

# MS RESEARCH UPDATE



**MSAA**

MULTIPLE SCLEROSIS  
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The logo features the letters 'MS' in a large, white, serif font inside a red square. Below this, the words 'RESEARCH' and 'UPDATE' are stacked in a bold, black, sans-serif font.

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The 2018 edition of MSAA's *MS Research Update* provides important new data on approved and experimental treatments for MS, serving as a valuable resource to the entire MS community. Please note that this update gives an overview of the research behind the 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](http://mymsaa.org) or call **(800) 532-7667**. Questions to MSAA's Client Services department may also be emailed to [MSquestions@mymsaa.org](mailto:MSquestions@mymsaa.org).

Additionally, please be aware that due to the timing of the national and international MS conferences, study data from 2018 conferences generally could not be included in the *Update*. Information in this publication includes data presented at the 2017 conferences, as well as any important updates that occurred in early 2018. Please visit MSAA's website at [mymsaa.org](http://mymsaa.org) for future summaries of 2018 conference highlights.

The 2018 *MS Research Update* is made possible through contributions in honor of:  
Randi and Carl Bushner, and an anonymous supporter.

The logo for the Multiple Sclerosis Association of America (MSAA) features the letters 'MSAA' in a large, blue, cursive font. Below this, the words 'MULTIPLE SCLEROSIS ASSOCIATION OF AMERICA' are written in a smaller, blue, sans-serif font. At the bottom, the tagline 'Improving Lives Today!' is written in a red, sans-serif font, followed by a registered trademark symbol.

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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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This 2018 *MS Research Update* has been designed to highlight experimental medications currently under investigation for the long-term treatment of multiple sclerosis (MS), to provide new clinical trial data on some of the already-approved disease-modifying therapies (DMTs), and to describe the most exciting emerging areas of MS research.

This 2018 edition of MSAA's *MS Research Update* is again being printed as a stand-alone issue, reflecting the great diversity and wide scope of research progress in MS. With so much ongoing research, it all cannot be covered here. Therefore, not all study results and medications are included.

The information presented is based on a wide range of sources, including extensive journal literature on MS and its management, a review of ongoing clinical trials, and papers presented at major national and international conferences. These include the 2017 conferences hosted by the American Academy of Neurology

(AAN), the Consortium of Multiple Sclerosis Centers (CMSC), and the Americas and European Committees for Treatment and Research in Multiple Sclerosis (ACTRIMS andECTRIMS).

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 know that the different lengths of text should in no way be considered as favoritism toward any one product. Additionally, references have only been cited for the newer study results.

As symptom-management medications do not fall under the scope of this report, for more information on the specific symptoms of MS and treatments for managing these symptoms, please visit [mymsaa.org](http://mymsaa.org) and select "**Symptoms**" under "**MS Information**."

In addition to exploring this *MS Research Update*, readers are encouraged to review a paper titled, “The Use of Disease-Modifying Therapies in Multiple Sclerosis: Principles and Current Evidence; SUMMARY.” The paper, available at [mymsaa.org/msc-dmt-summary](http://mymsaa.org/msc-dmt-summary), outlines in a reader-friendly fashion the evidence supporting the use of FDA-approved DMTs for the long-term treatment of MS.

The paper is the result of a 2016 conference in which experts from member organizations of the Multiple Sclerosis Coalition (MSC), including the Multiple Sclerosis Association of America (MSAA), collaborated to assess the current data on the effectiveness of these medications. One goal of this meeting was to demonstrate the strong evidence base for MS therapies in order to support broad access to these approved medications for people with MS. Ultimately, the goal is to enable individuals with MS and their medical professionals to select the most appropriate medication available.

A version of this paper is also available for medical professionals, which is written in a more-detailed and highly scientific style. The professional version may be accessed on MSAA’s website for anyone to review by going to [mymsaa.org/msc-dmt-full](http://mymsaa.org/msc-dmt-full).

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 2018 *MS Research Update*, and other MSAA publications and services are welcomed, and can be directed to the organization at (800) 532-7667 or [editor@mymsaa.org](mailto:editor@mymsaa.org).

## Overview of MS Research Progress

Developments over the past year or more provide yet another reminder that while research inevitably leads us forward, the path is not straight and smooth, with detours, dead-ends, and disappointments – as well as breakthroughs – encountered along the way.

As last year’s edition of the *MS Research Update* was prepared for publication, the “breaking news” included at the 11th hour was the FDA’s March 2017 approval of Ocrevus™ (ocrelizumab). This new DMT was not only approved for relapsing forms of MS (RMS), but was also the first DMT approved for primary-progressive MS (PPMS). During the 25 years since 1993, when the FDA approved Betaseron® (interferon beta-1b) as the first MS treatment, the MS community has seen numerous milestones, and this new ability to treat PPMS truly ranks among the most important of those achievements.

The “breaking news” this year is mixed. March 2018 saw Biogen and AbbVie announce the withdrawal of their monoclonal antibody Zinbryta® (daclizumab) from markets worldwide. That decision follows reports from Europe of inflammation of the brain or nearby tissues in a dozen people taking the immune-modulating medication. The withdrawal comes less than two years after Zinbryta was approved for use in the United States for treating relapsing forms of MS. Recent months also saw disappointing trial results for medications that had encouraging initial findings. To cite one example, the experimental medication laquinimod missed its primary endpoints in trials evaluating its efficacy in RMS and PPMS.

# INTRODUCTION

However, March 2018 also saw the publication of results from the Phase III EXPAND trial, which evaluated the selective sphingosine 1-phosphate (S1P) receptor modulator siponimod in secondary-progressive multiple sclerosis (SPMS), a disease state sorely in need of effective therapies. The multi-national trial involved more than 1,600 patients with SPMS. It showed that, compared to placebo, siponimod cut the annualized relapse rate in half, reduced confirmed disability progression, and slowed the rate of brain volume loss.<sup>1</sup> On the basis of these and other findings, Novartis announced in late March that it will seek FDA approval for siponimod for SPMS in the first half of 2018.<sup>2</sup>

Other breaking news, as this edition of the *MS Research Update* was being prepared, is the FDA's February 2018 approval of a second dose option for Glatopa® (glatiramer acetate injection), at 40 mg given three-times weekly for relapsing forms of MS.<sup>3</sup> Additionally, in May 2018, the FDA approved Gilenya® (fingolimod) as the first treatment specifically indicated to treat pediatric MS.

The past year also saw several other significant advances in the development of experimental therapies. These include ibudilast, an experimental medication also known as MN-166, which showed a 26-percent reduction in confirmed disability progression in a Phase II trial of people with progressive MS. Based on those findings, the company developing ibudilast in MS is making plans for a 700-patient Phase III trial.<sup>4</sup>

Meanwhile, a December 2017 study published in *The Lancet* reported that the

over-the-counter medication clemastine fumarate showed evidence of promoting remyelination, which is the restoring of the myelin sheath that covers central nervous system (CNS) cells and supports their function. This effect was seen in 50 patients with RMS who were experiencing chronic demyelinating optic neuropathy while on immunomodulating therapy.<sup>5</sup> While this was a small, single-center study whose findings need to be confirmed on a larger scale, it represents another step toward the goal of understanding and addressing demyelination, the central process in the development of MS.

In other cases, medications with promising data may face delays as they navigate the regulatory process. For example, on the basis of positive results from two large Phase III trials, Celgene submitted a New Drug Application (NDA) to the FDA for use of ozanimod in relapsing forms of MS. Ozanimod belongs to a class of drugs called S1P receptor modulators, which essentially trap immune cells in the lymph nodes so that they cannot enter the CNS and create lesions. In February 2018, however, the FDA declined to accept the NDA, saying that two sections of the NDA were insufficient to allow a complete review. In response, Celgene expressed its confidence in ozanimod and said it would work with the FDA to address outstanding items.

Exciting work is also being done in examining whether medications long used to treat other conditions – including antibiotics and the anti-epilepsy agent phenytoin – may have re-purposed roles in treating MS. Stem cell and genetic research is advancing as well,

and there is an increasing and intriguing focus on how diet and the gut microbiome (bacteria) - or immunologic milieu of the gastrointestinal tract - affect MS and its treatment.

Finally, two growing areas of research are outgrowths of the progress made over the past two decades in offering people with MS a variety of therapies. The first area concerns “comparative effectiveness,” and typically draws on large databases and sophisticated statistical methods to assess which medication is likely to be most effective and safe in a given type of patient. This is key to helping physicians and patients make the best possible decision about treatments.

The second area examines the long-term safety of disease-modifying therapies. By analyzing data from “extension studies” of the clinical trials that led to the initial approval of medications, and from patient registries, long-term safety studies are created. These provide critical information on medications that tens of thousands of patients may now be taking for 10 or even 20 years or longer.

Keeping up with the vast array of medications, techniques, and new areas of inquiry in MS is challenging, and at times can be overwhelming to healthcare professionals, patients, and family members alike. Of all the challenges we face in MS, having too many advancements is perhaps the most-welcomed one! We hope this *MS Research Update* serves as a useful guide to many of the highlights as well as the hurdles facing our field, and provides insight into the many steps needed to investigate and prove that a new treatment strategy is both safe and effective.

In reporting on recent research, this publication describes clinical trials involving numerous participants. It is important to remember that those study populations are made up of individual men and women who each made the decision to participate in a trial. By making this decision, a person chooses to take an active role in furthering our understanding of MS and its treatment, to the potential benefit not only of herself or himself, but of all people with multiple sclerosis.

We 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. We open this *MS Research Update* with this note of gratitude to all the individuals with MS who made these trials possible. For more information about participating in clinical trials for the treatment of MS and its symptoms, readers may visit [mymsaa.org/clinicaltrials](https://mymsaa.org/clinicaltrials).

**Editor’s note:** Initial study results from therapeutic medications under investigation should be considered as preliminary, because additional studies and/or evaluations may be needed to prove the safety and efficacy of these medications. 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.

## Ocrevus® (ocrelizumab)

Company: Genentech and Roche Pharma AG

- 600 mg given via IV infusion every six months
- Approved in 2017 for RMS and PPMS

Ocrevus is an anti-CD20 monoclonal antibody. While it is similar to the medication Rituxan® (rituximab), Ocrevus has the potential advantage of being a more humanized antibody than Rituxan. Humanized monoclonal antibodies are antibodies from non-human species (such as mice) whose protein sequences have been modified to increase their similarity to antibodies produced naturally in humans.

In March 2017, Ocrevus won FDA approval for use in both RMS and PPMS. The approval

was based largely on the results of three important studies announced in 2015. In relapsing MS, ocrelizumab 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 total combined enrollment for both studies was 1,656 individuals with relapsing forms of MS.

In the OPERA studies, individuals received either 600 mg of ocrelizumab via intravenous (IV) infusion every six months, or the approved 44 mcg dose of Rebif® (interferon beta-1 a), given via subcutaneous injection three-times weekly. Participants receiving ocrelizumab had significant reductions in both studies in annualized relapse rate of 46 and 47 percent over a two-year period versus the interferon groups. Additionally, in the ocrelizumab

### 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.



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.

A further analysis of the OPERA trials' data reported in February 2018 found that patients receiving Ocrevus fared better than those receiving interferon beta-1a on a composite measure that assessed absence of relapse, confirmed disability progression, and MRI disease activity. The endpoint is known as "no evidence of progression or active disease," or NEPAD. The researchers found that 39.3 percent of the 740 patients who received Ocrevus had NEPAD at 96 weeks after study start, versus 21.5 percent of the 753 people receiving interferon beta-1a. <sup>6</sup>

The FDA's approval of Ocrevus in PPMS was based in part on results from the ORATORIO study, which was published in 2015. **Prior to this study, no Phase III studies in PPMS had been successful, despite multiple attempts.** ORATORIO was a randomized, double-blind, and global multi-center trial that studied the effectiveness and safety of Ocrevus compared to placebo in 732 people with PPMS. Every six months, two 300 mg infusions (for a total of 600 mgs) were given two weeks apart. Members of the treatment group were compared to a placebo group. The study's primary endpoint was time to the onset of confirmed disability progression, defined as an increase in the Expanded Disability Status Scale (EDSS) sustained for at least 12 weeks. (The EDSS scores function on a scale of 1 to 10; a higher score refers to more disability.)

The ORATORIO study met its primary endpoint, showing that ocrelizumab significantly reduced the progression of clinical disability (sustained for at least 12 weeks) by 24 percent compared with placebo. Walking speed, as measured by the timed 25-foot walk, was improved by 29 percent. MRI hyper-intense T2 lesions were actually reduced by Ocrevus, and brain-volume loss as viewed on MRI was reduced by 17.5 percent. The incidence of adverse events associated with Ocrevus was similar to placebo; the most common adverse events were mild-to-moderate infusion-related reactions.

In a post hoc set of analyses reported in February 2018, investigators found that Ocrevus reduced the risk of progression of severe upper extremity disability, a functional impairment that frequently occurs in PPMS. When patients entered the ORATORIO trial, and every 12 weeks thereafter throughout the study, participants completed a test that involves placing pegs in holes. Confirmed progression was measured by changes in the time required to perform the test. Compared to placebo, Ocrevus reduced the risk of confirmed significant progression (a 35-percent or greater increase in test time) in both hands by 49 percent at week 12 and by 41 percent at week 24. Ocrevus also reduced the risk of progression in terms of the patient's self-identified best hand and worst hand. <sup>7</sup>

The period since the FDA's approval of Ocrevus has also seen the first reported cases of progressive multifocal leukoencephalopathy (PML), a rare and potentially fatal brain infection, in patients taking the medication. Assessing what role, if any, Ocrevus may have

played in the development of PML or other adverse events can be quite complicated, particularly when an individual had previously taken other DMTs known to be associated with risk for those events.

For example, the first person taking Ocrevus who was reported to have PML had taken Tysabri® (natalizumab) for three years prior to beginning Ocrevus. An increased risk for PML has previously been linked to Tysabri, which the FDA approved in 2004 for use in relapsing forms of MS. Also, as of December 2017, the post-marketing surveillance of Ocrevus had recorded 24 deaths among the 30,000 patients who have been treated with the medication worldwide (an additional eight people died during

clinical trials that involved roughly 2,000 participants). The causes of death have been varied, and in some cases unknown, with no cancer deaths reported. While physicians, regulators, the medication's manufacturers, and others are monitoring the post-approval efficacy and safety profile of Ocrevus, it is very difficult at this point to discern the significance, if any, of these data.

Meanwhile, in January 2018, the European Commission approved Ocrevus for use in treating both RMS and PPMS.<sup>8</sup> Ongoing research into Ocrevus includes an open-label study of more than 600 people with RRMS, to assess the impact of the medication on these individuals who have had a suboptimal response to other DMTs.<sup>9</sup>

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## **Zinbryta® (daclizumab)** WITHDRAWN FROM MARKET

Company: Biogen and AbbVie

- 150 mg given via subcutaneous injection once monthly
- Approved in 2016 for RMS; voluntarily withdrawn from market in March 2018

In early March 2018, Biogen and AbbVie announced the voluntary worldwide withdrawal of Zinbryta® for relapsing MS. The move came after the European Medicines Agency had raised new safety concerns related to reports of inflammation of the brain or its surrounding tissues (inflammatory encephalitis and meningoencephalitis) among people taking the immunomodulating therapy. Because of previously

identified risks, the medication generally had been reserved for use in people who had experienced an inadequate response to two or more other MS medications.<sup>10</sup>

To minimize the potential for confusion or disruption of care in individuals taking Zinbryta, the FDA worked closely with the medication's manufacturers to ensure the medication's withdrawal from the market. As this *MS Research Update* was published, the manufacturers of Zinbryta planned to have the medication available as needed until April 28, 2018. People taking Zinbryta were told to contact their doctor for instruction on stopping Zinbryta and switching their medication, and to immediately tell him or her about any new or unexplained symptoms.<sup>10,11</sup>

The withdrawal of Zinbryta underscores the fact that clinical trials, no matter how large and

rigorously performed, cannot identify all of the safety issues that may emerge when a medication moves to widespread use following approval by the FDA or regulatory agencies in other countries. At the same time, clinical trials did reveal other safety considerations that prompted the medication's FDA-approved indication to note that it

generally should be used only when patients had not had a satisfactory response to at least two other medications. Similarly, it would appear that the post-approval surveillance system worked well in flagging rare but serious conditions that may be associated with the use of Zinbryta.

