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MS RESEARCH UPDATE

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MSAA's 2017 edition of the *MS Research Update* provides important new data on approved and experimental treatments for MS, and is 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 any symptom-management medications or therapies.

For additional information about MS, symptoms and symptom management, as well as MSAA's programs and services, please visit **mymsaa.org** or call **(800) 532-7667**. Questions to MSAA's Client Services department may also be emailed to **MSquestions@mymsaa.org**.

Additionally, please note that due to the timing of the national and international MS conferences, study data from the 2017 conferences could not be included in this writing. Information in this publication includes data presented at the 2016 conferences, as well as any important updates that occurred in early 2017. Please visit MSAA's website at **mymsaa.org** for future summaries of 2017 conference highlights.

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

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INTRODUCTION

This year's *MS Research Update* has been designed to highlight numerous experimental drugs 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 new areas of MS research. Please note that in order to keep this annual *MS Research Update* current and up to date, historical background and completed trials of approved DMTs are no longer included.

This 2017 edition of MSAA's *MS Research Update* is again being printed as a stand-alone issue, reflecting the incredible diversity and scope of research progress in MS. Of course, there is nonetheless far too much ongoing research in MS therapeutics for all of it to be covered here. This is therefore not a complete list, and not all study results could be included.

This information 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 2016 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 and ECTRIMS).

In 2016, experts from member organizations of the Multiple Sclerosis Coalition (MSC), including the Multiple Sclerosis Association of America (MSAA), collaborated to develop and update a 2014 paper that summarized the current evidence that supports the FDA-approved DMTs for the long-term treatment of multiple sclerosis. The objectives were to provide evidence for the effectiveness of these medications and to provide support for broad access to these approved therapies for people with MS in the United States. Ultimately, the goal is to enable individuals with MS and their medical professionals to select the most appropriate medication available.

This professional paper, titled "The Use of Disease-Modifying Therapies in Multiple Sclerosis: Principles and Current Evidence," is available on MSAA's website for anyone to review. It has been written expressly for medical professionals, in a highly detailed and scientific style. This paper for professionals may be accessed by going to **mymsaa.org/msc-dmt-full**.

Following the release of the professional paper, member organizations of the MSC have collaborated to develop a summary, written in a more reader-friendly style to better serve the broader MS community. This paper is available on MSAA's website as well and is titled, "The Use of Disease-Modifying Therapies in Multiple Sclerosis: Principles and Current Evidence; SUMMARY." This summary directly correlates to the different sections found within the professional version, but has simplified the information to highlight main points and incorporate more commonly used terminology. In addition, the summary is followed by an extensive glossary to assist with those terms specific to describing the MS process. This paper on the approved DMTs is a valuable counterpart to this *MS Research Update*, which is focused on summarizing new and emerging data covering available therapies as well as emerging treatments still in development. This paper for the MS community may be accessed by going to **mymsaa.org/msc-dmt-summary**.

Please note that the authors of this *MS Research Update* have reported 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 drugs 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** and select "**Symptoms**" under "MS Information."

Readers may also note that studies involving progressive forms of MS are highlighted with the mention of progressive MS appearing in bold type. This is because all but one of the 15 presently approved DMTs are for relapsing forms of MS, and the authors of this publication want to also bring studies for progressive MS to the readers' attention.

INTRODUCTION

Overview of MS Research Progress

A dramatic shift has taken place in the treatment of people with MS since the United States Food and Drug Administration (FDA) approved the first MS treatment, Betaseron® (interferon beta-1b), 24 years ago. The "watch and wait" approach to MS therapy has become a thing of the past, in favor of a proactive strategy to prevent MS-disease activity and disability. Treatment is now typically started after a person has experienced the first episode of MS, or a clinically isolated syndrome (CIS). CIS is defined as a single attack (or the first appearance of one or more symptoms characteristic of MS), with a very high risk of developing MS, when no other diseases or causes for symptoms are apparent. The use of magnetic resonance imaging (MRI) scans to identify lesions characteristic of MS has expedited diagnosis. Numerous studies with multiple types of DMTs have confirmed that early treatment at the time of CIS is beneficial in the long term.

Until recently, all of the approved DMTs were for relapsing forms of MS. In March 2017, Ocrevus™ (ocrelizumab) was the first treatment to be approved for two types of multiple sclerosis (MS): relapsing forms of MS (RMS) and primary-progressive MS (PPMS). Given via IV (intravenous) infusion twice per year, this was the first time that a medication was available to individuals with primary-progressive MS, representing a great advancement in the treatment of this form of the disease.

Ocrevus joins multiple new DMT options that have been approved in the last three years for relapsing forms of MS, including: Zinbryta® (daclizumab), a monoclonal antibody self-administered subcutaneously (under-the-skin) once per month; a new 40 mg formulation of Copaxone® (glatiramer acetate), dosed three times per week; Glatopa®, a generic equivalent of the daily 20 mg dose of glatiramer acetate; Plegridy® (peginterferon beta-1a), an interferon which is dosed once every two weeks; Lemtrada® (alemtuzumab), a new agent given by a series of infusions once yearly that was approved by the FDA at the end of 2014. With the success of research initiatives and the expanding number of approved medications, the choice of disease-modifying therapy has grown more complex.

In addition to the medications that have achieved FDA approval, there have been both major recent successes and setbacks in MS research. Although there was disappointment in the failure of Tysabri and Gilenya to succeed in progressive forms of the disease, the field saw two significant advances with the success of Ocrevus in primary-progressive MS in 2015 and siponimod in secondary-progressive MS in 2016. While Ocrevus was approved in 2017, siponimod is still moving through regulatory review, the final step before it too can be used to treat people with MS.

An attempt to develop a therapy to boost remyelination, anti-LINGO-1, disappointed in a recent clinical trial, but the use of a high-dose of the vitamin Biotin (in a small Phase IIb/III study) surprised many people with success in progressive MS, and is moving on into further study. The field of MS research has also moved forward with several types of stem-cell based

research, which have generated positive, although complicated, results in 2016.

It can be challenging to keep up with the vast array of medications, techniques, and new areas of inquiry all seeking to make breakthroughs in this disease, and we view that as a "good problem to have." We hope this *MS Research Update* serves as a useful guide to many of the highlights as well as the challenges 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 for people with MS.

As always, no research successes can be achieved without the participation of people with MS in clinical trials, and 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 begin this *MS Research Update* with this note of gratitude to all the people 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**

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

TRIAL PHASES FOR INVESTIGATING TREATMENTS

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

Please note that not all of the approved treatments for MS have been included in this section. For a full listing, please see the chart on pages 40 to 43.

Ocrevus® (ocrelizumab)

Company: Genentech and Roche Pharma AG

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

This newly approved disease-modifying therapy is an anti-CD20 monoclonal antibody. Although similar to the experimental medication Rituxan, Ocrevus has the potential advantage of being a more humanized antibody than Rituxan. As noted in the introduction to the section on monoclonal antibodies (under "Experimental Medications"), humanized monoclonal antibodies are antibodies from non-human species whose protein sequences have been modified to increase their similarity to antibodies produced naturally in humans.

