
- 77** MediciNova, Inc. press release. Oct. 26, 2017. "MediciNova announces positive top-line results from the SPRINT-MS Phase 2b trial of MN-166 (ibudilast) in progressive MS: achieved both primary endpoints including a significant reduction in whole brain atrophy and safety and tolerability." <https://investors.medicinova.com/news-releases/news-release-details/medicinova-announces-positive-top-line-result-s-sprint-ms-phase>
- 78** Goodman A, et al. AAN 2019. [Presentation 007: Session S12]
- 79** MediciNova, Inc. press release, April 1, 2019. "MediciNova Announces Results of Subgroup Analysis from the SPRINT-MS Phase 2b Trial of MN-166 (ibudilast) in Progressive MS." <https://www.apnews.com/Globe%20Newswire/23e846bb5075003f0f096c9ae599009b>
- 80** Eshaghi A, et al. ECTRIMS 2018. [Abstract P1219]
- 81** ClinicalTrials.gov Identifier: NCT03387670.
- 82** MS Society press release, September 12, 2018. "MS-STAT2 trial for secondary progressive MS begins UK-wide recruitment." <https://www.mssociety.org.uk/research/latest-research/latest-research-news-and-blogs/ms-stat2-trial-for-secondary-progressive-ms-begins-recruitment-across-the-uk>
- 83** Fitzgerald K, et al. ECTRIMS 2018. [Abstract 364]
- 84** Brenton JN, et al. ECTRIMS 2018. [Abstract P958]
- 85** Katz Sand I, et al. ECTRIMS 2018 [Abstract P450]
- 86** Cortese M, Chitnis T, Ascherio A, Munger KL. Total intake of different minerals and the risk of multiple sclerosis. *Neurology.* 2019; 92 (18). DOI: <https://doi.org/10.1212/WNL.0000000000006800>
- 87** Bistrom M, et al. ECTRIMS 2018. [Abstract P1757]
- 88** Cortese M. ECTRIMS 2018. [Abstract 321]
- 89** Koduah P, et al. ECTRIMS 2018. [Abstract 1781]
- 90** Cree BA, et al. ECTRIMS 2018. [P1221]
- 91** Ciron J, et al. ECTRIMS 2018. [Abstract P1222]
- 92** Rolla S, et al. ECTRIMS 2018. [Abstract P770]
- 93** Haigh S, et al. ECTRIMS 2018. [Abstract P446]
- 94** Wing A, et al. ECTRIMS 2018. [Abstract P649]
- 95** ClinicalTrials.gov Identifier: NCT03161028.
- 96** Spain R, Powers K, Murchison C, et al. "Lipoic acid in secondary progressive MS: a randomized controlled pilot trial." *Neurol Neuroimmunol Neuroinflamm.* 2017 Jun 28;4(5):e374.
- 97** Burt RK, Balabanov R, Burman J, et al. "Effect of nonmyeloablative hematopoietic stem cell transplantation vs continued disease-modifying therapy on disease progression in patients with relapsing-remitting multiple sclerosis: a randomized clinical trial." *JAMA.* 2019;321(2):165-174.
- 98** Das J. ECTRIMS 2018. [Abstract 230]
- 99** BrainStorm Cell Therapeutics Inc. Dec. 17, 2018. "FDA accepts BrainStorm's NurOwn® IND application for progressive multiple sclerosis." <http://ir.brainstorm-cell.com/news-releases/news-release-details/fda-accepts-brainstorms-nurown-ind-application-progressive>.
- 100** ClinicalTrials.gov Identifier: NCT03799718.
- 101** Cotsapas C, et al for the International Multiple Sclerosis Genetics Consortium. *Cell.* 2018;175:11679-1687.
- 102** Castro K, Ntranos A, Amatrada M, et al. "Body mass index in multiple sclerosis modulates ceramide-induced DNA methylation and disease course." *E BioMed.* 2019. <https://doi.org/10.1016/j.ebiom.2019.03.087>
- 103** Sorosina M, et al. ECTRIMS 2018. [Abstract P1068]
- 104** Sinnecker T. ECTRIMS 2018. [Abstract 138]
- 105** Maggi P, et al. ECTRIMS 2018. [Abstract P815]
- 106** Tavazzi E, et al. AAN 2019. [P5]
- 107** Kappos L. ECTRIMS 2018. [Abstract 286]
- 108** Yaldizli O. ECTRIMS 2018. [Abstract 262]

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