## Tecfidera® (dimethyl fumarate)

Company: Biogen

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

The exact mechanism by which Tecfidera, or dimethyl fumarate, exerts its therapeutic effects in MS is not known. The medication has been shown to activate a pathway involved in the cellular response to oxidative stress, which is induced by inflammation. However, it is unclear whether this pathway activation plays a role in the impact Tecfidera has on the MS disease process.<sup>12</sup>

The FDA approved Tecfidera for use in RRMS in 2013. That approval followed completion of two randomized, double-blind, placebo-controlled trials showing that the medication reduced the annualized relapse rate by 44 percent to 53 percent relative to placebo. These trials also showed that Tecfidera had a favorable impact on disability progression and MRI measures of MS activity, compared to placebo.<sup>12</sup>

In 2017, the prescribing information for

Tecfidera was amended to direct physicians to obtain a complete blood-cell count and to measure liver enzymes and other values before initiating the drug. 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.<sup>12</sup>

Recent research into Tecfidera has focused on its relative effectiveness compared with other disease-modifying therapies (DMTs) and on how comorbidities - other health conditions - affect the use and effectiveness of this medication in people with RRMS. The results of that research were presented in October 2017.

Italian investigators drew on a database of more than 3,000 people newly diagnosed with RRMS between 2010 and 2016 to compare how these individuals responded to initial treatment with Tecfidera, Aubagio® (teriflunomide), interferon beta-1a, or glatiramer acetate. The first two medications are oral therapies; the second two are injectables. The researchers used a method called propensity score, which matches people treated with different medications by

their age, sex, and other factors, thus allowing comparisons.

Employing this process, they found that patients receiving Tecfidera had a significantly lower risk of relapse compared to individuals receiving interferon beta-1a. They found no significant difference in time to first relapse among people taking Aubagio relative to

those receiving interferon beta-1a or glatiramer acetate. Similarly, they did not identify a difference in time to relapse between interferon beta-1a and glatiramer acetate, but noted that in some cases, larger numbers of matched patients would be needed to assess differences.<sup>13</sup>

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## **Tysabri® (natalizumab)**

Company: Biogen

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

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

Tysabri received FDA approval in 2004 on the basis of the Phase III AFFIRM trial, in which the medication reduced the risk of progression of disability by 42 to 54 percent, and reduced the annual rate of relapse by two-thirds. Tysabri was voluntarily withdrawn from the market the next year, however, after three cases of progressive multifocal leukoencephalopathy (PML), a rare but potentially fatal brain infection caused by the JC virus, were identified in people taking the medication. Tysabri became available again in 2006, based on the implementation of a comprehensive risk-man-

agement program, which includes testing potential Tysabri users to see if they have anti-JC virus antibodies.<sup>14</sup>

Now it appears that extending the dosing of Tysabri from every four weeks to every 12 weeks can significantly reduce the risk of developing PML. Research presented in February 2018 at the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS) Forum 2018, drew on six years of safety data and found that using an extended dosing regimen could reduce the risk of PML by up to 94 percent.<sup>15</sup>

A French study presented at theECTRIMS-ACTRIMS Meeting in October 2017 gave further support to extended-interval dosing by reporting that administering Tysabri every five or six weeks, rather than every four weeks, did not diminish the efficacy of the agent. The study followed 70 individuals who moved to extended-interval dosing after receiving Tysabri every four weeks for two years. After 18 to 20 months on the longer dosing intervals, no significant differences were found between four-week dosing and five- or six-week dosing in terms of the patients' annualized relapse rates, EDSS scores, number of T2 lesions seen on MRI, or a measure of how

well the drug is reaching target cells.<sup>16</sup>

The identification of strategies for reducing the risk of PML is particularly welcome given that other recent research has further demonstrated the effectiveness of Tysabri in treating RRMS.

The impact of Tysabri on cognitive function, health-related quality of life (HRQoL), and work capacity in people with early RRMS was examined in the Observational Study of Tysabri in Early Relapsing-Remitting Multiple Sclerosis in Anti-JC Virus Antibody Negative Participants (STRIVE). This open-label, single-arm, multi-center study followed 222 individuals over the course of two years of treatment with Tysabri. At baseline, the patients had been diagnosed with MS an average of 1.6 years earlier. Half of the participants had not received another disease-modifying therapy

(DMT) before starting Tysabri.<sup>17</sup>

The study results were presented at theECTRIMS-ECTRIMS Meeting in October 2017. Researchers found that after two years of Tysabri therapy, patients had significant improvement in cognitive function and HRQoL based on change from baseline on standardized test scores. These individuals also showed improvement in work capacity as measured by hours missed from work due to MS and non-MS reasons, work productivity affected by MS, and daily activities affected by MS.<sup>17</sup>

Meanwhile, data from the 10-year Tysabri Observational Program (TOP) involving almost 2,500 patients found that people who switched to another therapy after two years on Tysabri had more than double the risk of relapse compared to individuals who remained on Tysabri.<sup>18</sup>

## Gilenya® (fingolimod)

Company: Novartis

- *0.5 mg capsule given orally once per day*
- *Approved in 2010 for RMS in adults; approved in 2018 for RMS in pediatric MS*

Gilenya is the first in a class of immunomodulatory drugs called “S1P-receptor modulators.” It 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.

Gilenya was approved for RMS in adults in 2010, and in May 2018, became the first medication approved to treat pediatric MS. The FDA approved Gilenya to treat RMS in children and adolescents ages 10 through 17 years on the basis of the Phase III PARADIGMS study. The trial, which included 214 children and adolescents with RMS, compared Gilenya to Avonex® (interferon beta-1a). Eighty-six percent of the individuals in the Gilenya group were relapse-free after 24 months of treatment, compared to 46 percent in the interferon beta-1a group. In PARADIGMS, the

## FDA-APPROVED MEDICATIONS: NEW DATA

side effects of Gilenya experienced by pediatric patients were similar to those seen in adults.

The most commonly reported adverse effects were headache, elevated liver enzymes, diarrhea, cough, flu, sinusitis, back pain, abdominal pain, and pain in the extremities.<sup>19</sup> This first FDA approval of a medication to treat pediatric MS is a very important and exciting development, and hopefully will be followed in the years ahead by the approval of other medications with demonstrated efficacy and safety profiles in children and adolescents with MS.

Returning to studies with adults, the 36-month INFORMS trial evaluated the effect of Gilenya relative to placebo on delaying the time to sustained disability progression in people with primary-progressive MS. The enrollment of 969 PPMS patients into the INFORMS trial was completed in 2011, and the trial's data analysis was completed in 2014. Novartis announced in December 2014 that unfortunately, the primary outcome of the study was not met. Gilenya did not show a significant difference from placebo on a combination of disability measures. Interestingly, a medication in the same class as Gilenya, siponimod, was able to show a benefit in SPMS (please see the section on siponimod on page 24).

Meanwhile, three studies examining the long-term efficacy and safety of Gilenya in RRMS all generated favorable results. The findings from these three studies were reported at theECTRIMS-ACRIMS Meeting in October 2017.

LONGTERMS, an open-label, single-arm

extension study, followed more than 3,100 people who had received Gilenya in Phase II and Phase III trials of the medication and who continued to receive the DMT for up to 10 years. Researchers found that the annualized rate of relapse declined with longer use of Gilenya, from 0.26 for those who used the agents for up to one year to 0.19 for individuals who stayed on Gilenya for up to 10 years.

Seventy-nine percent of patients remained free of confirmed disability progression through five years of treatment, and 68 percent avoided disability progression through 10 years. MRI assessments also showed that ongoing use of Gilenya was associated with stability in brain volume. Importantly, long-term use of Gilenya did not see new safety concerns emerge over time. The most common adverse events reported were viral upper respiratory tract infection (15 percent of individuals), headache (12 percent), and hypertension (9 percent).<sup>20</sup>

PANGAEA is a non-interventional study designed to investigate the long-term safety, effectiveness, and patient-reported outcomes of the medication for up to five years in daily clinical practice. The German study has enrolled more than 4,200 participants, and by January 2017, had accumulated long-term data on 474 of those individuals.

The annual rate for discontinuing Gilenya was 10 percent to 12 percent, and the main reasons for stopping therapy included patient's decisions (33 percent), adverse event (27 percent), switch of physician (12 percent), and disease

progression (11 percent). Common adverse events included low levels of lymphocytes (white blood cells with important immune system functions), nasopharyngitis, and elevated liver enzyme values.<sup>21</sup>

The third long-term study on the effects of Gilenya reported at the 2017ECTRIMS-ACTRIMS Meeting found that after eight years of treatment, 50 percent of individuals receiving the DMT had seen their degree of MS-related disability remain stable or improve. Another 20 percent had fluctuating scores on the Expanded Disability Status Scale (EDSS), and 30 percent had worse scores, compared to baseline.

No differences were seen between those with an improved or stable EDSS score and those with fluctuating or worsening scores in terms of the number of relapses they had experienced before entering the trial, suggesting that the differences seen in the study were due to the effect of Gilenya. The investigators noted that people in the improved disability group were more likely to have had shorter disease duration. They

concluded that this finding shows that early diagnosis and initiation of therapy is important to help reduce long-term disability.<sup>22</sup>

Meanwhile, another Gilenya-related study reported at the 2017ECTRIMS-ACTRIMS Meeting sought to better understand how the DMT provides its beneficial effects. Investigators enrolled 77 people with MS in a two-year, Phase IV study. Thirty-seven of these individuals were treated with Gilenya; the other 40 did not receive treatment. All participants had a neurological examination every six months, and MRI imaging at the start of the study and after 12 and 24 months.

At the end of two years, 89 percent of the untreated patients had new lesions in the cortical region of the brain, compared with just 13.5 percent of patients receiving Gilenya. Individuals in the Gilenya-treated group also had less loss of volume in several - but not all - areas of the brain. While the relatively small sample and short duration of the study require that its results be replicated in a longer, larger trial, the research nonetheless provides valuable insights.<sup>23</sup>

## 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 first treatment course.*

- *Approved in 2012 for RMS*

Lemtrada® (alemtuzumab) is a monoclonal antibody. Its exact mechanism of action is unknown, but 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 typically is reserved for

## FDA-APPROVED MEDICATIONS: NEW DATA

patients who have had an inadequate response to two or more other MS disease-modifying therapies.

Researchers assessed the long-term efficacy and safety of Lemtrada in 349 patients with active RMS.<sup>24</sup> The data they reported covered an initial two-year core study, called CARE-1, and a three-year extension study. During the follow-up period, patients were eligible to be re-treated with Lemtrada if they had a relapse or MRI activity.

At the end of Year 5, 88 percent of the participants had not had a relapse, 87 percent did not have a brain or spinal cord lesion seen on gadolinium-enhanced MRI, and 85 percent were free of clinical disease activity. Sixty percent of participants saw their EDSS score remain stable, while 22 percent saw their EDSS score improve and 18 percent had their score worsen.

Adverse events occurred more frequently in the two years of the core study than in the following three years of the extension study, and 97 percent of the adverse events reported in Years 3-5 were mild to moderate in severity. However, one patient died of sepsis in Year 3, in what was judged to be a treatment-related adverse event. Thyroid issues were the most common autoimmune adverse events reported during the extension period; they peaked in Year 3 at a 15-percent incidence.

During the extension period, 67.3 percent of the participants received neither Lemtrada re-treatment or treatment with any other disease-modifying therapy (DMT), leading the investigators to conclude that Lemtrada had enduring efficacy in the three years following

conclusion of its two-course treatment.

The long-term effects of Lemtrada also were the focus of several presentations at theECTRIMS-ECTRIMS Meeting in 2017. Investigators drew on data from another long-term follow-up study (TOPAZ; NCT02255656) of people with RMS who had participated in earlier Lemtrada trials. Researchers reported that:

- People with RMS who switched from interferon beta-1a to Lemtrada saw improved clinical outcomes, decreased MRI disease activity, slowed brain volume loss, and durable efficacy in the five years after being treated with Lemtrada.<sup>25,26,27</sup>
- Through seven years of follow-up from the time of initial Lemtrada treatment, 74 percent of participants were free from six-month confirmed disability worsening, and the annualized relapse rate (ARR) at Year 7 was 0.13.<sup>28</sup> Furthermore, 68 percent of these individuals were free of MRI disease activity at Year 7, and Lemtrada consistently slowed brain-volume loss throughout the study period.<sup>29</sup>

Related research presented at the 2017ECTRIMS-ECTRIMS Meeting reported that over a median follow-up period of 5.8 years, 18 percent of Lemtrada-treated patients converted from relapsing-remitting MS to secondary-progressive MS. The investigators termed this a low rate of conversion based on criteria they specified at the outset of their study.<sup>30</sup>

Taken as a whole, these findings provide



reassurance that Lemtrada has a long-term favorable effect on the course of RMS as measured by a number of different standards. This re-assurance is important for clinicians and patients alike, given the well-documented

safety concerns involved with Lemtrada. These data will aid in decision-making when the patient and physician need to consider next steps following an inadequate response to another MS therapy.

## Rebif® (interferon beta-1a)

Company: EMD Serono

- *Subcutaneous injection; 22 mcg or 44 mcg three times per week*
- *Approved in 2002 for RMS*

Between one-third and one-half of untreated people who have a clinically isolated syndrome (CIS) will convert to clinically definite multiple sclerosis (CDMS) within two years. Delaying, or potentially even avoiding that conversion has been a focus of considerable research. A study published last year indicated that one of the longest-established treatments for relapsing forms of MS, Rebif® (interferon beta-1a), can play an ongoing role in delaying that conversion.<sup>31</sup>

The REFLEXION trial enrolled 402 individuals who had experienced a clinically isolated syndrome and who had participated in an earlier trial of Rebif, called REFLEX. Participants who had received once-weekly or three-times-weekly Rebif over a two-year period in the REFLEX trial and who had not

converted to CDMS continued to receive Rebif on their established schedules. These individuals made up the early treatment groups in REFLEXION. Meanwhile, people in the placebo arm of REFLEX who had not developed clinically definite MS began receiving Rebif three-times a week in the REFLEXION trial, and made up the delayed treatment group. This approach allowed researchers to compare the effects of early versus later interferon beta-1a therapy in CIS.

After five years, the cumulative probability of conversion to CDMS was 44.6 percent in the delayed treatment group versus 39.2 percent in those who had received three-times-weekly Rebif since the REFLEX study and 40.7 percent for individuals who had received weekly Rebif injections in the REFLEX and REFLEXION studies. It should be noted that these differences did not achieve statistical significance. MRI findings were also more favorable for the early treatment groups relative to the delayed treatment group. Researchers concluded that these findings supported the early use of Rebif in CIS.<sup>31</sup>

## MSAA's Video Library

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## Aubagio® (teriflunomide)

Company: Genzyme

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

The exact mechanism by which teriflunomide exerts a therapeutic effect in relapsing forms of MS is unknown, but may involve reducing the number of activated lymphocytes - immune-system cells - in the central nervous system. The agent 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.<sup>32</sup>

Aubagio won FDA approval for use in relapsing forms of MS following positive results from four randomized, controlled, double-blind clinical trials. In the first study, 1,088 participants were randomized in a 1:1:1 ratio to receive Aubagio 7 mg, Aubagio 14 mg, or placebo, and followed for up to 26 months. Participants receiving Aubagio had a statistically significant reduction in the annual relapse rate (ARR) - the study's primary endpoint - compared to individuals 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 end point. Both doses of Aubagio again showed statistically significant advantages over placebo in terms of a lower relapse rate and on other measures of efficacy.

The third study followed a similar design, but focused on participants who had experienced a first clinical event consistent

with acute demyelination (CIS) occurring within 90 days of randomization. After following them for up to 108 weeks, the study found that significantly higher proportions of Aubagio-treated patients remained free of relapse relative to individuals receiving placebo.