In a Phase II study of ocrelizumab[1] in 220 individuals with RRMS, reductions in the total number of brain lesions detected by MRI scans (the primary endpoint of the study) were highly significant at 96 percent for 2,000 mg ocrelizumab and 89 percent for 600 mg compared to placebo. The annualized relapse rate was significantly lower versus placebo at week 24, with a reduction of 73 percent for ocrelizumab 2,000 mg, and 80 percent for ocrelizumab 600 mg. Ocrelizumab's effectiveness was maintained through week 72; the proportion of relapse-free patients at week 72 was 84 percent for the 600 mg group, and 82 percent for the 2,000 mg group.

The findings of three important studies of ocrelizumab in MS were announced in 2015.[2] 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, which included individuals with relapsing forms of MS who either had relapsing-remitting MS or secondary-progressive MS with relapses.

Taking place at 307 sites in 40 countries, individuals received either 600 mg of ocrelizumab via intravenous (IV) infusion every six months, or the approved 44 mcg dose of Rebif® (interferon beta-1a), given via subcutaneous injection three-times weekly. Participants given 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 groups, new MRI lesions were decreased by 94 and 95 percent, brain atrophy was decreased by 24 and 25 percent, and progression of sustained clinical disability was decreased by 40 percent.

The third ocrelizumab study, ORATORIO, was conducted in patients with **PPMS**. 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 ocrelizumab 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 primary endpoint of this study was time to the onset of confirmed disability progression, defined as an increase in EDSS that is sustained for at least 12 weeks.

The ORATORIO study met its primary endpoint, showing that treatment with 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 ocrelizumab, and brain-volume loss as viewed on MRI was reduced by 17.5 percent. In conclusion, this is the *first study* where a disease-modifying therapy has shown effectiveness in treating PPMS. The incidence of adverse events associated with ocrelizumab was similar to placebo; the most common adverse events were mild-to-moderate infusion-related reactions.[3]

Although Phase III trials in rheumatoid arthritis reported significant rates of serious and opportunistic infections, and one patient died of a systemic inflammatory response of unknown cause, the number of serious adverse events in the ORATORIO, OPERA I, and OPERA II studies were small and similar among the groups, and no opportunistic infections were identified in these trials. (Opportunistic infections are a result of micro-organisms found in the body that only infect a person with a weakened immune system.)

As might be expected, more infusion-related reactions were seen in the ocrelizumab groups versus placebo. Importantly, several more cases of cancer were seen in the ocrelizumab groups versus the control patients. The possible association of ocrelizumab to the development of cancer will be carefully reviewed to assess if this represents a safety concern with this agent, as this also may be a chance finding.

Zinbryta® (daclizumab)

Company: Biogen and AbbVie

- *150 mg given via subcutaneous injection once monthly*
- *Approved in May 2016 for RMS*

Zinbryta® (daclizumab) joined the arsenal of FDA-approved medications for RRMS in 2016. Zinbryta is a genetically engineered monoclonal antibody that binds to CD25, a receptor on T cells that is thought to become activated in response to MS. Zinbryta is believed to work by selectively targeting these activated T cells without causing general T-cell depletion. It is approved by the FDA for use in rheumatoid arthritis and other autoimmune diseases. Daclizumab high-yield process (DAC HYP) is administered subcutaneously once every four weeks, rather than via IV infusion.

Participants in the Phase II CHOICE study had either RRMS or **SPMS**, with worsening disease activity while taking one of three approved interferon therapies. The study showed that DAC HYP was well tolerated when added to an interferon. A statistically significant 72-percent reduction in the frequency of gadolinium-enhancing MRI lesions was seen in the high-dose group (300 mg every four weeks).

The Phase IIb SELECT trial, with 600 participants who have RRMS, was a one-year study of treatment with DAC HYP. This study was subsequently extended for a second year as the SELECTION trial. The study included three treatment arms, with two dose levels (at 150 mg and 300 mg) and a placebo group (given an inactive treatment).

Results of the SELECT trial announced in August 2011 indicated that the annualized relapse rate was decreased by 54 percent in the 150 mg-dose group and by 50 percent in the 300 mg-dose group. It also met its secondary endpoints: in the 150 mg and 300 mg groups respectively, new gadolinium-enhancing lesions were reduced by 69 percent and 78 percent; new or newly enlarging T2-hyperintense lesions were reduced by 70 percent and 79 percent; and the proportion of patients who relapsed was reduced by 50 percent and 51 percent. Sustained disability progression at one year was reduced by 57 percent and 43 percent.

Participants who completed this trial were enrolled in an extended trial called SELECTION. One-year results were presented[4] in 2012. Patients who were on placebo and began treatment with DAC HYP in the extension trial had a 59-percent reduction in annualized relapse rate compared to the year prior, while patients who continued on DAC HYP maintained their low relapse rate from the prior year.

In 2013, further data from this trial were presented.[5] During the second year of treatment, brain-volume loss (atrophy) was 27-percent lower in the treated groups compared with the placebo group at year one. The authors of the study note that this reduction in the rate of brain atrophy may be consistent with neuroprotection.

DAC HYP was further studied in the DECIDE trial,[6] a Phase III study of 1,841 participants with relapsing MS, comparing DAC HYP to Avonex® (interferon beta-1a). DAC HYP was administered subcutaneously once every four weeks for 96 to 144 weeks with a dose of 150 mg. This was compared to a weekly 30-mcg intramuscular injection of Avonex. The study began in March 2010 and was completed in the spring of 2014.

Initial results of the DECIDE trial were presented in 2014. Treatment[7] with daclizumab resulted in a 45-percent reduction in annualized relapse rate (ARR), a 54-percent reduction in new and newly enlarging T2 lesions, and a 65-percent reduction in new gadolinium-enhancing lesions in comparison to Avonex. Risks associated with daclizumab treatment included infections, rash dermatitis, and liver enzyme abnormalities, some of which were serious. More than a third of people on daclizumab reported cutaneous (skin) issues – twice as many as on Avonex – including some cases severe enough to warrant discontinuing the drug. One death of a daclizumab-treated patient from the Phase II study was due to complications of a muscle abscess, and a second death was due to autoimmune liver inflammation. The safety profile of this medication, including the nature of the cutaneous (skin) side effects, will be closely evaluated in further analyses.

In abstracts presented at the 2015 ECTRIMS meeting, DAC HYP was shown to be more effective in patients at risk for high disease activity, as well as for those with less active disease, compared to individuals taking Avonex. Over the course of three years, DAC HYP was also associated with less brain-volume loss with RRMS, compared to individuals taking interferon beta-1a. The safety profile has been well characterized in clinical studies for periods up to six years.

By testing approved medications for relapsing MS in progressive disease, the possibility of extending the use of these well-known medications for progressive MS may be rigorously explored. Unfortunately, as discussed in the following sections on Tysabri and Gilenya, success in relapsing MS does not always predict similar efficacy in those with progressive disease.

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.

A small Phase II clinical trial, Natalizumab Treatment of Progressive Multiple Sclerosis (NAPMS), was performed at Copenhagen University Hospital to study the safety and efficacy of Tysabri treatment of **primary-progressive MS (PPMS)** and **secondary-progressive MS (SPMS)**.[8] It enrolled 24 patients and showed a reduction in markers of inflammation in the spinal fluid, as well as evidence of protection of brain tissue on modern MRI measures. This proof-of-concept study provided encouraging evidence that Tysabri may have beneficial effects in progressive forms of MS.

To continue this line of investigation, a large, randomized trial of Tysabri in SPMS called ASCEND[9] evaluated the effects on the accumulation of disability in people with SPMS. There were 889 SPMS patients enrolled, the majority of whom required assistance for walking and were no longer experiencing MS relapses. Subjects were randomized to receive either Tysabri 300 mg or placebo intravenously every four weeks for 96 weeks.

The results of the ASCEND study were officially presented at the 2016 AAN meeting in Vancouver, British Columbia. The main question under study was whether SPMS patients on Tysabri had decreased overall disability progression during the trial versus those on placebo. The study investigators found that there was no statistical difference in the number of patients with disability progression on Tysabri (44 percent) versus those on placebo (47 percent) and thus the study did not meet its primary aim. There was, however, less progression seen in Tysabri patients in terms of worsening of upper arm function. Also, as would be expected, fewer relapses and new MRI lesions were seen in the Tysabri group. In summary, Tysabri does not seem to be effective in preventing overall disability progression in SPMS, although it may have some benefit in those who continue to have relapses or new MRI disease activity.

Gilenya® (fingolimod)

Company: Novartis

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

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.

Although Gilenya was approved for relapsing-remitting MS (RRMS) in 2010, clinical trials have continued to evaluate its role in MS. The 36-month INFORMS trial evaluated the effect of Gilenya relative to placebo on delaying the time to sustained disability progression in patients with **PPMS**.

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.

A novel, primary-composite disability endpoint was used in the trial, based on the increase in disability as measured by the Expanded Disability Status Scale (EDSS), the 25-Foot Timed-Walk Test (T25FW), and the 9-Hole Peg Test (9-HPT). Other key endpoints were the formation of new lesions and percentage of brain-volume change (PBVC), or brain atrophy (the shrinking or reduction of brain volume). Detailed results of the trial were presented in spring 2015. Gilenya did not prevent the accumulation of disability in patients with PPMS any greater than placebo. Furthermore, PBVC did not differ between the Gilenya and placebo groups. Interestingly, a drug in the same class as Gilenya, siponimod, was able to show a benefit in **SPMS** in 2016 (please see the section on siponimod).

It is certainly disappointing that Gilenya did not significantly slow disease progression in PPMS. These findings, like those of Tysabri in SPMS, have important implications for the understanding of progressive disease, and will no doubt allow researchers to refine how this is studied moving forward.

Another ongoing Gilenya clinical trial is a Study Evaluating Safety and Efficacy of Two Doses of Fingolimod Versus Copaxone.[10] This 12-month trial will compare the marketed dose of Gilenya with one-half this dose, using Copaxone as a comparison, on annual MS relapses and several MRI measures of disease. The goal of this study, which was required by the FDA, is to assess if a lower dose of this medication may be equally effective at reducing the number of relapses in patients with relapsing forms of MS.

Laquinimod (also known as Nerventra®)

Company: Teva Neuroscience, Inc. and Active Biotech

- *Oral medication taken once daily; dosing TBD*
- *Being studied in RRMS and PPMS*

Although its exact mechanisms of action are unknown, laquinimod is an immunomodulator, apparently through its effects on cytokines (small proteins that may stimulate or inhibit the function of other cells) and interleukins (immune-system signaling chemicals). It enhances T-regulatory cell activity, which reduces Th1-inflammatory T-cell activity. It also appears to reduce white-blood-cell penetration of the CNS. In addition to its immunomodulatory actions, laquinimod increases levels of the brain-derived neurotrophic factor (BDNF), possibly contributing to neuroprotection (protecting the nerves and myelin from damage) in MS patients. BDNF is a protein found in the brain that helps to support nerves and their development.

The Phase III ALLEGRO study of 1,106 individuals with RRMS showed that, compared to placebo, laquinimod reduced the annualized relapse rate by 23 percent and the progression of disability by 36 percent. It also was effective on several MRI outcomes, including a reduction in brain atrophy by 33 percent.

The BRAVO Phase III trial was another global, 24-month, double-blind study with 1,300 participants. It was designed to evaluate laquinimod's efficacy, safety, and tolerability versus placebo. In August 2011, the sponsors announced that the study had failed to achieve its primary goal of reducing the annualized relapse rate, although a trend was seen in that direction if the data are adjusted for differences in MRI characteristics at the start of the study.

Because the effect of laquinimod on relapses was more modest than has been seen with other disease-modifying therapies for RRMS, the drug was not considered for approval in the United States in 2012. In 2013, the results of two separate analyses of pooled data from the Phase III ALLEGRO and BRAVO trials studying laquinimod were presented.[11]

The first analysis compared the expected risk of disability progression (given a particular relapse rate) with that seen in the pooled data. In this analysis, the effect of laquinimod on reducing the risk of disability progression was larger than predicted. The second analysis examined the relationship between relapses and disability by looking at disability progression in both relapsing and relapse-free patients in the two trials. About one-third of the patients who progressed were relapse-free, suggesting that these two outcome measures are mediated through different pathways.

Since laquinimod may have more of an effect on disability than on relapses, a new trial looking primarily at laquinimod's disability-preventing impact was designed. This 24-month trial, The Efficacy and Safety and Tolerability of Laquinimod in Subjects With Relapsing Remitting Multiple Sclerosis (CONCERTO[12]), was designed to compare two doses of laquinimod (including a 1.2 mg

dose, which was higher than that tested in prior Phase III studies) with placebo, looking at confirmed disease progression (CDP) as the primary outcome. This is the first modern RRMS trial to prioritize prevention of disability over prevention of relapses. The trial began enrollment of 1,800 patients in 2013, and is expected to run into 2018.

Furthermore, based on its effect on disability in prior trials, laquinimod is also being studied in a **PPMS** trial (ARPEGGIO) that began in 2015.[13] This trial will primarily evaluate the effect of laquinimod on brain atrophy, and secondarily on clinical outcomes. It was designed to enroll approximately 375 people and is anticipated to run through the end of 2017.

Although both the CONCERTO and ARPEGGIO trials were designed to study both the 0.6 mg dose of laquinimod evaluated in prior trials along with higher doses, in January 2016, Teva announced the decision to discontinue the higher doses of laquinimod in both ongoing studies. Eight patients in the high-dose arms of the CONCERTO and ARPEGGIO trials had cardiovascular events versus none in the lower-dose and the placebo arms, so the decision was made to continue to study with only the lower, 0.6 mg dose in which no such events had occurred. In May 2017, an announcement stated that CONCERTO's primary endpoint (time to CDP) was not met, but encouraging results were seen in secondary endpoints.

EXPERIMENTAL MEDICATIONS: MONOCLONAL ANTIBODY MEDICATIONS

About Monoclonal Antibodies

Monoclonal antibodies are derived from cells that are identical (cloned from a single cell and then replicated). They are produced from animal tissue, most commonly laboratory mice. Humanized monoclonal antibodies are antibodies from non-human species, again commonly a mouse, whose protein sequences have been modified to increase their similarity to antibodies produced naturally in humans. Monoclonal antibodies can be extremely powerful and effective, as they can be 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," including alemtuzumab (Lemtrada), daclizumab (Zinbryta), ocrelizumab (Ocrevus), and natalizumab (Tysabri) , which are already approved for MS. Several other monoclonal antibodies have shown promise in MS, and two of these are reviewed in this section.