The fourth study examined MRI characteristics of 179 patients with RMS. The mean number of unique active lesions per brain MRI scan during the 36-week treatment period was lower in patients treated with Aubagio as compared to placebo.<sup>32</sup>

More recently, researchers examined the long-term impact of Aubagio on the performance status of people with relapsing MS. A study presented at theECTRIMS-ACTRIMS Meeting in 2017 reported on 172 individuals who had received either 7 mg or 14 mg of Aubagio for up to 14 years, including time spent in an earlier trial of the medication. Researchers found consistently low EDSS scores in individuals who received Aubagio 14 mg throughout the initial and extension phases of the original study (2.28), at Year 5 (2.33) and at Year 10 (2.26). After Year 10, EDSS scores remained stable, but the number of participants had become small.<sup>33</sup>

Another study presented at the 2017ECTRIMS-ACTRIMS Meeting examined the long-term disability outcomes of various subgroups of patients who had participated in earlier trials of Aubagio. Analysis of data on more than 1,300 patients found that the risk of confirmed disability worsening (CDW) five years after initiating treatment with 14 mg of Aubagio was broadly similar across subgroups stratified by sex, age, and EDSS score, among other factors.<sup>34</sup>

## ALKS 8700

Company: Biogen and Alkermes plc.

- *Oral medication; 462 mg taken twice daily*
- *Being studied in RRMS*

ALKS 8700 is a “prodrug,” which is a biologically inactive compound that can be metabolized in the body to produce a drug. This medication is designed to convert to monomethyl fumarate in the body, and to offer features differentiated from Tecfidera (dimethyl fumarate) – so that it would work in much of the same manner as Tecfidera, but with a lower rate of gastrointestinal side effects. In November 2017, Biogen – the company that markets Tecfidera – announced that it had entered into an agreement with Alkermes, the Ireland-based developer of ALKS 8700, to collaborate on the further development and commercialization of this medication.<sup>35</sup>

ALKS 8700 is in Phase III development for

RRMS. Research into ALKS 8700 includes a study to demonstrate that it is bioequivalent to Tecfidera and a two-year safety study known as EVOLVE-MS-1. Initial safety data from EVOLVE-MS-1 were presented at theECTRIMS-ACTRIMS Meeting in 2017. Data from the first month of the study showed that from among 580 individuals receiving ALKS 8700, no serious gastrointestinal adverse events occurred. The most common adverse events during the first month of treatment were flushing, pruritus (itching), and diarrhea.<sup>35</sup>

EVOLVE-MS-1 will ultimately follow participants for up to 96 weeks, and will assess clinical relapses, laboratory results, and MRI findings, as well as adverse events and other measures.<sup>36</sup>

The ALKS 8700 research program also includes a head-to-head study (EVOLVE-MS-2) evaluating the gastrointestinal tolerability of ALKS 8700 compared to Tecfidera. Initial data from that trial are expected this year.<sup>35</sup>

## Cladribine (also known as Mavenclad™)

Company: Merck

- *Oral medication taken for a maximum of 20 days over two years*
- *Being studied in RRMS*

Cladribine, which is marketed in several countries under the trade name Mavenclad, selectively targets the immune system’s B cells and T cells, leading to depletion of those cells. This is followed by a distinct pattern of “reconstitution,” as new B cells and T cells are

produced. The medication has an interesting dosing regimen, with two annual courses given for a maximum of 20 days over two years. Its developers note that this approach avoids continuous suppression of the immune system.<sup>37</sup>

This medication received marketing authorization from the European Commission in August 2017. In December 2017, Canadian health authorities approved cladribine as a monotherapy for the treatment of adults with RRMS to reduce the frequency of clinical exacerbations and delay the progression of disability. Merck has said it plans to seek

## EXPERIMENTAL MEDICATIONS: ADMINISTERED ORALLY

regulatory approval in other countries, including the United States. <sup>37</sup>

In announcing the Canadian approval, Merck noted that cladribine generally is recommended for patients who have had an inadequate response to, or are unable to tolerate, one or more other MS therapies. They added that in clinical trials, cladribine demonstrates efficacy across key measures of disease activity in patients with RRMS, including disability progression, annualized relapse rate, and MRI activity. <sup>37</sup>

In the 96-week, Phase III CLARITY trial, 1,326 patients with RRMS were randomized in a roughly 1:1:1 ratio to receive 3.5 mg of cladribine per kilogram (kg) of body weight, 5.25 mg/kg. Cladribine, or placebo, was given in two or four short courses for the first 48 weeks. This was followed by two short courses starting at Week 48 and Week 52, for a total of 8 to 20 days of treatment per year. <sup>38</sup>

Patients receiving cladribine at either dose had annualized relapse rates that were less than half the rate of individuals receiving placebo. Roughly 79 percent of the cladribine-treated patients did not have a relapse over the 96-week study period, as compared to 61 percent of people in the placebo group. Individuals receiving cladribine, at either dose, also had a lower risk of sustained progression of disability and a greater reduction in the number of brain lesions identified on MRI relative to the placebo group. However, patients receiving cladribine had a higher rate of adverse events. In particular, lymphopenia - abnormally low counts of white blood cells that play a role in fighting infection - was seen in 21.6 percent of those receiving the lower dose

of cladribine, 31.5 percent of those on the higher dose of cladribine, and just 1.8 percent of people in the placebo group. Similarly, 20 patients receiving cladribine reported herpes zoster infection, while no one in the placebo group developed this infection. <sup>38</sup>

Other studies in the cladribine clinical development program include:

**The CLARITY extension study:** a two-year Phase III placebo-controlled study, following on from the CLARITY study to evaluate the safety and efficacy of cladribine over four years.

**The ORACLE MS (Oral Cladribine in Early MS) study:** a two-year Phase III placebo-controlled study to evaluate the efficacy and safety of cladribine as a monotherapy in patients at risk of developing MS because they have experienced a first clinical event suggestive of MS.

**The ONWARD (Oral Cladribine Added ON To Interferon beta-1a in Patients With Active Relapsing Disease) study:** a Phase II placebo-controlled study to evaluate the safety and tolerability of adding cladribine to interferon-beta therapy in RMS patients who have experienced breakthrough disease while on interferon-beta.

**PREMIERE (Prospective Observational Long-term Safety Registry of Multiple Sclerosis Patients Who Have Participated in Cladribine Clinical Studies) trial:** an interim long-term follow-up data from the prospective registry, PREMIERE, to evaluate the safety and efficacy of cladribine. This will include more than 10,000 patient years of data with more than 2,700 patients included in the clinical trial program, and more than 10 years of observation in some patients. <sup>37</sup>

At the JointECTRIMS-ACTRIMS Meeting in October 2017, Czech investigators reported that cladribine has an effect on relapses comparable to Gilenya® (fingolimod), and an impact on MS-related disability similar to Gilenya and interferon-beta. They added that cladribine may be associated with superior recovery from disability relative to Gilenya, interferon-beta, and Tysabri® (natalizumab).

They reached those conclusions by analyzing one-year relapse and disability outcomes for more than 5,200 patients in an MS registry. Using a method called propensity-score matching, they compared similar types of patients taking the various medications. While the size of the cladribine group was small – 37 patients versus 1,410 to 1,940 for the other three groups – statistical analyses supported the validity of the findings.<sup>39</sup>

## Laquinimod (also known as Nervenra®)

Company: Teva Neuroscience, Inc. and Active Biotech

- *Oral medication taken once daily; dosing TBD (0.6 mg was used in studies)*
- *Being studied in RRMS and PPMS*

The past year saw disappointing results from two trials – one in RRMS and the other in PPMS – for the immunomodulator laquinimod.

In May 2017, the medication’s developers announced that The Efficacy and Safety and Tolerability of Laquinimod in Subjects With Relapsing Remitting Multiple Sclerosis (CONCERTO) trial – evaluating 0.6 mg/daily capsule of laquinimod versus placebo – did not meet its primary endpoint of improvement in time to confirmed disability progression (CDP) after at least three months. While favorable results were seen in other endpoints, laquinimod did not achieve a statistically significant advantage over placebo in time to CDP over longer periods.<sup>40</sup>

Those disappointing results follow mixed findings from earlier studies. In the Phase III ALLEGRO study of 1,106 patients, for example, laquinimod reduced the annualized relapse rate by 23 percent and the progression of disability by 36 percent compared to placebo. However, in the BRAVO Phase III trial, which involved 1,300 participants, laquinimod failed to achieve its primary goal of reducing the annualized relapse rate. Based on the results of CONCERTO, Teva announced in May 2017 that “we have no current plans to further pursue laquinimod in RRMS.”<sup>40</sup>

In December 2017, Active Biotech, which is partnering with Teva in developing laquinimod, announced that the medication had not met the primary endpoint of a Phase II proof-of-concept study in PPMS.<sup>41</sup> While these results make it unlikely that laquinimod will play a role in the treatment of MS, this medication continues to be studied for use in Huntington disease, a neurodegenerative disorder.

## ***About Monoclonal Antibodies***

Antibodies are proteins that are produced by the immune system in response to a foreign substance, to help protect the body from infection and disease. Monoclonal antibodies are derived from a single antibody cell and are identical to that single cell (cloned 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 specifically directed toward a certain part of a system while leaving the other parts of the system untouched. This can be very desirable when trying to impact a structure as complex as the immune system. The name of all monoclonal antibodies ends with “mab” (standing for Monoclonal AntiBodies) including alemtuzumab (Lemtrada), ocrelizumab (Ocrevus), and natalizumab (Tysabri), which are already approved for MS. Several other monoclonal antibodies have shown promise in MS, and three of these are reviewed in this section.

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## **Rituxan® (rituximab)**

Company: Genentech and Biogen

- *Administered via IV infusion*
- *Being studied in both RRMS and SPMS*

Rituxan is a monoclonal antibody (CD20, from mouse tissue) 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.

In a 2018 retrospective study of almost 500 Swedish people with RRMS who were treated with a variety of disease-modifying therapies (DMTs), Rituxan demonstrated lower rates of clinical relapses and disease activity (as seen on neuroradiological imaging) than other injectable DMTs and Tecfidera. Rituxan’s

discontinuation rate, i.e., the proportion of people who stopped taking the medication due to side effects or other issues, was also considerably lower than that of the other injectable DMTs, Tecfidera, and Gilenya.<sup>42</sup>

Those findings add to the evidence on the role of Rituxan in MS that dates back more than a decade. A Phase II trial, completed in 2006, examined the effect of a single course of Rituxan treatment in RRMS, with two infusions of 1,000 mg each, administered two weeks apart, versus placebo. At 48 weeks, the number of active lesions was reduced by 91 percent and relapses were reduced by 58 percent, compared to a placebo group not taking any active medication. Twice as many people were taking the active medication versus those on placebo.

This medication was also tested in a study of 30 people with RRMS who had

experienced continued clinical activity despite treatment with one of the approved disease-modifying therapies. Participants received two doses of Rituxan, two weeks apart, while continuing to take their usual medication. Results showed that gadolinium-enhancing lesions were reduced after treatment with Rituxan: 74 percent of post-treatment MRI scans were free of gadolinium-enhancing activity as compared with 26 percent who were free of gadolinium-enhancing activity at baseline. Overall, an 88-percent reduction was seen in the average number of these lesions compared to baseline scans.

A Phase I/II double-blind study of 80 people with SPMS, sponsored by the National Institute of Neurologic Diseases and Stroke, tested a combination of intravenous (IV) and intrathecal (IT) - which is given directly into the spinal fluid - rituximab versus placebo (the RIVITaLISe study).<sup>43</sup> The study's authors hypothesized that this combination method of Rituxan administration would cause more complete destruction of B cells both in the blood and the spinal fluid. Theoretically, the addition of the IT medication could be more effective for individuals with progressive MS in which the immune cells provoking the continued attack may reside exclusively in the central nervous system, without circulating through the blood.

The study enrolled 27 patients but analyzed data in an interim analysis from 22 of the participants (14 on active drug and nine on placebo) who had received at least two doses of the drug. While the study had originally aimed to measure progression of brain atrophy after two years of treatment, it was terminated

early when the study authors did not find that the combination of IV and IT Rituxan was adequately decreasing B cells in the spinal fluid. Although multiple reasons might account for this finding (which includes that fact that lower doses of Rituxan were used in this study versus previous studies), this trial raises questions about rituximab's ability to decrease active inflammatory cells in the central nervous system. Additionally, the small size of the study group did not allow for a true analysis of clinical outcome measures.

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 Tysabri. 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.

At this point, it appears that Rituxan may not be further developed for use in MS given the availability of other monoclonal antibodies already having FDA approval for treating multiple sclerosis.

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## **Ofatumumab (also known as Arzerra®)**

Company: Novartis

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

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. Genmab, the pharmaceutical company that was developing this medication prior to Novartis, announced positive interim results for a Phase II safety and pharmacokinetics (how the body processes the drug) study of ofatumumab in 2010. This trial consisted of 38 participants with RRMS who were randomized to ofatumumab or placebo in a cross-over design. Statistically, the number of gadolinium-enhancing lesions and new or enlarging T2 lesions was significantly less in patients treated with ofatumumab compared to placebo in this 48-week study.

Results from MIRROR, a 12-week Phase II study comparing several doses of ofatumumab

in RRMS, were reported in 2014.<sup>44</sup> In the MIRROR study, 231 people with RRMS were assigned to one of four doses of ofatumumab or placebo. This “dose-ranging study” included doses of 3 mg every 12 weeks, 30 mg every 12 weeks, 60 mg every 12 weeks, and 60 mg every four weeks. After 12 weeks, the placebo group received 3 mg of ofatumumab. The study treatments were given for 24 weeks. The primary endpoint was suppression of MRI-lesion activity during the first 12 weeks. Results suggested a 90-percent or greater reduction in the active, enhancing lesions for all cumulative doses of ofatumumab 30 mg or greater.

Five serious adverse events were reported, all in the highest-dose treatment group. This study design allows for an “optimal dose” to be utilized in future studies of ofatumumab. The aim is to achieve suppression of MS-disease activity without completely eliminating B cells, with the intent of minimizing adverse events.

The MIRROR trial extension data presented in fall 2015 demonstrated continued suppression of new MRI lesions at Week 48 and a dose-responsive effect on B cells.<sup>45</sup> The success of these early trials prompted a Phase III study program with two trials in 2016. The trials, ASCLEPIOS I and II, are enrolling at least 900 patients each to study the effect of ofatumumab versus the FDA-approved oral medication, Aubagio® (teriflunomide). The trial time is 24 weeks plus an extension.

Ofatumumab is intriguing – not only because it is a unique but similar drug to Rituxan and Ocrevus – but because it also has an easier route of administration, as it is dosed subcutaneously every four weeks rather than via IV infusion.<sup>46</sup>

## **MCAA's Programs and Services**

MCAA provides many vital services to the MS community, including equipment, education, MRI assistance, Helpline consultation, and more! Please visit [mymsaa.org](http://mymsaa.org) for details.



## Ublituximab (also known as TG-1101)

Company: TG Therapeutics

- *Given via IV infusion; dosing to be determined*
- *Being studied in RMS*

Like Ocrevus, Rituxan, and ofatumumab, ublituximab targets the CD20 molecule in order 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. 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.<sup>47</sup>

The initial results of a 52-week, multi-center Phase II study of this medication were reported at the October 2017 JointECTRIMS-ACRIMS Meeting. The study was designed to assess the safety, tolerability, and optimal dose and infusion time of ublituximab. Participants were randomized to ublituximab or placebo for 28 days, receiving infusions on Day 1 and Day 15. Participants randomized to placebo then received ublituximab after the 28-day observational period and were followed for 52 weeks.<sup>47</sup>

The data pertained to 16 study participants up to Week 24 of the 52-week study. At Week 4, ublituximab-treated patients had 99-percent median B-cell depletion from baseline, with that depletion maintained to Week 24. During the first 24 weeks of the study, no participants reported relapses; 83 percent of participants had at least one relapse in the year prior to screening.<sup>47</sup>

No gadolinium-enhancing lesions were found on MRI in any of the participants at Week 24, and no serious adverse events or clinically significant laboratory abnormalities were reported. Ublituximab also was infused at a faster rate than that employed for other CD20-targeting agents, including infusing 450 mg of the medication in one hour, without an increased frequency of infusion-related reactions.<sup>47</sup>

In fall 2017, TG Therapeutics opened enrollment for two Phase III trials that will further evaluate the safety and efficacy of ublituximab. ULTIMATE I and ULTIMATE II are global, randomized, multi-center, double-blinded studies comparing ublituximab to Aubagio in people with relapsing forms of MS. Each trial will enroll roughly 440 individuals who will be randomized in a 1:1 ratio. The primary endpoint for both studies is the annualized relapse rate (ARR) following 96 weeks of treatment.<sup>48</sup>

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- For people with no health insurance or a high, unmet insurance deductible, the Fund will pay for an MRI through one of MSAA's contracted imaging centers
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To learn more and apply, please visit [mymsaa.org/mri](http://mymsaa.org/mri) or call (800) 532-7667, ext. 120.