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.

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.

The drug 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[14] study). 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 (including lower doses of Rituxan used in this study than in previous studies), this study 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.

Rituxan is not likely to be further developed for FDA approval. However, next-generation anti-CD20 monoclonal antibodies have been developed to build on the encouraging data from Rituxan's MS studies, including Ocrevus, which was approved in March 2017 and discussed earlier in the "Approved Medications" section.

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 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 study had 38 people 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.[15] 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[16] demonstrated continued suppression of new MRI lesions at week 48 and a dose-responsive effect on B cells. The

success of these early trials prompted a Phase III study program with two trials in 2016. The trials, ASCLEPIOS I and II, are slated to enroll 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 has an easier route of administration, as it is dosed subcutaneously every four weeks rather than via IV infusion.[17]

EXPERIMENTAL MEDICATIONS: NEW S1P RECEPTOR MODULATORS

About S1P Receptor Modulators

Several investigational oral agents are currently under study that work in a similar manner as 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, 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 less 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.

In RRMS, results from a Phase II dose-finding study of siponimod were 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.

Some of the most exciting news in MS research from the last year surrounded the announcement of the results of EXPAND, a Phase III trial of siponimod in **SPMS**.[18] The trial randomized 1,651 patients with SPMS to siponimod versus placebo in a 2:1 ratio (two times as many patients were given siponimod versus placebo). The primary endpoint of the EXPAND trial was time to three-month confirmed disability progression (CDP). CDP was met when a participant developed an increase in his or her disability that is confirmed by a repeat exam three-months later.

This trial was able to show a small, yet statistically significant, decrease in three-month CDP of 21 percent in those on the study drug compared to those on placebo. Participants in the siponimod arm also showed 23.4 percent slower decrease in their brain volume as compared to placebo. However, no difference was observed between the two groups in changes in the timed 25-foot-walk. Relapses were decreased in the group taking siponimod. Overall, patients tolerated the drug well, though more serious adverse events and infections occurred in the siponimod group. The EXPAND trial represents a breakthrough in the treatment of **SPMS**; until now, no convincing evidence had shown any current MS treatment to be effective in this form of the condition.

Ozanimod (formerly RPC1063)

Company: Celegne

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

Ozanimod (RPC1063) is a selective modulator of one type of S1P receptor, S1P1. [Correction: Ozanimod is actually a selective modulator of two types of S1P receptors: S1P1 and S1P5. This note was added after publication.] It is given as a once-daily pill, and was studied in a Phase II trial called RADIANCE, where the 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 yearlong 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 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 (a potential risk related to the eye for patients who take Gilenya) were reported in the subjects receiving ozanimod.[A3]

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.

The drug has moved into a larger, Phase III program with two trials that compare its efficacy against Avonex. The first trial, SUNBEAM, enrolled more than 1,300 patients in 20 countries who were followed for at least 12 months. Celgene reported that the trial was a success in February 2017, having met its primary endpoint of decreased relapse rate and its secondary endpoints of decreased lesion formation. The second trial is expected to run through the end of 2017.

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.[19] 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 of ponesimod may have the best benefit-to-risk profile in this trial. An extension trial over two years (presented in 2013) demonstrated continued efficacy and no new safety issues.

In spring 2015, Actelion decided to advance this agent to a Phase III trial in RRMS: OPTIMUM,[20] a multicenter, randomized, double-blind study to compare the efficacy and safety of ponesimod to Aubagio in subjects with relapsing forms of multiple sclerosis. The study aims to determine whether ponesimod is more effective than Aubagio in reducing relapses. The study is expected to enroll approximately 1,100 subjects, randomized in two groups in a 1:1 ratio to receive ponesimod 20 mg per day or Aubagio 14 mg per day, and is expected to last approximately three years.[A4]

A second, large trial is currently underway that employs a combination approach; 600 participants will be randomized either to Tecfidera alone or Tecfidera plus ponesimod in order to understand if there is an added benefit in terms of disease control when the two agents are combined. The POINT study (POnesImod aNd Tecfidera) is of interest as it is the largest study in MS to look at a combination of oral agents.

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.

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**[25] showed a trend toward benefit; however, the results were not statistically significant.[26]

In 2012, results from a Phase II study of 30 patients taking masitinib were released. These indicated what is termed "proof of concept," showing that this agent may have potential in treating both **PPMS** and relapse-free **SPMS**. The study investigated the hypothesis that masitinib's action of targeting and inhibiting mast cells may delay the onset of symptoms associated with progressive forms of MS.

The results showed that for the primary endpoint of Multiple Sclerosis Functional Composite (MSFC) score, which measures upper and lower limb function as well as cognition, 32 percent of those treated with masitinib showed a response to treatment versus none on placebo. Responses were seen in the third month and were sustained over the 18-month duration of the study.

A Phase IIb/III multicenter, randomized, double-blind, placebo-controlled trial[27] is currently underway. The investigators planned to recruit 450 people with **PPMS or SPMS without relapses**. The primary endpoint will be an improvement in the MSFC scale at 96 weeks. In summer 2015, the trial sponsor announced that after one third of participants enrolled in the trial were treated for a total of 48 weeks (halfway through the trial), they were assessed for an array of disability endpoints. The observed changes were significant enough for the masitinib trial to be declared "non futile" by the Independent Data Safety Monitoring Committee. This decision indicates that the Phase III clinical trial has the potential to succeed and is thus justified to continue.

Ibudilast

Company: MediciNova

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

Ibudilast (MN-166) is an oral agent with novel immune-modulating and potential neuroprotective properties that is being studied in progressive forms of MS. This agent has also been studied in a range of conditions including chronic pain, headache, and in the treatment of 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)**[28] was launched in fall 2013. It includes 28 enrolling clinical sites across the United States.

The trial is designed to evaluate the safety, tolerability, and efficacy of ibudilast administered twice daily to individuals with **PPMS** or **SPMS**. Primary outcomes of this trial will be MRI findings, including brain atrophy, as this is felt to be an important aspect of progression in MS. There will also be several other imaging and clinical-disability outcomes evaluated.

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.

Tcelna™ (formerly Tovaxin®)

Company: Opexa Therapeutics

- *Given via five subcutaneous injections per year*
- *Has been studied in SPMS*

Tcelna is a T-cell vaccine. In the process of administering this vaccine, myelin-reactive T cells are removed from a small amount of the patient's blood, inactivated, and then injected back into the patient. The body's immune system may then potentially protect the myelin from these cells.

The TERMS placebo-controlled, one-year study in 150 people with clinically isolated syndrome (CIS) and RRMS to evaluate Tcelna's efficacy, safety, and tolerability has been completed. The treatment did not achieve statistical significance in the primary endpoint, which was a reduction in the cumulative number of gadolinium-enhancing lesions.

However, a 37 percent decrease was seen in the annualized relapse rate of individuals given Tcelna versus placebo. The drug was well tolerated with mild skin reactions in some individuals; no serious safety concerns were raised by this study. In a subgroup of 70 people who had at least one relapse in the 12 months prior to enrolling in the study and who had no previous exposure to MS therapy, Tcelna reduced their annualized relapse rate by 64 percent compared to placebo. Additionally, 76 percent of Tcelna-treated patients remained relapse-free at one year compared with 60 percent of placebo patients.

Tcelna was more recently studied in a **Phase II trial in SPMS**, the Abili-T study.[29] Abili-T enrolled 183 individuals with SPMS in a placebo-controlled two-year trial. The Abili-T study results were reported in a press release in October 2016. Unfortunately, the study did not find a reduction in brain atrophy (the primary endpoint) or in disability progression (the secondary endpoint) in the individuals given Tcelna versus placebo. Although vaccines are an attractive strategy in MS treatment, to date there is not any convincing evidence that they have the potential for becoming an effective therapy option.

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 magnetic resonance imaging (MRI) data, with minocycline decreasing gadolinium-enhancing activity by 50 percent over 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 at ECTRIMS in 2012,[30] and disappointingly, minocycline did not provide significant improvement to either clinical or MRI outcomes.

Another Phase III trial looking at minocycline reported positive data in fall 2015. This Canadian Phase III double-blind study began in 2009, and enrolled 142 people with a clinically isolated syndrome (CIS). The participants were randomized to oral minocycline at 100 mg twice daily or to an identical placebo. Treatment was continued for up to two years, or until MS was confirmed. Those receiving minocycline had a 44.6 percent lower risk of conversion to MS at six months, and a 37.6 percent lower risk at 12 months, versus individuals taking a placebo. The authors suggest that with the known safety and low cost of minocycline, this medication could be considered for the initial treatment of individuals with a first clinical demyelinating event, particularly in geographic regions without access to approved disease-modifying therapies.

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 patients on 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.[31] This Phase II study evaluated whether high-dose simvastatin can slow the rate of whole-brain atrophy, and/or disability, in **SPMS**.[32] In the MS-STAT trial, 140 people were randomized, and the simvastatin group had a statistically significant benefit over placebo on the Expanded Disability Status Scale (EDSS) at two years. The rate of brain atrophy was also decreased. This serves as a positive proof-of-principle project that may allow for a larger trial, which can look at the clinical outcomes as the primary outcomes measure. As effective treatments for SPMS remain an unmet need, and since these are readily available medications, this is an exciting avenue for future research.

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 pilot 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 this 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 agent with potential remyelinative 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,[33] involving 64 healthy adult volunteers and 42 people with relapsing 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.[34] The study recruited individuals with newly-diagnosed MS involving the visual pathways (optic neuritis) to evaluate the drug'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 thickness of the retinal layers (optic nerve neurons and axons), or on visual function. Anti-LINGO-1 was generally well-tolerated in this study, noting that 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)[35] 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. It remains to be seen how this medication will be carried forward into further MS research.

Other experimental treatments under investigation to potentially foster remyelination or myelin repair include agents in early stages of development – and still with experimental names – such as **GSK239512**[36] and **rHIgM22**.[37]

Amiloride, Phenytoin, and Sodium Channel Blockade: The accumulation of salt and potassium within the cells of MS lesions may possibly contribute to cellular injury and neurodegeneration (the breakdown of nerves). This hypothesis would suggest that by blocking certain channels in these cells, the buildup of these molecules can be prevented and neurodegeneration can also be prevented. This strategy was tested and data presented in 2013,[38] looking at the use of amiloride – a potassium-sparing diuretic approved for the treatment of high blood pressure and congestive heart failure. This medication may have the potential to provide this neuroprotective activity.

The effect of **amiloride** has been studied in 14 people with **PPMS** using MRI markers of neurodegeneration as outcome measures of neuroprotection. Individuals underwent MRI scans before and during amiloride treatment, at a standard dose used for high blood pressure, for a period of three years.

Researchers found 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 patients. These findings suggest that amiloride may exert neuroprotective effects. Because amiloride does not readily cross the blood-brain barrier to gain access to the CNS, the precise mechanism for these results is not clear. This pilot study was the first effort in people with MS to focus on neuroprotection using amiloride, and supports further investigation of this drug as a potential neuroprotective agent in MS.

It is worth noting that this strategy was successful in a study of the anti-seizure medication **phenytoin** (brand name Dilantin®), which also works by modulating sodium channels. A Phase II clinical trial assessed whether phenytoin could be neuroprotective in acute optic neuritis[39] (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 this AON 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.

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.

This intriguing study 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.

Amiloride is also being studied in a larger study, MS-SMART. This ongoing study[40] is 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 to see if any differences occur in the rate of brain atrophy. This study is expected to finish in 2018 and is intriguing as 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.

Clemastine is an older anti-histamine that is available over the counter. It was discovered[41] to hold potential for re-myelination through the innovative laboratory work of a researcher in San Francisco. This finding led to a small Phase II placebo-controlled crossover study (participants are initially assigned to one study group and then switched midway through) 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 improvement in visual function. Overall, the treatment was safe, though 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 functional improvement through re-myelination.

Idebenone (Catena® or Sovrima®): This experimental drug, similar to coenzyme Q10, was initially developed to treat Alzheimer's disease and other cognitive defects. Coenzyme Q10 is produced within your 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,[42] sponsored by the National Institute of Neurological Disorders and Stroke, recruited 44 participants with **PPMS** who had little to moderate disability. The trial began in July 2009 and was scheduled for completion in September 2016, with an extension trial continuing through 2018.

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 primarily tested 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** presented interim results in 2012. This open-label, dose-escalation/confirmation trial showed MIS416 to be well-tolerated and identified a clinical dose for further evaluation. Moreover, during the dose-confirmation portion of the study, eight of 10 participants with SPMS who were treated with MIS416 for 12 weeks showed some improvement. A further Phase II study[43] in SPMS was planned to be completed in late 2016.

Transdermal Administration of Peptides: A small Polish study of 30 individuals[44] with RRMS evaluated the efficacy and safety of transdermal (skin patch) administration of two dose levels of three myelin peptides: **MBP 85-99**, **PLP 139-151**, and **MOG**, versus placebo. In the lower-dose group, which received 1 mg each of the three peptides, the annual relapse rate at one year was reduced by 65 percent compared with placebo. Progression, as measured by the Expanded Disability Status Scale (EDSS), was slightly lower, indicating that disability did not worsen, and may have slightly improved. Additionally, 56 percent were relapse-free versus 10 percent in the placebo group. The treated group also showed a decrease in gadolinium-enhancing lesion volume and T2-lesion volume. The treatment was safe and well-tolerated. This approach of using a combination of peptides may be pursued in future studies.

IL-17 Modulators: Secukinumab (AIN457) and CJM112. **IL-17** is one of several cytokines produced by the immune system. Cytokines

are small proteins that may stimulate or inhibit the function of other cells. IL-17 appears to be a major inflammatory component in MS.

Secukinumab is a humanized monoclonal antibody to IL-17 that is FDA-approved to treat psoriasis. A proof-of-concept trial in RRMS[45] enrolled 73 participants and showed a reduction in gadolinium-enhancing MRI lesions compared with placebo.[46]

A larger, Phase II trial was planned to enroll approximately 380 individuals with relapsing MS; the design of the study was presented at ECTRIMS in fall 2013, but was cancelled in favor of the clinical development of **CJM112**, which also targets IL-17 and is administered by subcutaneous injection. The design of the Phase II trial was presented at ECTRIMS in the fall of 2015. To date, no individuals with MS have received this experimental treatment.