## About S1P Receptor Modulators

Several investigational oral medications that are currently under study, work in a manner similar to Gilenya in that they also trap the immune cells in the lymph nodes so that they cannot get into the CNS to create lesions. It is hoped that these agents, which include siponimod (BAF312), ozanimod (RPC1063), and ponesimod, will maintain or potentially improve on the efficacy and safety of Gilenya. However, researchers continue to remain vigilant with regard to risks, including cardiovascular side effects such as bradycardia (slowed heart rate) and infections.

### Siponimod (BAF312)

Company: Novartis

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

Siponimod is a drug with a mechanism of action similar to Gilenya. Like Gilenya, it works at the S1P receptor family to block the movement of lymph cells from lymph nodes; however, siponimod appears to interact with fewer of the receptors than Gilenya does - with its primary actions at the S1P1 and the S1P5 receptors. Siponimod has a relatively short half-life compared to Gilenya, which means that the drug does not stay in the body as long. Researchers hope that these small differences will minimize cardiac issues.

EXPAND, a Phase III, multi-national study of siponimod involving more than 1,600 people with secondary-progressive MS, was published in *The Lancet* in March 2018. The participants were randomized in a 2:1 ratio to receive siponimod or placebo. The trial was scheduled to run for three years or until a pre-specified number of confirmed disability progression events (CDP) occurred. The primary endpoint was time to three-month CDP.<sup>1</sup>

The study found that, relative to placebo, siponimod reduced the risk of three-month CDP by 21 percent, cut the risk of six-month CDP by 26 percent, slowed the rate of brain volume loss by 23 percent, and reduced the annual relapse rate by 55 percent. No significant difference was found between siponimod and placebo in terms of two walking tests studied in the trial. Eighteen percent of patients in the siponimod group and 15 percent of those receiving placebo experienced serious adverse events. 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 occurred more often in patients receiving siponimod than in those in the placebo group. The rate of infections, cancer, and death did not differ between the groups, and adjusting the initial dose of siponimod mitigated cardiac effects seen in early treatment with the medication.<sup>1</sup>

Novartis, which is developing siponimod, announced that it will file a New Drug Application (NDA) with the FDA in 2018, seeking approval for use of the S1P receptor modulator in SPMS.

In RRMS, meanwhile, results from a Phase II dose-finding study of siponimod were first reported in 2012. The trial had a complex design, with the primary goal to determine the most appropriate dose to carry forward into future trials. Approximately 300 people participated in the study. At six months, the proportion of relapse-free patients was 84 percent for the 10-mg group, 92 percent for

the 2-mg group, and 77 percent for the 0.5-mg group, as compared to 72 percent in the placebo group. After six months, the ARR (annualized relapse rate) was lower for the individuals who were taking one of the three higher doses. Additionally, regarding MRI parameters, the 2 mg dose reached statistical significance versus placebo, with a reduction in active lesions of approximately 80 percent.

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## Ozanimod (formerly RPC1063)

Company: Celgene

- *Oral medication studied at several doses*
- *Being studied in RRMS*

Ozanimod (RPC1063) is a selective modulator of two types of S1P receptors: S1P1 and S1P5. It is given as a once-daily pill, and was studied in a trial called RADIANCE, where this experimental medicine was compared at two different doses with placebo. A total of 258 individuals with RRMS were studied in this trial, which began with a seven-day gradual titration of ozanimod up to the full dose under investigation. (Titration refers to starting with a lower dose and gradually increasing the dose until the full dose is reached. This helps to 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, patients 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 (inflammation of the nasal passages and upper part of the throat) and headache. However, both of these events were reported more commonly in placebo-treated individuals compared with ozanimod-treated participants. Notably, no serious cardiac events, infections, or episodes of macular edema were reported in the subjects receiving ozanimod. (Macular edema is a swelling behind the eye, which is a potential risk for individuals who take Gilenya.)<sup>49</sup>

In February 2016, the 72-week extension data of the RADIANCE trial were released. These showed a continued reduction in relapses and gadolinium-enhancing lesions for those individuals who remained on ozanimod, with all 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.

This medication was then evaluated in two larger, Phase III trials that compared its efficacy

## EXPERIMENTAL MEDICATIONS: NEW S1P RECEPTOR MODULATORS

against Avonex® (interferon beta-1a). The first trial, SUNBEAM, enrolled more than 1,300 people with RMS in 20 countries who were followed for at least 12 months. The second trial, RADIANCE Part B, enrolled 1,320 individuals with RMS over two years. Both studies assessed 1 mg and 0.5 mg of ozanimod compared with Avonex. Results from the two studies were announced in late October 2017 at MSParis2017, the 7th JointECTRIMS-ACTRIMS Meeting.

The SUNBEAM study showed a significant reduction in the annualized relapse rate (ARR) for both the 1-mg and 0.5-mg doses of ozanimod over an average of 13.6 months of treatment. Both doses of ozanimod also demonstrated a significant reduction in new or enlarging T2 lesions and gadolinium-enhanced MRI lesions over one year compared to Avonex. Further, at one year, whole-brain volume loss - which is associated with MS progression - was reduced by one-third with the 1-mg dose of ozanimod and by 12 percent with the 0.5-mg dose compared with Avonex.<sup>50</sup>

In SUNBEAM, 75 percent of patients receiving Avonex and just under 60 percent receiving ozanimod reported an adverse event related to treatment. Among individuals receiving ozanimod, the most common adverse events reported were nasopharyngitis, headache, and upper respiratory infection. The incidences of serious adverse events were 2.9 percent for patients receiving 1 mg of ozanimod, 3.5 percent for those taking 0.5 mg of ozanimod, and 2.5 percent for study participants receiving Avonex.<sup>50</sup>

The results of the two-year RADIANCE Part

B study were similar to those of the one-year SUNBEAM trial. Individuals receiving ozanimod saw a significant reduction in annualized relapse rate (ARR) compared to individuals receiving Avonex. Those rates were 0.17 for people taking 1 mg of ozanimod, 0.22 for those on 0.5 mg of ozanimod, and 0.28 for individuals receiving interferon. Ozanimod-treated individuals also had a significant reduction in new or enlarging T2 lesions and gadolinium-enhanced MRI compared with those in the Avonex arm of the study. Additionally, a reduction in brain-volume loss (BVL) was seen for both ozanimod doses relative to interferon. Whole BVL was reduced by 27 percent with the 1-mg dose of ozanimod and by 25 percent in the 0.5-mg group versus Avonex.<sup>51</sup>

Eighty-three percent of study participants receiving Avonex reported an adverse event related to treatment, compared with 75 percent of patients on ozanimod 1-mg and 74 percent of those on ozanimod 0.5-mg. Most of the adverse events were mild. The most common were nasopharyngitis, headache, increased liver enzymes, flu-like symptoms, high blood pressure, pharyngitis, and urinary tract infection. Serious adverse effects were experienced by 6.5 percent of the participants taking ozanimod 1 mg, 7.1 percent of individuals on ozanimod 0.5 mg, and 6.4 percent of those receiving Avonex.<sup>51</sup>

At the outset of the studies, investigators planned (or “pre-specified”) a pooled analysis of the SUNBEAM and RADIANCE Part B studies to assess outcomes, including confirmed disability progression (CDP). In this pooled analysis, ozanimod did not reach

statistical significance compared with Avonex in the time to three-month confirmed disability progression. This may, however, reflect the fact that a very low rate of disability progression was present in all three of the treatment groups, which could make statistically significant differences difficult to emerge. For example, in SUNBEAM, the number of patients with three-month confirmed disability progression by the end of the study was 13 (2.9 percent) in the ozanimod 1-mg group, 17 (3.8 percent) in the ozanimod 0.5-mg group, and 19 (4.2 percent) in the Avonex group.<sup>51</sup>

On the basis of those study results, Celgene submitted a New Drug Application (NDA) to the FDA for use of ozanimod in treating patients with relapsing forms of MS. In late February 2018, however, the FDA declined to accept the NDA, saying that the nonclinical and clinical pharmacology sections of the NDA were insufficient to allow a complete review of the application. In response to that “Refusal to File” letter from the FDA, Celgene expressed its confidence in ozanimod and said it would work with the FDA to address any outstanding items.<sup>52</sup>

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## Ponesimod

Company: Actelion

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

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

However, the 40-mg dose generated an increase in adverse events, which included swelling of the extremities and difficulty breathing. With an 83-percent decrease in gadolinium-enhancing lesions and a favorable adverse event profile, the 20-mg dose may have the best benefit-to-risk profile.

The company developing ponesimod, Actelion, further studied the efficacy and safety of the 10-mg and 20-mg doses in an extension of the Phase II trial. In October 2017, researchers presented an interim analysis of the extension trial’s findings at theECTRIMS-ACRIMS Meeting. They found that over the course of six years, the 20-mg dose reduced the risk of six-month confirmed disability accumulation (6 m-CDA) by about twice the extent seen with the 10-mg dose. Similarly, the annual relapse rate for the 20-mg dose was about one-half that of the 10-mg dose (0.153 vs. 0.227). The 20-mg dose also had more favorable findings on several MRI measures, including mean number of T1 gadolinium-enhancing lesions and new or enlarging T2 lesions per study subject. Meanwhile, the percentages of patients experiencing any adverse event, serious adverse events, and adverse events leading to treatment discontinuation, were largely similar between

## EXPERIMENTAL MEDICATIONS: NEW S1P RECEPTOR MODULATORS

the two arms. For example, 15.1 percent of patients receiving 20 mg of ponesimod and 13.8 percent receiving the 10-mg dose had serious adverse events, while 12.2 percent of individuals in the 20-mg dose group and 10.3 percent of those receiving the 10-mg dose stopped treatment because of adverse events. <sup>53</sup>

These data suggest that the 20-mg dose may offer greater efficacy than the 10-mg dose with a comparable rate of adverse events, further refining the benefit-to-risk considerations for use of ponesimod.

The role of ponesimod in RRMS is being further evaluated in two ongoing trials, OPTIMUM and POINT. OPTIMUM is a multicenter, randomized, double-blind study

comparing the efficacy and safety of ponesimod to Aubagio. <sup>54</sup> The study aims to determine whether ponesimod is more effective than Aubagio in reducing relapses. The study seeks to enroll approximately 1,100 subjects, randomized in two groups in a 1:1 ratio to receive ponesimod at 20 mg per day or Aubagio at 14 mg per day. <sup>55</sup>

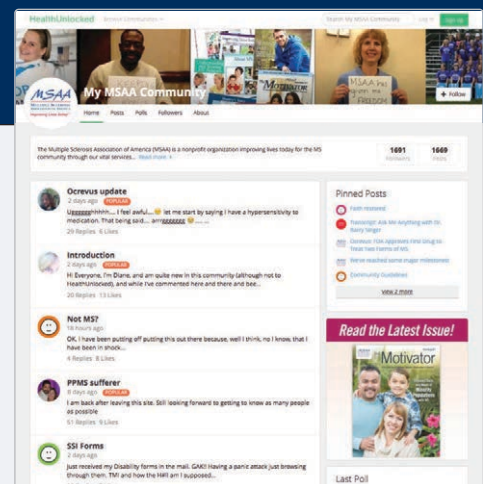
The POINT (POnesImod aNd Tecfidera) study employs a combination approach; 600 participants will be randomized either to Tecfidera alone or Tecfidera plus ponesimod to assess whether there is an added benefit in terms of disease control when the two medications are combined. The POINT study is the largest study in MS looking at a combination of oral medications.

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## Ibudilast

Company: MediciNova

- *Oral medication taken twice daily*
- *Being studied in progressive MS*

Ibudilast (MN-166) is an oral medication with novel immune-modulating and potential neuroprotective properties that is being studied in progressive forms of MS. This experimental medication has also been studied in a range of conditions, including chronic pain, headache, and methamphetamine-dependent addiction.

Based on early MS-trial evidence that ibudilast had a primary, neuroprotective role, independent from a substantial effect on overt inflammation, the **Phase II Secondary and Primary Progressive MS Ibudilast NeuroNEXT trial (SPRINT-MS)** was launched in fall 2013 at 28 enrolling clinical sites across the United States. More than 250 individuals with PPMS or SPMS were enrolled and randomized to ibudilast or placebo in a 1:1 ratio. The trial focused primarily on how the twice-daily administration of ibudilast affected whole-brain atrophy at 96 weeks, and on the safety and tolerability of the medication.

In October 2017, researchers announced that ibudilast reduced the rate of whole-brain atrophy by 48 percent compared to placebo and also demonstrated a favorable safety and tolerability profile. Individuals receiving ibudilast did not have an increased rate of serious adverse events compared to those receiving placebo, and there were no opportunistic infections, heart attacks, strokes, cancers, or deaths related to ibudilast use.

In February 2018, SPRINT-MS investigators reported that ibudilast also reduced confirmed disability progression by 26 percent compared to placebo. MediciNova, the company developing ibudilast, announced in February that on the basis of these results, it is examining a Phase III trial with approximately 700 participants to validate the efficacy of ibudilast in reducing confirmed disability progression.<sup>4</sup>

Ibudilast has received Fast Track designation from the FDA. This designation is intended for drugs under development for treating serious diseases and with the potential to address unmet medical needs for such diseases. According to the FDA, Fast Track designation for a medication makes it eligible for things such as more frequent communications with the FDA, priority review, and the potential for accelerated approval.

## Masitinib (also known as Kinavet® and Masivet®)

Company: AB Science

Masitinib is termed a protein-kinase inhibitor. It selectively inhibits molecules (kinases) that play a major role in the activation of mast cells. Although mast cells are best known for their role in allergies, they are also involved in the immune response, in the recruitment of lymphocytes to the brain, and also in inflammatory processes associated with MS. As noted earlier, lymphocytes are immune-system cells produced to fight infection and disease. Additionally, lymphocytes can initiate myelin damage.

## EXPERIMENTAL MEDICATIONS: OTHER THERAPEUTIC STRATEGIES

Masitinib has a role in veterinary medicine (it is used to fight mast cell tumors in dogs) and is being studied for several human indications, including cancers and degenerative diseases. A small Phase II trial of masitinib in progressive forms of MS showed a trend toward benefit; however, the results were not statistically significant.

A double-blind, randomized, placebo-controlled trial with more than 650 patients currently is assessing the safety and efficacy of masitinib in PPMS or SPMS without relapses. The primary endpoint is the change during the course of 96 weeks in EDSS, which measures disability in MS, including changes in disability over time.

In January 2018, AB Science announced that a planned interim analysis was performed after half of the trial's participants had completed 96 weeks of treatment. The analysis was conducted to assess, among other things, whether the trial had an adequate number of patients to address the question it is studying and whether the data obtained so far warrant continuing the trial. An Independent Data Safety Monitoring Committee (IDMC) reviewing the available data recommended that the trial continue without any change to the "sample size," or number of participants. Based on the protocol developed for the trial, this indicates that the data available so far suggest that the predictive probability of success of the study with the current sample size is more than 80 percent. This is a hopeful sign that builds anticipation for the release of final study results, which are expected in the first half of 2019.<sup>56</sup>

### **Tetracycline Antibiotics**

The tetracycline antibiotics, including minocycline and doxycycline, have immunomodulatory and neuroprotective activities. They appear to decrease the passage of lymphocytes across the blood-brain barrier. In 2009, a small double-blind, placebo-controlled Phase II trial of Copaxone plus minocycline showed favorable MRI data, with minocycline decreasing gadolinium-enhancing activity by 50 percent during a period of six months. A subsequent 24-month trial showed a significant decrease in lesion activity and clinical status.