ATL1102 is an oral agent 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[47], 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 2016, the company announced its intent to run a Phase IIb trial of ATL1102, although it is unclear when it will begin.

Pixantrone (PIX) is under investigation as an alternative for the effective but cardio-toxic drug Novantrone® (mitoxantrone or MIX) in the treatment of aggressive RRMS or **SPMS**. In a Phase I/II study of 18 people with aggressive disease, results published in 2015[48] suggested that pixantrone was as effective as Novantrone, but with less cardiotoxicity. Although via a different mechanism of action than Rituxan and Ocrevus, pixantrone was shown in this study to reduce B cells by 95 percent. According to the authors,[49] pixantrone is structurally similar to Novantrone and both medications have similar immuno-suppressive properties in animal studies. However, the authors state that pixantrone is less toxic to the heart.

SR-CRH-01 is a stabilized, neuropeptide, also known as **Aimspro®**. In a Phase II double-blind, placebo-controlled study of 20 people with **SPMS** presented in 2014,[50] SR-CRH-01 was well-tolerated when given by subcutaneous injection twice weekly for four weeks, resulting in significant improvements in several secondary endpoints. These endpoints included the MS Functional Composite (MSFC), the Timed 25-Foot Walk (T25-FW), and the mean 9-Hole Peg Test (9-HPT). Larger, longer-term studies are warranted given these promising results. However, no new trials are presently being conducted.

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.[51] 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 Mokry and colleagues[52] 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.

In animal models of MS, Vitamin D was found to directly terminate the production of disease-causing proteins, which may shed light on the mechanism of Vitamin D in MS. When Vitamin D is given to mice with EAE (an animal model of MS), it blocks the gene that encodes a protein that is known to cause inflammation, IL-17, stopping its production. This study also demonstrates that Vitamin D increases suppressive T cells that combat inflammation.

An important longitudinal cohort study presented in 2012 by Mowry and colleagues[53] 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.

A number of new clinical trials, mostly using Vitamin D as an add-on to existing therapies in Phase IV studies, are ongoing to assess if supplemental Vitamin D can exert such disease-modifying effects. To follow are examples of these types of investigations.

The results of the SOLAR study, the largest randomized trial of Vitamin D therapy in MS patients to date, were presented at ECTRIMS 2016. The SOLAR study[54] 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 length was changed to 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, or no worsening of disability.

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[55] 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.[56] 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 presently enrolling, with a goal of 172 participants, and is expected to run through June 2018.

Mowry's trial is one among a group of trials around the world that continue to study Vitamin D supplementation in MS. One trial of particular interest that is currently running in Austrailia and New Zealand, PrevANZ, is a

Phase II study that is 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.

Please note that while 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 always 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[57] from Oregon conducted a two-year study which followed 27 individuals with MS who were given lipoic acid, a readily available anti-oxidant supplement thought to aid the function of mitochondria, and 24 patients who were given placebo. (Mitochondria are cell structures that break down nutrients to create energy.) After 96 weeks, the researchers found that the subjects 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 arm had kidney issues during the trial, however, a kidney doctor thought this was unrelated to the lipoic acid treatment.

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 patients 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 are 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, they would be virtually undetectable in clinical practice. MD1003 was well-tolerated. The overall incidence of adverse events was similar across the two groups. One patient treated with MD1003 died from suicide; however, this event was not considered to be related to the medication.[58]

These results suggest a possible therapeutic effect of high-dose biotin in progressive MS, and certainly merit further study. A Phase III study comprised of 600 individuals with progressive MS is currently running. The study commenced 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. Both groups will then be given the high-dose biotin and followed for an additional 12 months.

Biotin is certainly an attractive option as it is a vitamin and not known to have significant risks. However, it is not generally recommended that individuals begin such a regimen at the present time. Further studies also need to determine if any toxic effects could result from taking such high doses of this vitamin.

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 – especially 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 immune system, typically with high-dose chemotherapy, occurs.

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. Then, the patient'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.

One 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.[59] 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[60]; 69 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 it was reported that 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 suicide attempts, neither completed, occurred in participants who 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 patients for three to 13 years. One early participant in this study died of transplant-related complications. This death 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 that was given in order 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 patients remained stable, with the other 30 percent showing evidence of disease progression.[61] 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 MS patients, but later on decreases in brain volume were more similar to that of aging persons without MS.

A study in Sweden published previously[62] 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 over a 10-year period.[63] 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 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 that 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[64] 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. Then, they filtered out any cells that promote inflammation, and the remaining stem cells were grown in larger numbers and then given back to the patients 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 understood, 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; this effect 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.[65] MESEMS is an international group of eight independent study centers that have created a shared study design in order to be able to increase the power and significance of their results. The group plans to enroll 160 patients 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 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 an open-label Phase I clinical trial,[66] which has been completed, but the full results have not been published. This small, single-center trial of 20 individuals with progressive MS involved infusing doses of stem cells harvested from the patients' own bone marrow directly into the cerebral spinal fluid (CSF), typically done via lumbar puncture, repeatedly over six months.

As an open-label study, the primary endpoint will be to determine the safety of this approach. Potential subsequent investigations may pursue efficacy, determine optimal dose and route of administration, and identify people most likely to benefit from this therapeutic approach. It is important to recognize that as an open-label, uncontrolled, unblinded Phase I study, this project is at the earliest stages of experimental, human research. It cannot, by its very design, provide meaningful information about efficacy, despite what has been reported by the media.

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 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, blood pressure helps determine the risk of stroke, and cholesterol levels are a biomarker and risk indicator for coronary and vascular disease. 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, PRMS, 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 MRI lesions), as well as on demographic factors that may be concerning for a more difficult disease course.

The search for biomarkers of MS is referred to throughout this publication, and studies are ongoing with all major MS drugs to find markers that will help determine who should be treated with that drug as well as how effective the drug is after therapy is 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.

A genetic study, with results reported in 2012, looking at the response to Copaxone, also suggested that multiple genetic markers may predict a favorable response to this medication. A further study of genetic predictors of response to Copaxone was presented at ECTRIMS in fall 2014[67] and suggested that a particular array of genetic markers could accurately predict a high response to Copaxone. This investigative procedure is to be evaluated in further studies.

An additional use of biomarkers will be 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.

For example, genes found to be expressed differently in MS effectively become biomarkers for disease progression and may change as the result of treatment. A recent study identified several candidate genes that could potentially serve as biomarkers of interferon treatment or targets for treatment in MS.

Additionally, a study using 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.

An ongoing 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

A growing body of evidence has been found for the genetic component in MS. The studies on biomarkers have arisen as the result of this work, and a number of genes that are linked to the development of MS have been identified. This field of research saw a major breakthrough in August 2011, when the journal *Nature* published the results of the largest MS genetics study ever undertaken.[68] 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 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.