A larger study called RECYCLINE enrolled 305 individuals with RRMS and used minocycline as an add-on to Rebif in people with RRMS. Data were presented atECTRIMS in 2012, and disappointingly, minocycline did not provide significant improvement to either clinical or MRI outcomes.

Another Phase III trial conducted at 12 centers across Canada enrolled 142 people with a clinically isolated syndrome (CIS). The participants were randomized to oral minocycline at 100 mg twice daily or placebo. The primary endpoint of the study was conversion to multiple sclerosis within six months of randomization. Treatment was continued for up to two years, or until MS was confirmed. The risk for conversion to multiple sclerosis within six months after randomization was 33.4 percent in the minocycline group versus 61 percent in the placebo group, meaning that the antibiotic reduced the risk by almost one-half.

In analyzing the data, based on how many gadolinium-enhancing lesions the participants



had on MRI at the start of the study, minocycline use still was associated with risk of conversion to MS at the six-month mark, but not by as great of a degree. At 24 months, no significant difference was seen between minocycline and placebo in terms of risk of conversion. Similarly, several MRI measures that were secondary outcomes of the study favored minocycline at six months, but not at 24 months. The rate of adverse events was higher among patients receiving minocycline than those on placebo (86.1 percent versus 61.4 percent), with hyperpigmentation, rash, nausea, dental discoloration, and dizziness found to be among the adverse effects experienced more often by individuals receiving the antibiotic. While the ultimate goal of treating CIS is to prevent conversion to MS, delaying conversion represents an important intermediate step toward that goal.<sup>57</sup>

## Statins

Statins are oral medications that are most commonly prescribed to lower cholesterol. Current interest is based on a non-controlled observational study (a study without a placebo group), suggesting that the risk of developing new brain lesions was reduced by about half in people with early forms of MS who were taking Lipitor® (atorvastatin). However, a three-year Danish study of individuals with RRMS failed to find any beneficial effect for simvastatin as an add-on therapy to Avonex. The use of statins to lower cholesterol in people taking interferons should be discussed with a healthcare professional to consider the

potential benefits versus risks.

Chataway and colleagues published the results of the MS-STAT trial in 2014. This Phase II study evaluated whether high-dose simvastatin could slow the rate of whole-brain atrophy, disability, or both, in 140 patients with SPMS. The trial showed that daily treatment with 80 mg of simvastatin was associated with a statistically significant benefit compared to placebo on the Expanded Disability Status Scale (EDSS) at two years. The rate of brain atrophy also was decreased in people receiving simvastatin.

Researchers then evaluated how simvastatin treatment affected other aspects of SPMS. These secondary analyses showed that the statin had a positive effect on the functioning of the brain's frontal lobe and on health-related quality of life, but did not show a benefit relative to placebo in terms of preserving or slowing the rate of decline of verbal and non-verbal memory.<sup>58</sup>

The initial results and subsequent analyses from the Phase II MS-STAT trial suggest the value of conducting larger studies of statins and their impact on clinical outcomes in SPMS. A Phase III trial, MS-STAT2, will further test the benefits of simvastatin for people with SPMS. This is an exciting area for further inquiry because of the need for effective treatments for this form of the disease.

## Managing MS Symptoms

To learn about common symptoms, management strategies, and medications, please visit [mymsaa.org/symptoms](http://mymsaa.org/symptoms).

## ***About New Therapies under Investigation***

The earlier listing of approved and experimental drugs is only a fraction of the many treatments currently being studied. Some of the following are among the most exciting potential therapies under investigation. These very brief snapshots of highly technical concepts will warrant more in-depth explanations in the future, if early clinical trials are encouraging.

**Anti-LINGO (opicinumab):** LINGO-1 is a protein in the central nervous system whose role is to halt myelination and prevent the survival of neurons. Although it may seem counterintuitive for the body to create a protein with this function, in a healthy individual it performs an important job. All of the cells that make up the organs in the body receive “instructions” regarding when to grow and when to cease growing. Without these sorts of cellular “checks and balances,” tissues could grow without restraint, as seen in some cancers. Anti-LINGO-1 (BIIB033) is an experimental medication with potential remyelinating properties, after animal studies showed that it blocks LINGO-1 from stopping the growth of myelin. It has been shown to promote spinal cord remyelination and axonal integrity in the animal model of MS (EAE).

Initial Phase I trials of anti-LINGO, involving 64 healthy adult volunteers and 42 people with RMS or SPMS, reported that the drug was well-tolerated, with no serious adverse events. Headache was the most frequent side effect reported.

The first Phase II trial of anti-LINGO reported successful results in 2015.<sup>59</sup> The study recruited individuals with newly-diagnosed MS involving the visual pathways (optic neuritis) to evaluate the medication’s

effect on remyelination. The primary outcome of RENEW was an assessment of recovery of optic-nerve function measured by the speed at which the nerve conducts visual signals. This was studied by evaluating a test called Full Field Visual Evoked Potential (FF-VEP) in participants treated with anti-LINGO-1, compared with placebo.

Individuals who were treated with at least five of the six doses of anti-LINGO-1 showed a 34-percent improvement in optic-nerve conduction latency (delay in the speed of the visual signal) at Week 24, compared with placebo. Further recovery in optic-nerve conduction was observed at the last study visit (Week 32), with a statistically significant 41-percent improvement. Together, the data demonstrate evidence of treatment effect with continuous improvement observed 12 weeks following the last study dose.

However, the study showed no effect on secondary endpoints, including change in the thickness of the retinal layers (optic nerve neurons and axons), or on visual function. Anti-LINGO-1 was generally well-tolerated in this study. Two participants had hypersensitivity (allergic) reactions at the time of infusion, and one patient had liver-function test abnormalities, which resolved after drug discontinuation. Taken together, these results

provided an encouraging indication that anti-LINGO-1 is safe and may facilitate remyelination.

To that end, a second, larger Phase II trial (SYNERGY) was conducted, although Biogen announced in mid-2016 that the SYNERGY trial was not successful. The study involved more than 400 people with either RRMS or SPMS. Participants were randomized to one of five groups; four groups were given Anti-LINGO in different doses (3 mg, 10 mg, 30 mg, and 100 mg) plus Avonex, and the fifth group was given Avonex plus placebo. SYNERGY aimed to see whether the addition of anti-LINGO to Avonex could lead to an improvement in disability scores when compared to Avonex alone.

Unfortunately, at the end of the 72-week study, no statistical difference was seen between the people on Anti-LINGO and those on placebo. There did seem to be some indication of a response in those participants who were under 40, those with RRMS, and those with MS for less than eight years in the low-to-mid dosing range.

A post-hoc analysis of the SYNERGY data examined whether any factors could predict which individuals with RRMS would have a greater and more enduring response to anti-LINGO than that seen in the overall study population. Researchers looked at nine demographic/clinical characteristics and 13 MRI findings. They found that three characteristics – shorter disease duration ( $\leq 20$  years), lower baseline magnetization transfer ratio in T2 lesions (an MRI finding that may indicate lower myelin content in the lesions), and lower baseline values for diffusion tensor

imaging – radial diffusivity (DTI-RD, an MRI finding that may indicate greater structural integrity) were predictive of a greater and longer-lasting treatment effect.<sup>60</sup>

Those findings helped inform the design of the Phase II AFFINITY trial, which was initiated in 2017. The multi-center trial seeks to evaluate the efficacy and safety of anti-LINGO (opicinumab) as an add-on therapy to interferon beta-1a. Investigators are recruiting 240 people with RMS who are adequately controlled on their interferon beta-1a therapy. The study's primary endpoint is Overall Response Score (ORS), a measure of improvement and worsening of disability over time. AFFINITY investigators note that analysis of the SYNERGY results enabled them to take a more precise biological approach in evaluating opicinumab in their trial. They also noted that the MRI findings, which were predictive of a response in SYNERGY, suggest the possibility for repairing MS lesions through remyelination.<sup>61</sup>

In addition to anti-LINGO, other experimental treatments are under investigation to potentially foster remyelination or myelin repair. These include medications that are in very early stages of development.

**Amiloride, Phenytoin, and Sodium Channel Blockade:** The accumulation of salt and potassium within the cells of MS lesions may contribute to cellular injury and neurodegeneration (the breakdown of nerves). This hypothesis would suggest that by blocking channels that facilitate salt and potassium entering these cells, the buildup of these molecules can be prevented, and with

## EXPERIMENTAL MEDICATIONS: NEW THERAPIES UNDER INVESTIGATION

that idea in mind, neurodegeneration might also be prevented.

This strategy was tested in a study of 14 people with primary-progressive MS (PPMS) who received amiloride – a diuretic approved for the treatment of high blood pressure and congestive heart failure. The study used MRI scans of the brain to examine whether the potassium-sparing activity of amiloride might have a neuroprotective effect. Patients received the standard dose of amiloride given to treat high blood pressure for three years.

In 2013, the researchers reported a significant reduction in the development of brain atrophy, as well as a slowing of the development of disability, during the treatment phase in this small group of participants. These findings suggest that amiloride may exert neuroprotective effects. However, because amiloride does not readily cross the blood-brain barrier to gain access to the CNS, the precise mechanism underlying these results is not clear. This pilot study was the first evaluation of the potential neuroprotective effects of amiloride in MS, and its results show that the agent warrants further investigation.

Amiloride is also being studied in the MS-SMART trial, an ongoing study comprised of 440 individuals with SPMS who have been randomized to four different arms: amiloride, Rilutek® (riluzole), Prozac® (fluoxetine), and placebo. Participants will be followed for 96 weeks. The main study measure is a comparison between the treatment arms and the placebo group in the rate of brain atrophy. This study, which is expected to be completed in 2018, is intriguing because it is

simultaneously looking at multiple safe, currently available medications that may lead to neuroprotection. Furthermore, MS-SMART has employed an interesting trial design in that it has a shared-placebo group. This efficient design avoids the need for three similar trials to be conducted separately.

While studies of amiloride in MS focus on potassium channels, research involving the anti-seizure medication phenytoin (brand name Dilantin®) focuses on sodium channels. A Phase II clinical trial assessed whether phenytoin, which modulates sodium channels, could be neuroprotective in acute optic neuritis (AON). The study was comprised of 86 people with AON randomized within two weeks of symptom onset to receive either phenytoin (4 mg per kg daily) or placebo for three months. The primary outcome of the study was an evaluation of the structure of the retinal nerve fiber layer (RNFL) and macular volume (MV) at six months. Visual function, optic-nerve imaging, and visual-evoked potentials were also measured.<sup>62</sup>

Of the original 86 participants, 81 were followed to study end. In these people, the average adjusted affected eye RNFL thickness at six months was higher in the active group versus placebo, resulting in a 30-percent protective-treatment effect. Adjusted MV (macular volume) showed a 34-percent protective-treatment effect. Vision generally recovered well, with no significant difference in visual outcomes between the treatment groups.

A follow-on study involving a subgroup of participants employed MRI to evaluate how phenytoin affected the tissue microstructure of

the optic nerve. The study looked at the measured optic nerve magnetization transfer ratio – a possible marker of neuroprotection. The study found that phenytoin appeared to have a beneficial impact on the tissue microstructure of the optic nerve following optic neuritis, but with varying impact in different sections of the nerve – based on their location relative to the lesion that caused the optic neuritis.<sup>63</sup>

This intriguing research into phenytoin may have broad implications, as it found that the administration of a well-known, relatively safe drug seemed to be neuro-protective in the period directly following optic neuritis. Both amiloride and phenytoin may also represent potential combination strategies in conjunction with immune-modulating, disease-modifying therapies.

**Clemastine** is an older anti-histamine that is available over the counter. It was discovered to hold potential for remyelination through the innovative laboratory work of a researcher in San Francisco. This finding led to a small Phase II placebo-controlled crossover study (participants were initially assigned to one study group and then switched midway through the study) of high doses of clemastine in individuals with evidence of damage to the optic nerve. Researchers reported that while on treatment, participants experienced a significant improvement in the transmission of the signal in the optic nerve and showed a trend toward improved visual function. Overall, the treatment was safe, although participants' fatigue scores worsened. This medication is an attractive option to researchers and clinicians given its availability

and favorable safety profile. However, it remains to be seen if it can truly work to bring about clinical improvement through remyelination.<sup>5</sup>

**Idebenone:** This medication, similar to coenzyme Q10, initially was developed to treat Alzheimer's disease and other cognitive defects. Coenzyme Q10 is produced within one's own body and is necessary for cells to grow and remain healthy. This substance also works as an antioxidant, helping to prevent injury from the oxidation process. It is being explored in MS because oxidative stress has been postulated to play a role in the death of myelin-producing cells, which has been linked to MS progression.

Oxidation is the body's natural metabolism of oxygen. When disturbances occur in this process, "oxidative stress" can result, causing damage to the body's cells and tissues. Oxidative stress is believed to be a contributing factor in many diseases, including those affecting the nerves and the immune system.

A double-blind, placebo-controlled, Phase I/II clinical trial of idebenone, sponsored by the National Institute of Neurological Disorders and Stroke (NINDS), recruited 77 individuals with PPMS who had little to moderate disability. Study participants were randomized in a 1:1 ratio, and after a one-year observational pre-treatment phase, received either 2,250 mg of idebenone daily or placebo for two years. The study's primary endpoint was change in the CombiWISE, a rating scale developed by NINDS researchers.

In March 2018, the Swiss company developing idebenone announced that while

## EXPERIMENTAL MEDICATIONS: NEW THERAPIES UNDER INVESTIGATION

the trial showed that the medication was well tolerated, topline results showed no difference between idebenone and placebo in terms of the CombiWISE scale, changes in the volume of the brain's ventricles, or other clinical assessments or biomarkers.<sup>64</sup> Those findings constitute another disappointment in the effort to develop additional disease-modifying therapies for PPMS.

**MIS416:** This “therapeutic vaccine” is a potent activator of the innate immune system, which provides immediate defense against infection, but does not result in long-lasting or protective immunity. As a side note to help explain this type of immune-system defense, the “innate” or “natural” immune response is nonspecific. It does not have any type of memory, and reacts in the same way each time it encounters a foreign entity, such as a virus or bacteria. MIS416 has been tested primarily in cancer and acquired infections, with the goal of enhancing the inherent capability of a person's immune system to fight disease.

A Phase I/II study to evaluate the safety and tolerability of IV-administered MIS416 in people with either PPMS or SPMS reported positive results. As a result, the Australian company developing the agent, Innate Immunotherapies, initiated a Phase IIB trial in which 93 people with SPMS were randomized in a 2:1 ratio to receive either MIS416 or saline placebo intravenously once weekly for a year. In June

2017, Innate Immunotherapies announced that an initial analysis of trial data showed no clinically meaningful or statistically significant difference between MIS416 and placebo across several measures of neuromuscular function or patient-reported outcomes. The company said it would further analyze the results to see if a subgroup of patients derived significant benefit from MIS416.<sup>65</sup>

These results are disappointing given the recent progress in leveraging immunotherapies to enhance the body's ability to fight a variety of blood-system and solid-tumor cancers. Hopefully, these advances in oncology will soon have parallels in the treatment of MS.

**ATL1102** is an oral medication that affects the VLA-4 system, the same molecular mechanism utilized by Tysabri. It does so via a novel mechanism of action, and falls into a class of “antisense oligonucleotides” not previously used in MS. The results of a Phase II trial were published in 2014, noting that ATL1102 decreased the emergence of new active brain lesions as compared with placebo, after only two months of treatment in approximately 70 individuals with RRMS. In October 2017, Antisense Therapeutics – the Australian company developing ATL1102 – announced that after consultations with the FDA, plans were under way for a Phase IIB study of the medication at a 25 mg/week dose for six months. The company added that it would talk further with the FDA regarding criteria for testing higher doses of the medication in people with MS and about the safety monitoring that would be employed in following individuals on higher doses.<sup>66</sup>

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## Vitamins and Electrolytes

### Vitamin D3

Vitamin D is a type of hormone and a powerful mediator of immune function. The data documenting an association between low Vitamin D and high MS risk, relapses, disability, and CNS inflammation now appear to be strong, consistent, and reproducible. Data from a number of areas of investigation suggest that Vitamin D may be one underlying common factor that begins to make sense of the large amount of data on the geographic distribution of susceptibility to MS.

Genetically, a link appears to exist between changes in the genes involved in the synthesis of the Vitamin D hormone and the Vitamin D hormone receptor, and the risk of developing MS. The strongest genetic risk factor for MS is a specific gene (HLA DRB1\*1501), whose activity appears to be influenced by Vitamin D. A study published in 2015 by Mowry and colleagues provided new insights about genetics and Vitamin D. This study identified four genetic variants, each correlated to a lower Vitamin D level. Using these variants and data obtained from the largest genetic association study to date of MS, conducted by the International Multiple Sclerosis Genetics Consortium, the authors found a direct relationship between the number of Vitamin D-lowering variants that individuals had and their risk for developing MS.

An important longitudinal cohort study presented in 2012 by Mowry and colleagues found that in people with MS, each 10 ng/ml higher Vitamin D level was associated with a 15-percent lower risk of a new T2 lesion, and a

32-percent lower risk of a gadolinium-enhancing lesion. Higher Vitamin D levels were associated with lower, but not statistically significant, relapse rates. While this was not a randomized treatment trial, it suggests that higher levels of Vitamin D may exert a protective role against MS disease activity.

Similar data were presented in 2013, as researchers looked at how Vitamin D may play a role in MS development and disease activity on a molecular level. The BENEFIT trial studied the effects of Betaseron in patients with CIS. Blood samples were taken at various intervals, along with MRIs. This study found that individuals with higher Vitamin D levels had lower numbers of gadolinium-enhancing lesions. These individuals generally experienced less disease activity, and genes associated with these higher Vitamin D levels appear to be involved. Studies indicate that roughly 350 genes are “significantly associated” with MS activity, and of these 350 genes, 155 are associated with Vitamin D regulation. The authors of this study explain that Vitamin D may directly and indirectly regulate gene expression in a manner that reduces MS activity.

Meanwhile, the SOLAR study randomized 229 individuals who were on high-dose interferon beta-1a therapy either to high-dose Vitamin D3 (14,000 IU daily) or placebo. Originally, the study was planned to be 96 weeks, but because of challenges with recruitment, the study was 48 weeks. The primary endpoint of the study was disease-activity-free (DAF) status at week 48. DAF was defined as having no relapses, no new MRI lesions, and no worsening of disability.

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This study did not find a difference in DAF status between the high-dose vitamin D3 group and the placebo group. While no difference was seen in the relapse rate, a 32-percent decrease was found in the number of new lesions in the Vitamin D3 group versus the placebo group. It is possible that the small study size precluded more significant results. The finding of a decrease in new lesion formation in the Vitamin D3 group is intriguing and deserves further study. However, as evidenced by the SOLAR study, in order to definitively answer the question of whether Vitamin D3 has a protective role in MS, it will be critical to design studies that are large enough and able to obtain full recruitment.

The French CHOLINE Phase II study recruited 250 individuals with RRMS who were already receiving ongoing treatment with Rebif. The aim of this study was to evaluate the efficacy and safety of supplementary treatment with Vitamin D3 in people with RRMS treated with Rebif.

The study participants were divided into two groups: one receiving Vitamin D3 100,000 IU twice monthly along with Rebif treatment, and the other group receiving placebo along with Rebif treatment. Its primary outcome measure is a reduction in relapse rate. Secondary outcome measures include: the time to a first documented relapse; the mean number of relapses per subject per year; the number of relapse-free individuals after two years of treatment; MRI measures of progression and lesion load; and change in quality of life.

The CHOLINE study began in January 2010 and was completed in 2015, but results

have not been reported. Mowry and colleagues at Johns Hopkins are currently running a multi-center clinical trial in which people with relapsing-remitting MS will receive high-dose (5,000 IU/day) or low-dose (600 IU/day) oral Vitamin D, in addition to Copaxone.<sup>67</sup>

Participants will be evaluated for two years, and the effect of high-dose Vitamin D supplementation on the rate of MS attacks as well as on the number of new lesions and changes in brain volume on MRI will be determined. This trial is ongoing.

One trial of particular interest that is currently running in Australia and New Zealand, PrevANZ, is a Phase II study looking at whether Vitamin D supplementation can decrease a person's risk for developing MS after a first demyelinating event (CIS). Although the associations between MS and Vitamin D deficiency have been well-documented, it is still not clear if giving a patient Vitamin D supplementation can actually impact the course of the condition.

Another study, reported at theECTRIMS-ACTRIMS Meeting in 2017, followed 200 individuals with MS during a period of 12 months. The study assessed how Vitamin D levels affected quality of life as measured by a standardized questionnaire developed specifically for people with MS. At baseline, 92 percent of the participants had a Vitamin D level at or below 30 ng/mL, and so were given supplements to raise those levels. The study found that increasing Vitamin D levels was associated with significant improvement in self-reported quality of life across all areas measured by the questionnaire.<sup>68</sup>



Although no major safety issues have been reported with these larger daily doses of Vitamin D3 (such as 5,000 to 10,000 IU/day), as with all medications and supplements, individuals should consult their physician before making any changes to their treatment plan.

### **Lipoic Acid**

A pilot trial of lipoic acid supplementation reported a positive result in SPMS in 2016. Researchers from Oregon conducted a two-year study that followed 27 individuals with MS who were given lipoic acid, and 24 patients who were given placebo. Lipoic acid is a readily available antioxidant supplement thought to aid the function of mitochondria, which are cell structures that break down nutrients to create energy.

After 96 weeks, the researchers found that the participants in the lipoic acid group had significantly less brain-volume loss and were able to walk faster than the placebo group. Overall, the drug was well-tolerated, though stomach symptoms were higher in the lipoic acid group. Two patients in the lipoic acid group had kidney issues during the trial, however, a kidney doctor thought this was unrelated to the lipoic acid treatment.<sup>69</sup>

Accelerated brain-volume loss has been linked to worsening in progressive MS. The findings of this trial suggest that lipoic acid may offer neuro-protection by slowing down this process. Larger studies will have to be completed to see whether lipoic acid works, not only to slow down brain loss as seen on MRI, but also to slow down the clinical progression of MS.

### **Biotin (MD1003)**

Biotin is a vitamin involved in key steps of energy metabolism and fatty acid synthesis, though most people think of it as being “good for hair and nails.” Among other actions, biotin activates an enzyme in myelin synthesis. Using this hypothesis and building upon data from a small, open-label pilot study, MD1003, a high-dose biotin preparation of 300 mg per day, was studied in a Phase III trial of individuals diagnosed with SPMS or PPMS. (This dose is hundreds of times higher than what can typically be purchased as a supplement of this vitamin.) In a relatively small study, 154 individuals were randomized to high-dose biotin or placebo.

The primary endpoint of the study was defined as the proportion of participants who improved at nine months, with a confirmation of the improvement at 12 months. Improvement was defined as either a decrease in EDSS (Expanded Disability Status Scale) or an improvement in T25FW (timed 25-foot walk) of at least 20 percent.

The primary endpoint was met, with 12.6 percent of participants in the MD1003 arm showing an improvement of EDSS or T25FW at nine months and confirmed at 12 months, compared to none of the people in the placebo arm. The primary endpoint was supported by secondary analyses showing evidence for a decrease in the risk of disease progression. These numbers were encouraging, although it is important to note that the decrease in disability experienced by the MD1003 group, and the disease progression seen in the placebo group, were both so small that they would be virtually

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undetectable in clinical practice. MD1003 was well-tolerated. The overall incidence of adverse events was similar across the two groups.<sup>70</sup>

However, a smaller, single-center Italian study reported in October 2017 raised potential concerns about use of biotin in progressive forms of multiple sclerosis. The investigators followed 41 individuals with either PPMS (39 percent of the participants) or SPMS (61 percent) who were treated with 300 mg daily of biotin. Following a mean treatment period of 13.7 months, the annualized relapse rate for the group increased from 0.10 in the prior year to 0.27 on treatment. Nine patients – or 22 percent of the group – had relapses during the treatment period, with some having more than one relapse during that time. Most of the relapses required treatment with steroids, and four left residual disability. Seven of the 41 patients had MRI evidence of disease activity. In 28 of the participants who took biotin for 12 months or more, only one had an improvement in EDSS score, while the score remained stable in 17 of the participants (61 percent of the group), and worsened in 10 individuals (35 percent of the group).<sup>71</sup> Again, these results are from a study conducted at a single center and with a small number of patients, but the findings are troubling nonetheless.

A Phase III study (SP12) involving 600 individuals with progressive MS will hopefully clarify the concerns and questions raised by the Italian study. The study began in late 2016 and will include people with either PPMS or SPMS who have shown signs of worsening in the past two years. Participants will be given

either high-dose biotin (100 mg three times daily) or placebo, and will be followed for 15 months to see if differences in progression or walking speeds are observed in the biotin group as compared to the placebo. Following the initial 15-month study, both groups will then be given the high-dose biotin and followed for an additional 12 months.

### Stem Cells

Based on encouraging results from a variety of studies, clinical trials are now starting to enroll people using three different broad classes of stem-cell-based approaches.

The first stem cell approach is **hematopoietic stem cell transplantation (HSCT)**. Hematopoietic stem cells from the bone marrow are the common precursor cells from which both red and white blood cells originate. The HSCT requires multiple steps. First, stem cells, which circulate throughout the bloodstream, are collected by taking blood from the patient. The stem cells are obtained by filtering the blood, while the other cells – particularly the white blood cells that are responsible for MS attacks – are removed. These stem cells are then set aside and preserved, while a wiping out or “ablation” of the patient’s immune system, typically with high-dose chemotherapy, is done.

This immunosuppressive chemotherapy regimen is, in essence, the “MS treatment” phase of the HSCT procedure. This intensive course of chemotherapy destroys most blood cells as well as the bone marrow, where the blood cells are formed. Once complete, the individual’s own hematopoietic stem cells can be transplanted back into the blood to rebuild

the immune system. HSCT is often thought to bring about a “reset” of the immune system, back to its original purpose of guarding against infection and away from inappropriately attacking itself.

Results from a Phase II trial of HSCT in 35 people with RRMS or SPMS were reported in October 2017. The participants, treated at a single center in Australia, all had failed two disease-modifying therapies and had experienced relapses and/or new lesions on MRI before stem-cell transplantation. After an average follow-up of almost two years after the procedure, 89 percent of study participants had not experienced disease progression, 94 percent had not had a relapse, and 91 percent did not have MRI evidence of new disease activity. Roughly one-third of these individuals saw an improvement in their EDSS scores that was sustained for six months or longer. Investigators reported that no significant neurologic adverse events occurred later, and that overall adverse events were consistent with the expected safety profile for stem-cell transplantation. The investigators added that younger patients and those with lower EDSS scores at the start of the study tended to have the best responses.<sup>72</sup>

Another trial of this technique is the High-Dose Immunosuppression and Autologous (stem cell) Transplantation for Multiple Sclerosis (HALT MS) Study, for poor-prognosis MS. The HALT Phase II study was originally conducted in 25 individuals with highly active RRMS who have failed conventional therapy. The two-year follow-up results of the HALT study were reported in 2013. The treatment

induced profound immune suppression and a high rate of sustained remissions at two years.

Further results covering five years of the study were published in 2017.<sup>73</sup> Sixty-nine percent of the participants had no new disease activity (compared to 78 percent stability at three years). At three years, treatment had failed in five subjects, and two deaths occurred; one attributed to MS progression and one secondary to asthma. In the five-year follow-up, one additional death was reported in an individual who had disease progression and seven participants had developed either MS progression (n=2), new relapse (n=3), or new MRI activity (n=2).

A total of 130 adverse events that were severe or life-threatening were previously reported, most relating to low blood counts induced by the treatment approach. Two patients unsuccessfully attempted suicide. Both reported to have an unremarkable history before the HSCT, meaning that neither had a history of psychological problems that might lead to suicide attempts. A total of 15 additional adverse events were reported in the most recent study, though none were of the most severe type. The results of the HALT MS study are certainly intriguing, yet they are tempered by the fact that three of 24 participants had died at five years, with multiple other significant adverse events reported.

Another study conducted by researchers in Canada was published in 2016. This study used HSCT in 24 individuals with aggressive MS and followed the participants for three to 13 years. One person early in this study died of transplant-related complications. This death

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and another life-threatening infection in a second individual prompted the study authors to change the protocol by decreasing the dose of one of the chemotherapy drugs. This change was made to decrease the risk for toxicity and infection. The authors reported that participants did not have any new relapses or MRI activity after transplantation. Overall, 70 percent of these individuals remained stable, with the other 30 percent showing evidence of disease progression.<sup>74</sup> Interestingly, researchers found a delayed effect of HSCT on the rate of brain atrophy; at three years, participants had rates of brain atrophy similar to untreated individuals with MS, but later, decreases in brain volume were more similar to that of same-aged persons without MS.

A study in Sweden published previously found a high proportion of people with aggressive, relapsing forms of MS, were free from disease activity following HSCT. A group of 41 individuals participated in this study. They had a mean annualized relapse rate of 4.1 in the year preceding treatment, which means that on average, these individuals with very active disease were each experiencing four relapses in one year.

With a mean average follow-up time of nearly four years (47 months) after receiving the HSCT procedure, 89 percent of participants were relapse-free and 77 percent of participants had no disability progression, as measured by EDSS. In addition to the serious though expected side effects, including sepsis and fever, a small number of people experienced other adverse events. These included a reactivation of herpes zoster

in seven patients and thyroid disease in four patients; no deaths occurred in this trial.

In 2015, Burt and colleagues published the results of a larger study, giving data on 123 individuals with RRMS and 28 people with SPMS who underwent HSCT during a 10-year period. The study was open-label, meaning that everyone in the study received the treatment and thus did not have a comparison group. The findings included a significant decrease in both relapse rates and new MRI lesions. Four-year data showed that 80 percent were relapse-free and 87 percent were free of progression. Importantly, a significant *improvement* in disability scores was also seen for those individuals in which long-term data were available.

While the data from this study are encouraging, it is important to point out the open-label nature of this study, which may have led to biased results. Also, this method of treatment is not without risks. The administration of potent chemotherapy and the ablation of the bone marrow put patients at risk for infections and other complications. In this trial, the main adverse events were related to the development of thyroid disease and other autoimmune conditions. Infections were not common, and those that did occur were not severe. Two cases of cancer occurred post-transplant, but it is unknown if there was any causal relationship with the HSCT. The group that carried out this study is currently conducting a randomized trial of HSCT versus standard MS therapies.

A second type of stem-cell therapy utilizes mesenchymal stem cells (MSC). Unlike HSCT, MSCs are not used to “reset” the immune

system. Instead, the aim of MSC therapy is to provide stem cells that have the potential to develop into cells that may promote the repair or regeneration of the nervous system.

Importantly, MSC therapy does not require high doses of chemotherapy to “wipe out” the immune system, thus it may be a safer option.

In a Phase IIa study published in 2012, 10 people with SPMS with involvement of the visual system were infused with self-derived (autologous) mesenchymal stem cells (MSCs). In order to obtain the MSCs, investigators removed bone marrow from the patient. The next step was to filter out any cells that promote inflammation, and the remaining stem cells were grown in larger numbers and then given back to the patient through an infusion.

The researchers found an improvement in visual function, as well as an improvement in other laboratory and imaging measures of optic-nerve function. No serious adverse events or deaths occurred. Although the mechanism by which mesenchymal stem cells exert their beneficial effects has not been fully identified, these cells do not need to penetrate into the nervous system and grow at the site of lesions, such as the optic nerve. The results of this study were suggestive of a more generalized neuroprotective effect, which is discussed in the next section.