Since that point in time, larger studies have greatly expanded upon that work, including[69] the most recent large-scale study of genetics and MS in which 47,351 persons with MS and 68,284 healthy controls were included. 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 subject submitted saliva for targeted genotyping and completed questionnaires online to capture demographics and risk factors. For each subject, 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 subjects (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 subjects 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. MS subjects have a significant excess of current smokers than asymptomatic subjects. Four out of the initial 1,583 asymptomatic subjects developed MS after enrollment, including the subject 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 duration of the study was two years.

In a follow-up study published in early 2017, investigators studied women in the highest[70] and lowest genetic risk categories. They reported that in 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 subjects with a higher genetic score when compared to those with a lower genetic score.

The GEMS study highlights the role of electronic communication, e.g., using social media and web-based questionnaires, in rapid and large-scale subject recruitment of first-degree relatives. It also provides a first estimate of the incidence of MS among this high-risk population, critically informing the design of a prospective study of high-risk family members. Identification of people at the highest risk for MS may one day allow for an intervention before a person has any symptoms.

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

Over the past decade, it has become clear that interactions between a person's microbiome and their 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. Specifically, researchers have hypothesized that imbalances in the number or types of different strains of bacteria could potentially cause the immune system to be inappropriately activated with autoimmune disease as the result.

Multiple groups presented research on the microbiome and its potential connection[71] to MS in 2016. In one study, 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 less diversity, something that was reversed in the control group. In another study, investigators from the MS Microbiome Consortium presented their 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[72]/experimental program and sequencing/bioinformatics program. The iMSMS has a goal of analyzing the microbiome of 2,000 MS patients and 2,000 healthy controls. They are also working with animal models.

Initial results from this group show significant differences in the microbiomes of patients treated with Copaxone compared to untreated subjects. 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.

Strikingly, when transferred into germ-free mice, gut microbiota from an individual with MS resulted in more severe EAE (an animal model of MS) than microbiota from a healthy control. This may be the most intriguing result from this project to date. Observed differences between cases and controls suggest a biological effect and warrant further investigation, as do effects of geographic, demographic, and dietary factors. Study of the human microbiome has the potential to yield important insights in understanding the basic processes underlying the disorder of MS as well as possible treatment strategies.

A separate study of microbiome in MS looked at differences in Vitamin D levels predicting alterations in gut bacteria. Analysis of 43 subjects showed increased abundance of a type of helpful bacteria called

Ruminococcaceae in untreated MS patients with a serum Vitamin D level above 40 ng/ml, versus patients 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

It is certainly intriguing to consider that dietary modification could be utilized in some way to impact the course of MS for a given individual. Up until this point, scant evidence has been found to show that changing one's diet is beneficial for MS, though multiple researchers are now looking into the question with well-designed trials.

A recently published study randomized 61 people to a low-fat plant based diet, versus a control group for 12 months. Investigators did not find any differences in MS activity between the groups, though improvements were seen in fatigue scores, body mass index (BMI) measures, and cholesterol panels. The study authors did note that the small size of the study may have impeded their ability to identify greater effects on the condition.[73]

One trial currently running is a study of 100 people randomized to a paleolithic[74] 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 people has commenced, which randomizes a group of patients to a modified Mediterranean diet versus controls. A third[75] study that is being conducted will place people in two dietary groups, either a calorie-restricted group (78 percent of recommended calories daily) versus 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 recommend calorie intake the other two days of the week. These dietary trials stand to inform and shape future treatment plans for individuals with MS.

Salt

An array of recent research ranging from molecular studies to animal models and even some preliminary human data, has implicated levels of dietary salt – sodium chloride, or NaCl – as potentially affecting MS outcomes. In research presented in 2013[76], high dietary salt was found to increase autoimmune neuro-inflammation by markedly boosting a Th17 helper T cell-driven autoimmune response in EAE (an animal model of MS). Th17 is an immune-system cell (lymphocyte) involved with the inflammation that causes damage to the myelin and nerves with MS. This Th17-boosting property of dietary salt was also seen in humans.

In a separate study,[77] higher-salt consumption was associated with increased clinical and MRI disease activity in people with MS. Seventy patients with RRMS were followed over two years, tracking sodium

intake. This was in conjunction with clinical and MRI assessment every three-to-six months or at the time of relapse. Researchers found that individuals with high-sodium intake had 3.4-times greater odds of developing a new lesion on the MRI, and on average, had eight more T2 lesions on MRI. MS relapse rates were higher among those with high-sodium intake as well.

In 2015, many additional studies were published showing a connection between salt and MS.[78] Krementsov and colleagues fed high-salt and low-salt diets to three genetically different groups of mice and compared their EAE disease course. The researchers showed that in certain strains of mice, high-salt diets led to worsening of EAE. Furthermore, in one strain of mice, this effect was gender-specific, occurring only in females. Because the investigators did not find an alteration in the Th1/Th17 ratio mentioned above, they postulated that the salt caused an increased permeability of the blood-brain barrier leading to attacks by the immune system.

Two other studies were able to show a change in immune cells after exposure to high-salt environments. Hafler and colleagues showed changes in a cell type important for the regulation of the immune system called the "Treg" cell. The Treg cell is thought to play a key role in suppressing those cells that might initiate autoimmune disease. The researchers found the effect of decreased Treg function both in individual cells exposed to high salt as well as in mice fed a high-salt diet.[79]

Muller and colleagues looked at a different type of immune cell that is important in MS: the macrophage. A macrophage is a type of white blood cell that works to ingest and destroy foreign substances. In cells, they found that a certain type of macrophage was less able to block the autoimmune activities of damaging T cells in a high-salt environment. In mice, they found that a high-salt diet led to decreased abilities of macrophages to aid in wound healing.

The theory that salt may increase MS inflammation remains to be proven, and interventional studies will need to be performed to establish causality. However, this theory could have far-reaching practical dietary implications for individuals with MS.

CLOSING NOTES

In summary, the future of MS disease-modifying therapies (DMTs) for MS continues to be promising, both in terms of new information about currently approved DMTs and exciting results for emerging therapies. Advances in genetic and biomarker studies hold the promise that, in the future, it will be possible to personalize the decisions about MS therapy in a precise, biologically-driven manner.

More than ever, the field of MS research relies upon the willing participation of patients in clinical trials. We now recognize how ethnically, racially, genetically, and culturally diverse the MS community is, but diversity in our clinical trial populations is lacking. In 2015, data from six randomized, placebo-controlled trials were used to examine the baseline characteristics and clinical outcomes in white, black, Asian, and Hispanic populations. The results were challenging to interpret due to the incredibly low number of non-white participants in clinical trials, which in turn makes our clinical trial results hard to interpret in the real world. The field of MS research needs a diverse population recruited into clinical trials to truly know that these medications are globally effective in MS.

This *MS Research Update* has summarized the breakthrough trials that have occurred in **PPMS** and **SPMS**, as well as investigations into neuroprotection, remyelination, and repair. For the first time in the history of MS therapeutics, clinicians are realizing the possibility of offering treatments not only for relapsing MS, but also for the progressive forms of the disease. Furthermore, the goal of reversing the damage caused by this disease is within reach.

In recent years, our arsenal of MS therapies has grown considerably, with more on the way. Along with these new therapies come a host of new challenges and risks, which will require vigilance and a thoughtful approach to medication selection and management. Finally, well-designed studies looking at the impact of dietary supplements and other diet modifications will bring the sort of scientific rigor needed to truly answer these questions for individuals with MS.