Multiple other Phase I or Phase II trials of mesenchymal stem cell therapies are currently either in the planning stages or recruiting, including a collaborative effort named MESEMS.<sup>75</sup> MESEMS is an international group of eight independent study centers that have created a shared-study design in order to

increase the power and significance of their results. The group plans to enroll 160 participants in total, with the goal of obtaining the data necessary to plan a more definitive Phase III trial.

A third approach to investigating stem-cell therapy, and perhaps the one most in-line with the common-sense notions about the potential uses of stem cells, is to utilize them for the purpose of directly regenerating myelin that has been damaged by MS. This approach requires multiple, complex steps in order to be successful. Techniques must be employed to: harvest an individual’s stem cells; grow and multiply them; administer them back to the individual; ensure that they get into the central nervous system; ensure that they are not destroyed by the body’s own immune system; ensure that they grow to become the correct type of cell (for instance, to restore myelin); and to ensure that they do not overgrow or cause damage to the nervous system.

This approach to stem-cell therapy was investigated in a pair of Phase I and Phase II clinical trials involving 20 individuals with progressive MS. The single-center trials infused doses of stem cells (harvested from each individual’s own bone marrow) directly into the cerebral spinal fluid (CSF) every three months by lumbar puncture. In results reported in October 2017, 15 of the 20 participants, or 75 percent, showed functional neurological improvement as measured by assessments of muscle strength, walking ability, and EDSS score. Half of the participants demonstrated improvement in bladder function. Adverse events included transient

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headache, which occurred with 72 percent of treatments, and fever, seen with 15 percent of treatments.

As an open-label, uncontrolled, unblinded Phase I study, this project was not designed to assess efficacy. The researchers are now conducting a Phase II trial that will compare the infusion of mesenchymal stem cell neural progenitors with a placebo infusion. Fifty individuals with EDSS scores between 3.5 and 6.5 will be randomized as matched pairs, and will cross-over, or switch from the placebo infusion to receiving stem cells, and vice-versa. Participants will receive six doses of stem cells at two-month intervals.<sup>76</sup>

### **Biomarkers**

In medicine, the term “biomarker” refers to anything that can be used as an indicator of a particular disease state; in effect, a biomarker is a surrogate for the disease state. It often refers to a protein measured in the blood, whose concentration reflects the severity or presence of disease and/or that which can be used to measure therapeutic effectiveness. Many types of biomarkers are being researched in MS, and these are likely to grow in importance in the coming years.

Although the term itself is relatively new, biomarkers have long been used in medicine. For example, body temperature is a well-known biomarker for fever. Biomarkers are often seen as the key to the future of “personalized medicine.” This refers to treatments that can be individually tailored to specific people for highly efficient intervention in disease processes.

The concept of personalizing MS care has been implemented in a general way by the use of disease-modifying therapies based on someone’s clinical course – CIS, RRMS, SPMS, or PPMS – categories entirely based on a patient’s clinical history. This approach has been refined as clinicians may recommend “more aggressive” therapies based on markers of disease severity (such as lesions seen on MRI), as well as on demographic factors that may be concerning because they are associated with a more difficult disease course.

Studies are ongoing with all major MS disease-modifying therapies to find markers that will help determine who should be treated with a specific medication, as well as how effective the medication is likely to be after therapy has begun. One type of blood test is already utilized to help predict ongoing therapeutic response – neutralizing antibodies to the interferons and Tysabri. A major goal of biomarker studies is to be able to decide which person is most likely to respond to which therapy before it is started, so the decision about which medication to start can be optimized.

For example, current studies are showing that it may soon be possible to determine who might be a suboptimal responder to interferons, based on immune system-related substances measured in the blood. Another study evaluated whether the type of cytokine present prior to treatment with Copaxone might act as a biomarker to identify those individuals with RRMS who are more likely to respond to immunomodulating treatments. It showed that people who responded to

Copaxone secreted higher levels of specific inflammatory cytokines prior to treatment.

Biomarkers may also be used to predict and minimize the risk of medication-related adverse events. This approach has already proved effective for new infectious biomarkers, such as the development of a blood test for JC virus antibodies, to identify who is at greater or lesser PML risk when treated with Tysabri. Based on this blood test, the option of using Tysabri can be more precisely personalized to maximize the benefit/risk ratio for this medication in practice. This type of biomarker strategy may also prove useful in predicting the risk on an individual basis of non-infectious adverse events to certain investigational medicines.

A strong link exists between biomarkers and genetics, and the line between them may sometimes appear blurred. This is because many of the biomarkers that are being discovered relate to the activity of specific genes that code for proteins involved in inflammation, or are otherwise linked to the response to disease-modifying therapies. Studies of the gene expression signature, through global gene expression analysis, reveals the pattern of the entire DNA in an individual. This type of study has become possible due to recent advances in high-speed genetic pattern analysis.

A study employing gene expression analysis of whole blood showed significant differences in expression profiles of patients with optic neuritis versus healthy controls. Another study showed that interferon therapy induces the expression of genes involved in interferon regulation and signaling; a

subgroup of people with a higher risk for relapses showed a different expression of specific genes.

A clinical trial sponsored by the National Institutes of Health (NIH) is studying more than 1,000 people with RRMS who participated in the CombiRx study. This study includes people on Avonex only, Copaxone only, or a combination of both. Samples of serum and white blood cells are being obtained from each person prior to the study and at regular intervals thereafter.

Although Copaxone and Avonex did not differ greatly in their efficacy in the CombiRx trial, certainly both drugs work well for some and less well for others. This study aims to identify biomarkers (genes and the proteins they encode) and link them to clinical and MRI-based outcomes, such as the extent of inflammation and rate of disease progression. It will examine how biomarkers may be related to disease development and progression, as well as differences among peoples' symptoms and response to treatment. Based on these genetic biomarkers, likely best-responders to either form of therapy can be identified.

### **Genetic Studies**

Several genes have been linked to the development of MS, and research into this area has proceeded at a brisk pace since 2011, when the journal *Nature* published the results of the largest MS genetics study ever undertaken.<sup>77</sup> A global collaboration of scientists identified 29 new genetic variants associated with MS, and confirmed 23 others that had been previously associated with the disease. The study confirmed that the immune

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system plays a major role in the development of MS; most of these genes are related to immune function, and more than one-third of them have previously been confirmed to be associated with other autoimmune diseases, such as Crohn's disease and type 1 diabetes.

Larger studies have greatly expanded upon that 2011 research, including a recent large-scale study of genetics and MS that included 47,351 persons with MS and 68,284 healthy controls.<sup>78</sup> Researchers were able to identify more than 200 important genetic variants associated with MS. Most genes again were related to the immune system. Interestingly, study investigators also identified new genetic variants located on the X chromosome, which they hypothesized might in part explain the increased risk in MS for a woman compared to a man.

Investigation of MS prevention requires early identification and understanding of the incidence in a high-risk population. The Genes and Environment in Multiple Sclerosis (GEMS) project has a goal of early detection in first-degree relatives of individuals with MS. Initial data were presented in spring 2015. Each participant submitted saliva for targeted genotyping and completed questionnaires online to capture demographics and risk factors. For each individual, a weighted genetic and environmental risk score (GERS) was calculated. This score included 64 genetic variants, as well as gender, whether or not he or she had infectious mononucleosis, and if the person has a history of smoking.

By leveraging patient-advocacy groups and social media, the GEMS investigators were able to recruit more than 2,600 first-

degree relatives of people with MS from across the United States. In an analysis of the initial 1,696 people (1,583 without symptoms and 113 with MS at enrollment), investigators found that 27 percent of the individuals with MS and 25 percent of the asymptomatic participants have a history of infectious mononucleosis, both doubling that of the general population. This higher proportion of infectious mononucleosis in asymptomatic family members is not attributable to known MS-genetic susceptibility.

The individuals with MS in this study also have a significant excess of current smokers than the asymptomatic participants. Four out of the initial 1,583 asymptomatic subjects developed MS after enrollment, including the individual with the highest genetic risk score, providing an incidence estimate (123 cases per 100,000 first-degree relatives annually), which is significantly higher than the incidence of sporadic MS in the United States. The average follow-up of the study was two years.

In a follow-up study published in early 2017, investigators studied women in the highest<sup>79</sup> and lowest genetic risk categories. They reported that 8 percent of study participants (four in the high-risk category and one in the lower-risk category) had MRIs that showed lesions consistent with MS. Surprisingly, researchers also found that they were significantly more likely to be able to detect subtle decreases in vibration sense in the big toe in people with a higher genetic score when compared to those with a lower genetic score.

These and other genetics studies do not as yet significantly improve our ability to provide



genetic counseling to individuals concerned about their risk of developing MS. However, they should help researchers to better define the biological pathways that lead to the development of MS, and may allow us to design better treatments for early MS.

## The Microbiome and MS

A growing body of research has documented how the interaction between an individual's microbiome and immune cells may contribute to the development and severity of many disease states, including MS. The *microbiome* refers to the many millions of bacteria that reside in a person's body, with current research focusing mainly on the bacteria that live in the intestines. Researchers have hypothesized that imbalances in the number or types of different strains of bacteria could cause the immune system to be inappropriately activated, with autoimmune diseases occurring as the result.

Some of the latest research in this area was presented at the October 2017ECTRIMS-ACTRIMS Meeting. In one study, investigators gave the probiotic VSL3 to nine individuals with relapsing-remitting MS and 13 healthy controls. Seven of the people with MS were taking Copaxone® (glatiramer acetate); the other two were not taking a disease-modifying therapy. Study participants took two doses of the probiotic daily for two months. Stool samples from each subject were collected prior to the start of probiotic therapy, at discontinuation of probiotic therapy, and three months afterward. Blood samples were also collected to profile immune cells and immune gene expression.

Analysis of the stool samples showed that VSL3 induced changes in the composition and function of the bacteria in the gastrointestinal tract associated with an anti-inflammatory peripheral immune system response in both people with MS and healthy patients. Additionally, analysis showed decreased expression of pro-inflammatory genes in controls and increased expression of anti-inflammatory genes in people with MS following VSL3 administration.<sup>80</sup> Although this is a small study that did not include clinical outcomes, it nonetheless raises the intriguing possibility of using probiotics in conjunction with other therapies to alter the course of MS.

In a study reported in 2016, a group of pediatric MS researchers analyzed the microbiome of a small group of children with pediatric MS versus control subjects. Although they were unable to find a characteristic bacteria "signature" that could identify the MS patients' microbiomes compared to the controls, they did find that individuals with MS who had more types of bacteria in their microbiome had increased amounts of inflammatory immune cells in their blood compared to those with fewer types of bacteria, something that was reversed in the control group. In another study, investigators from the MS Microbiome Consortium presented work that demonstrated differences in the microbiome that correlated to whether a person was treated with an MS medication or not, and if treated, whether they were on an oral or injectable MS therapy.

The iMSMS (international MS Microbiome Study) is an international multi-disciplinary collaboration composed of researchers from

the United States, England, and Argentina. Together, they have initiated a microbiome-oriented basic<sup>81</sup> experimental program and sequencing/bioinformatics program. The iMSMS has a goal of analyzing the microbiome of 2,000 individuals with MS and 2,000 healthy controls. They are also working with animal models.

Initial results from this group show significant differences in the microbiomes of individuals treated with Copaxone compared to untreated participants. Women taking Copaxone showed significant enrichment of members of the Enterobacteriaceae family of bacteria, compared to gender-matched controls who were not taking Copaxone. Geographical differences were noted, as well.

Another study of the microbiome in MS looked at differences in Vitamin D levels predicting alterations in gut bacteria. Analysis of 43 participants showed increased abundance of a type of helpful bacteria called Ruminococcaceae in individuals with MS who were untreated and had a serum Vitamin D level above 40 ng/ml, versus individuals with a Vitamin D level below 40. The authors conclude that high levels of Vitamin D in untreated MS patients are associated with increased amounts of Ruminococcaceae in the gut. This has relevance to MS, as a decreased amount of Ruminococcaceae has previously been associated with Crohn's disease. Hence, lower amounts of Ruminococcaceae might be linked to increased inflammation in MS. Further studies are underway to explain the mechanism by which Vitamin D regulates the composition of the microbiota in MS.

## Diet and MS

The potential to alter the course of MS through diet is intriguing, and has been a focus of researchers since at least 1948, when Dr. Roy Swank formulated a diet low in saturated fats and high in polyunsaturated fats for people with MS. Too often, however, dietary approaches to managing MS have not been supported by large-scale, rigorously conducted studies. Furthermore, the outcomes of many studies have been equivocal, leaving us without clear answers or direction. Fortunately, a number of well-designed trials now are taking up important questions related to diet and MS.

One study randomized 61 people to a low-fat plant based diet for 12 months, and compared them to a control group not bound by dietary restrictions. Researchers did not find any differences in MS activity between the groups, although improvements were seen in fatigue scores, body mass index (BMI) measures, and cholesterol panels. The study authors noted that the small size of the study may have impeded their ability to identify greater effects on the condition.<sup>82</sup>

A study currently under way has randomized 100 people to a paleolithic diet (no dairy or gluten) versus a low-fat diet (the Swank diet). This study lacks a control group, which may hinder the results. A smaller pilot study of 30 participants also has commenced; it randomizes a group of people with MS to a modified Mediterranean diet versus controls. A third study will place people in two dietary groups, either a calorie-restricted group (78 percent of recommended calories daily) or a

group that will practice intermittent fasting; the intermittent fasting group will eat the recommended calorie intake for five days of the week and will eat only 25 percent of recommended calorie intake the other two days of the week. These dietary trials stand to inform and shape future treatment plans for individuals with MS.

## Closing Notes

The study results and ongoing trials reported in this 2018 *MS Research Update* show the breadth and depth of efforts to develop effective therapies across the spectrum of multiple sclerosis to better understand how currently approved therapies can be used to optimize patient care.

The array of hypotheses being pursued, compounds being evaluated, and investigative strategies being employed is almost overwhelming, and is cause for great hope and encouragement. While disappointments and dead ends are an inevitable part of the process, the pace of our collective efforts seems to accelerate year after year, as each new finding – positive or negative – helps us refine and better direct our efforts.

A tremendous amount of work, however, still needs to be done, both at the molecular level and in terms of translating laboratory findings into individualized care that reaches all people with MS. Secondary-progressive MS remains an area where effective therapies are vitally needed. Similarly, to echo comments made in the closing section of the 2017 Update, it is imperative that we achieve greater ethnic, racial, and other diversity in study populations. This *MS Research Update*

has summarized key trials in relapsing forms of MS, secondary-progressive MS, and primary-progressive MS, as well as promising investigations into neuroprotection, remyelination, repair, the genetic basis of MS, and the role the microbiome and diet, among other topics.

The number of available MS treatments has grown considerably in recent years, and now includes a therapy for primary-progressive MS, with more on the way. These new therapies are accompanied by new challenges, and also new risks, as we seek to identify the right medicine for the right patient at the right time... and to thoughtfully balance the benefits and risks of treatment strategies.

People with MS, as much as clinicians, need to be highly informed so that they are empowered to participate fully in the shared decision-making process. We hope that this update will be a valuable resource for individuals with MS and their families as they pursue that goal. For more information about clinical trials, please visit [www.clinicaltrials.gov](http://www.clinicaltrials.gov); for participation opportunities, please visit [mymsaa.org/clinicaltrials](http://mymsaa.org/clinicaltrials). For more information about MS and its treatments, please contact MSAA at **(800) 532-7667**, or visit [mymsaa.org](http://mymsaa.org).

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# APPROVED DISEASE-MODIFYING THERAPIES FOR MS

## SELF-INJECTED MEDICATIONS

NAME	TYPE OF MEDICATION	HOW ADMINISTERED AND SIDE EFFECTS
<b>Avonex®</b> (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
<b>Betaseron®</b> (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
<b>Copaxone®</b> (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
<b>Extavia®</b> (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
<b>Generic Glatiramer Acetate Injection</b> (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
<b>Glatopa®</b> (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
<b>Plegridy®</b> (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
<b>Rebif®</b> (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

## INFUSED MEDICATIONS

NAME	TYPE OF MEDICATION	HOW ADMINISTERED AND SIDE EFFECTS
<b>Lemtrada®</b> (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
<b>Novantrone®</b> (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
<b>Ocrevus™</b> (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
<b>Tysabri®</b> (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

## ORAL MEDICATIONS

NAME	TYPE OF MEDICATION	HOW ADMINISTERED AND SIDE EFFECTS
<b>Aubagio®</b> (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
<b>Gilenya®</b> (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
<b>Tecfidera®</b> (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.

## REFERENCES

- 1 Kappos L, Amit B-O, Cree BA, et al. "Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study." *The Lancet*. 2018. Doi.org/10.1016/S0140-6736(18)30475-6.
- 2 Novartis press release, March 23, 2018. "Phase III data in *The Lancet* show Novartis siponimod significantly improves outcomes in patients with secondary progressive MS." <https://www.novartis.com/news/media-releases/phase-iii-data-lancet-show-novartis-siponimod-significantly-improves-outcomes-patients-secondary-progressive-ms>.
- 3 Sandoz press release, Feb, 13, 2018. "Sandoz announces US FDA approval and launch of Glatopa® 40 mg/mL three times-a-week generic option for relapsing forms of multiple sclerosis." <https://www.sandoz.com/news/media-releases/sandoz-announces-us-fda-approval-and-launch-glatopar-40-mgml-three-times-week>.
- 4 MediciNova press release, Feb. 1, 2018. "MediciNova announces MN-166 (ibudilast) demonstrated a 26% reduction in confirmed disability progression in the SPRINT-MS Phase 2b trial in progressive MS: Potential best-in-disease drug." <https://globenewswire.com/news-release/2018/02/01/1330487/0/en/MediciNova-Announces-MN-166-ibudilast-Demonstrated-a-26-Reduction-in-Confirmed-Disability-Progression-in-the-SPRINT-MS-Phase-2b-Trial-in-Progressive-MS-Potential-Best-in-Disease-Dr.html>.
- 5 Green AJ, et al. "Clemastine fumarate as a remyelinating therapy for multiple sclerosis (REBUILD): a randomised, controlled, double-blind, cross-over trial." *The Lancet*. 2017;390:2481-2489.
- 6 Traboulsee A, et al ACTRIMS 2018. [Abstract 2459]
- 7 Fox E, et al. ACTRIMS 2018. [Abstract P050]
- 8 Roche press release, January 18, 2018. "Roche's OCREVUS (ocrelizumab) approved in the European Union for relapsing forms of multiple sclerosis and primary progressive multiple sclerosis." <https://www.roche.com/investors/updates/inv-update-2018-01-12.htm>.
- 9 ClinicalTrials.gov Identifier: NCT02637856.
- 10 Biogen press release, March 2, 2018. "Biogen and Abbvie announce the voluntary worldwide withdrawal of marketing authorizations for ZINBRYTA® (daclizumab) for relapsing multiple sclerosis." <http://media.biogen.com/press-release/autoimmune-diseases/biogen%C2%A0and-abbvie-announce%C2%A0voluntary%C2%A0worldwide-withdrawal-market>.
- 11 FDA press release, March 14, 2018. "FDA working with manufacturers to withdraw Zinbryta from the market in the United States." <https://www.fda.gov/Drugs/DrugSafety/ucm600999.htm>.
- 12 Tecfidera® (dimethyl fumarate) prescribing information. December 2017. Biogen Inc.: Cambridge, MA.
- 13 Signori A, et al. ECTRIMS 2017. [Abstract P1891]
- 14 Bloomgren G, Richman S, Hotermans C, et al. "Risk of natalizumab-associated progressive multifocal leukoencephalopathy." *N Engl J Med*. 2012;366:1870-1880.
- 15 NYU Langone Health press release, February 5, 2018. "Extending dosing intervals reduces deadly side effect risk from popular multiple sclerosis drug." <https://nyulangone.org/press-releases/extending-dosing-intervals-reduces-deadly-side-effect-risk-from-popular-multiple-sclerosis-drug>.
- 16 Ciocanu D, et al. ECTRIMS 2017. [Abstract P1201]
- 17 Perumal J, et al. ECTRIMS 2017. [Abstract P1264]
- 18 Butzkueven H, et al. ECTRIMS 2017. [Abstract P733]
- 19 FDA. "FDA expands approval of Gilenya to treat multiple sclerosis in pediatric patients." May 11, 2018. Available at <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm607501.htm>. Accessed May 14, 2018.
- 20 Cohen J, et al. ECTRIMS 2017. [Abstract P1879]
- 21 Cornelissen C, et al. ECTRIMS 2017. [Abstract P1192]
- 22 Reder A, et al. ECTRIMS 2017. [Abstract P1186]
- 23 Bajrami A, et al. ECTRIMS 2017. [Abstract P1176]
- 24 Havrdova E, Arnold DL, Cohen JA, et al. "Alemtuzumab CARE-MS 5-year follow-up." *Neurology*. 2017;89:1107-1116.
- 25 Oreja-Guevara C, et al. ECTRIMS 2017. [Abstract P1190]
- 26 Rovira A, et al. ECTRIMS 2017. [Abstract P728]
- 27 Pelletier D, et al. ECTRIMS 2017. [Abstract P724]
- 28 Coles A, et al. ECTRIMS 2017. [Abstract P1188]
- 29 Arnold D, et al. ECTRIMS 2017. [Abstract P1189]
- 30 Horakova D, et al. ECTRIMS 2017. [Abstract P1195]
- 31 Comi G, De Stefano N, Freedman MS, et al. "Subcutaneous interferon B-1a in the treatment of clinically isolated syndromes: 3-year and 5-year results of the phase III dosing frequency-blind multicentre REFLXION study." *J Neurol Neurosurg Psychiatry*. 2017;88:285-294.
- 32 Aubagio® (teriflunomide) prescribing information. November 2016. Genzyme Corporation: Cambridge, MA.
- 33 Freedman M, et al. ECTRIMS 2017. [Abstract P1203]
- 34 Vermersch P, et al. ECTRIMS 2017. [Abstract P1191]
- 35 Biogen press release, November 27, 2017. "Biogen and Alkermes announce license and collaboration agreement to develop and commercialize ALKS 8700 for the treatment of multiple sclerosis." <http://media.biogen.com/press-release/corporate/biogen-and-alkermes-announce-license-and-collaboration-agreement-develop-and>.
- 36 Naismith R, et al. ECTRIMS 2017. [Abstract P1170]
- 37 Merck press release, Dec. 4, 2017. "Merck's Mavenclad (cladribine tablets) approved for relapsing-remitting multiple sclerosis in Canada." <https://www.prnewswire.com/news-releases/mercks-mavenclad-cladribine-tablets-approved-for-relapsing-remitting-multiple-sclerosis-in-canada-661779283.html>.
- 38 Giovannoni G, Comi G, Cook S, et al. "A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis." *N Engl J Med*. 2010;362:416-426.
- 39 Kalincik T, et al. ECTRIMS 2017. [Abstract P1138]
- 40 Teva Pharmaceuticals press release, May 5, 2017. "Teva and Active Biotech announce CONCERTO trial of laquinimod in RRMS did not meet primary endpoint." [http://www.tevapharm.com/news/teva\\_and\\_active\\_biotech\\_announce\\_concerto\\_trial\\_of\\_laquinimod\\_in\\_rrms\\_did\\_not\\_meet\\_primary\\_endpoint\\_05\\_17.aspx](http://www.tevapharm.com/news/teva_and_active_biotech_announce_concerto_trial_of_laquinimod_in_rrms_did_not_meet_primary_endpoint_05_17.aspx).
- 41 Active Biotech press release, Dec. 1, 2017. "Active Biotech announce results in ARPEGGIO Phase II trial with laquinimod in Primary Progressive MS." <http://www.activebiotech.com/en/media/pressreleases/?id=2153402&date=1512129600>
- 42 Granqvist M, et al. "Comparative effectiveness of rituximab and other initial treatment choices for multiple sclerosis." *JAMA Neurol*. 2018;75(3):320-327.
- 43 Komori M, et al. "Insufficient disease inhibition by intrathecal rituximab in progressive multiple sclerosis." *Annals of Clinical and Translational Neurology*. Feb 1, 2016; 3(3):166-79.

- 44** Amit Bar-Or, et al. "The MIRROR Study: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study to Investigate the Safety and MRI Efficacy of Subcutaneous Ofatumumab in Subjects with Relapsing-Remitting Multiple Sclerosis (RRMS)." *Neurology*. April 8, 2014; 82(10) Supplement S23.006.
- 45** Sorensen S, et al. ECTRIMS 2015. [Poster P048]
- 46** ClinicalTrials.gov Identifier: NCT02792218.
- 47** Fox E, et al. ECTRIMS 2017. [Abstract P793]
- 48** TG Therapeutics press release, Sept. 15, 2017. "TG Therapeutics, Inc. announces the Phase 3 ULTIMATE trials evaluating TG-1101 in patients with multiple sclerosis are now open for enrollment." <http://ir.tgtherapeutics.com/releasedetail.cfm?releaseid=1040573>.
- 49** 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." *The Lancet Neurology*. April 2016; 15(4):373-381.
- 50** Celgene press release, Oct. 27, 2017. "Efficacy and safety results from first Phase III trial of oral ozanimod (SUNBEAM™) versus an active comparator in relapsing multiple sclerosis presented at MSParis2017 - 7th Joint ECTRIMS-ACTRIMS Meeting." <http://ir.celgene.com/releasedetail.cfm?releaseid=1045797>.
- 51** Celgene press release, Oct. 28, 2017. "Efficacy and safety results from second Phase III trial (RADIANCE™ Part B) of oral ozanimod versus an active comparator in relapsing multiple sclerosis presented at MSParis2017 - 7th Joint ECTRIMS-ACTRIMS Meeting." ["http://ir.celgene.com/releasedetail.cfm?releaseid=1045853](http://ir.celgene.com/releasedetail.cfm?releaseid=1045853).
- 52** [Celgene February 27, 2018]
- 53** Havrdova E, et al. ECTRIMS 2017. [Abstract P1151]
- 54** ClinicalTrials.gov Identifier: NCT02425644.
- 55** Actelion press release, September 29, 2016. "Actelion to investigate all-oral combination therapy for patients with relapsing multiple sclerosis." [<https://www1.actelion.com/mobile/newsresults.page?newsId=2045336&bb=js>]
- 56** AB Science press release, Jan. 4, 2018. "AB Sciences announces that based on interim analysis, IDMC recommended the continuation of the masitinib phase 3 study in progressive forms of multiple sclerosis with no requirement to increase the study sample size." ([http://www.ab-science.com/file\\_bdd/content/1515084540\\_InterimMSVfENG.pdf](http://www.ab-science.com/file_bdd/content/1515084540_InterimMSVfENG.pdf))
- 57** Metz LM, Li DKB, Traboulsee AL, et al. "Trial of minocycline in a clinically isolated syndrome of multiple sclerosis." *N Engl J Med*. 2017;376:2122-33.
- 58** Chan D, Binks S, Nicholas JM, et al. "Effect of high-dose simvastatin on cognitive, neuropsychiatric, and health-related quality-of-life measures in secondary progressive multiple sclerosis: secondary analyses from the MS-STAT randomised, placebo-controlled trial." *Lancet Neurol*. 2017;16:591-600.
- 59** ClinicalTrials.gov Identifier: NCT01721161
- 60** Sheikh S, et al. ECTRIMS 2017. [Abstract P718]
- 61** Biogen press release, Oct. 25, 2017. "Biogen announces AFFINITY Phase 2 trial initiation of opicinumbab (Anti-LINGO-1) in multiple sclerosis." <http://media.biogen.com/press-release/autoimmune-diseases/biogen-announces-affinity-phase-2-trial-initiation-opicinumbab-anti> i.
- 62** Raftopoulos R, et al. "Phenytoin for neuroprotection in patients with acute optic neuritis: a randomised, placebo-controlled, phase 2 trial." *The Lancet Neurology*. March 2016; 15(3):259-69.
- 63** Toosy A, et al. ECTRIMS 2017. [Abstract P714]
- 64** Santhera Pharmaceuticals press release, March 5, 2018. "Santhera reports outcomes of exploratory trial with idebenone in PPMS conducted at the NIH." [http://www.santhera.com/assets/files/press-releases/2018-03-05\\_PR\\_PPMS\\_e\\_final.pdf](http://www.santhera.com/assets/files/press-releases/2018-03-05_PR_PPMS_e_final.pdf).
- 65** Innate Immunotherapeutics press release, June 27, 2017. "Innate Immunotherapeutics announces top-line results for trial of MIS416 in patients with secondary progressive multiple sclerosis." [http://www.innateimmuno.com/irm/PDF/1424\\_0/TopLineResultsforTrialofMIS416](http://www.innateimmuno.com/irm/PDF/1424_0/TopLineResultsforTrialofMIS416).
- 66** Antisense Therapeutics press release, Oct. 2, 2017. "ATL1102 for multiple sclerosis and Duchenne muscular dystrophy update." [http://www.antisense.com.au/wp-content/uploads/2017/01/ASX-17\\_-2-October\\_ATL1102-for-MS-and-DMD-Update\\_Final.pdf](http://www.antisense.com.au/wp-content/uploads/2017/01/ASX-17_-2-October_ATL1102-for-MS-and-DMD-Update_Final.pdf).
- 67** ClinicalTrials.gov Identifier: NCT01490502.
- 68** Beckmann Y, et al. ECTRIMS 2017. [Abstract EP1504]
- 69** Spain S, et al. "Lipoic acid in secondary progressive MS." *Neuro Immunol Neuroinflamm*. 2017;4e374;doi:10.1212/NXI.0000000000000374.
- 70** Tourbah A, et al. "MD1003 (high-dose biotin) for the treatment of progressive multiple sclerosis: A randomised, double-blind, placebo-controlled study." *Multiple Sclerosis Journal*. September 1, 2016.
- 71** Granella F, et al. ECTRIMS 2017. [Abstract P750]
- 72** Massey J, et al. ECTRIMS 2017. [Abstract P1134]
- 73** Nash RA, et al. "High-dose immunosuppressive therapy and autologous hematopoietic cell transplantation for relapsing-remitting multiple sclerosis (HALT-MS): a 3-year interim report." *JAMA Neurology*. Feb 2015; 72(2):159-69.
- 74** Atkins HL, et al. "Immunoablation and autologous haemopoietic stem-cell transplantation for aggressive multiple sclerosis: a multicentre single-group phase 2 trial." *The Lancet*. August 6, 2016; 388(10044):576-585.
- 75** Uccelli A, et al. "MESEMS: a randomized, double blind placebo-controlled cross-over study to evaluate safety and efficacy of intravenous administration of autologous mesenchymal stem cells in patients with multiple sclerosis." *JAMA*. 2015; 313(3):275-284.
- 76** Sadiq S, et al. ECTRIMS 2017. [Abstract P721]
- 77** International Multiple Sclerosis Genetics Consortium. "Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis." *Nature*. Aug 10, 2011; 476(7359):214-9.
- 78** Patsopoulos N (on behalf of the International Multiple Sclerosis Genetics Consortium). "200 loci complete the genetic puzzle of multiple sclerosis."
- 79** Zongqi X, et al. "Assessment of early evidence of multiple sclerosis in a prospective study of asymptomatic high-risk family members." *JAMA Neurol*. March 2017; 74(3):293-300.
- 80** Tankou S, et al. ECTRIMS 2017. [Abstract P792]
- 81** Baranzini SE. "The international MS microbiome study (iMSMS): investigating the role of gut microbiota in multiple sclerosis through open collaboration." ECTRIMS Online Library. Sep 15, 2016; 146272.
- 82** Yadav V, et al. "Low-fat, plant-based diet in multiple sclerosis: A randomized controlled trial." *Multiple Sclerosis and Related Disorders*. September 2016; 9:80-90.

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