As clinicians have more numerous and more complex treatment options to offer individuals with MS, the need for patient education and awareness has become more crucial. Now more than ever is the age of empowered, highly-informed patients, who can be true participants in their MS care in collaboration with their treatment team. We hope this update is a valuable part of that process. For more information about clinical trials, please visit **www.clinicaltrials.gov**; for participation opportunities, please visit **mymsaa.org/clinicaltrials**. For more information about MS and its treatments, please contact MSAA at **(800) 532-7667**, or visit **mymsaa.org**.

APPROVED LONG-TERM TREATMENTS FOR MS:
SELF-INJECTED MEDICATIONS

NAME AND TYPE OF MEDICATION	HOW ADMINISTERED AND SIDE EFFECTS	ADDITIONAL NOTES
Avonex® (interferon beta-1a); immune system modulator with antiviral properties	30 micrograms taken via weekly intermuscular injection; side effects include flu-like symptoms and headache, blood count and liver test abnormalities	Side effects may be prevented and/or managed effectively through various treatment strategies; side effect problems are usually temporary. Blood tests may be given periodically to monitor liver enzymes, blood-cell counts, and neutralizing antibodies.
Betaseron® (interferon beta-1b); immune system modulator with antiviral properties	250 micrograms taken via subcutaneous injection every other day; side effects include flu-like symptoms, injection-site skin reaction, blood count and liver test abnormalities	Side effects may be prevented and/or managed effectively through various treatment strategies; side effect problems are usually temporary. Blood tests may be given periodically to monitor liver enzymes, blood-cell counts, and neutralizing antibodies.
Copaxone® (glatiramer acetate); synthetic chain of four amino acids found in myelin; it is an immune system modulator that blocks attacks on myelin	20 (daily) or 40 (three times weekly) milligrams taken via subcutaneous injection; side effects include injection-site skin reaction as well as an occasional systemic reaction – occurring at least once in approximately 10 percent of those tested	Systemic reactions occur about five to 15 minutes following an injection and may include anxiety, flushing, chest tightness, dizziness, palpitations, and/or shortness of breath. Usually lasting for only a few minutes, these symptoms do not require specific treatment and have no long-term negative effects. Copaxone was originally approved at 20 milligrams daily, but in 2014, a new dose of 40 milligrams three times weekly was approved by the FDA. Both dosing regimens remain available.
Extavia® (interferon beta-1b); immune system modulator with antiviral properties	250 micrograms taken via subcutaneous injection every other day; side effects include flu-like symptoms, injection-site skin reaction, blood count and liver test abnormalities	Side effects may be prevented and/or managed effectively through various treatment strategies; side effect problems are usually temporary. Blood tests may be given periodically to monitor liver enzymes, blood-cell counts, and neutralizing antibodies.

NAME AND TYPE OF MEDICATION	HOW ADMINISTERED AND SIDE EFFECTS	ADDITIONAL NOTES
Glatopa® (glatiramer acetate); as a generic version of Copaxone, Glatopa is a synthetic chain of four amino acids found in myelin; it is an immune system modulator that blocks attacks on myelin	20 milligrams taken daily via subcutaneous injection; using study results from trials with Copaxone, side effects include injection-site skin reaction as well as an occasional systemic reaction – occurring at least once in approximately 10 percent of those tested with Copaxone	Using study results from trials with Copaxone, systemic reactions occur about five to 15 minutes following an injection and may include anxiety, flushing, chest tightness, dizziness, palpitations, and/or shortness of breath. Usually lasting for only a few minutes, these symptoms do not require specific treatment and have no long-term negative effects.
Plegridy® (interferon beta-1a); immune system modulator with antiviral properties	125 micrograms taken via subcutaneous injection once every two weeks; side effects include flu-like symptoms, injection-site skin reaction, blood count and liver test abnormalities	Side effects may be prevented and/or managed effectively through various treatment strategies; side effect problems are usually temporary. Blood tests may be given periodically to monitor liver enzymes, blood-cell counts, and neutralizing antibodies.
Rebif® (interferon beta-1a); immune system modulator with antiviral properties	44 micrograms taken via subcutaneous injection three times weekly; side effects include flu-like symptoms, injection-site skin reaction, blood count and liver test abnormalities	Side effects may be prevented and/or managed effectively through various treatment strategies; side effect problems are usually temporary. Blood tests may be given periodically to monitor liver enzymes, blood-cell counts, and neutralizing antibodies.
Zinbryta® (daclizumab); genetically engineered monoclonal antibody that binds to CD25, a receptor on T cells that is thought to become activated in response to MS	150 milligrams taken via subcutaneous injection once per month; side effects include cold symptoms, upper-respiratory tract infection, rash, influenza, throat pain, eczema, enlargement of lymph nodes, depression, and increased liver enzymes	Zinbryta has a boxed warning stating that the drug can cause severe liver injury and monthly blood tests to monitor the patient's liver function are required. Other risks include: immune conditions, hypersensitivity reactions (anaphylaxis or angioedema), increased risk of infections, and depression and/or suicidal ideation. Zinbryta should be used only in patients who have had an inadequate response to two or more MS drugs.

APPROVED LONG-TERM TREATMENTS FOR MS:
INFUSED MEDICATIONS

NAME AND TYPE OF MEDICATION	HOW ADMINISTERED AND SIDE EFFECTS	ADDITIONAL NOTES
Lemtrada® (alemtuzumab); humanized monoclonal antibody that rapidly depletes or suppresses immune system cells (T and B cells), which can damage the myelin and nerves of the CNS	Five-day course of 12 mgs daily via intravenous (IV) infusion and followed one year later by a second three-day course; side effects include rash, itching, headache, pyrexia, nasopharyngitis, nausea, diarrhea and vomiting, insomnia, numbness/ tingling, dizziness, pain, flushing, and infection	Adverse events include infusion reactions, increased risk of infection, emergent autoimmune diseases, a potentially severe bleeding disorder called ITP, and an increased risk of malignancies including thyroid cancer, melanoma, and lymphoproliferative disorders. Lemtrada is only available through the Lemtrada REMS (Risk Evaluation and Mitigation Strategy) program.
Novantrone® (mitoxantrone); antineoplastic agent; immune system modulator and suppressor	IV infusion once every three months (for two to three years); side effects include nausea, thinning hair, loss of menstrual periods, bladder infections, and mouth sores; urine and whites of the eyes may temporarily turn bluish	Carries risk of cardiotoxicity (heart damage) and leukemia; it may not be given beyond two or three years. Testing required for cardiotoxicity, white blood cell counts, and liver function. Due to risks, Novantrone is seldom prescribed for MS. Those taking Novantrone now or previously need annual heart evaluations.
Ocrevus™ (ocrelizumab); humanized monoclonal antibody designed to selectively target CD20-positive B cells, a type of immune cell important to the MS-disease process.	600-milligram dose given via IV every six months; initial dose given in two 300-milligram doses; side effects include infusion reactions, which can be serious, increase in infections (upper and lower respiratory tract infections and skin infection most commonly seen in studies)	Should not be used in patients with hepatitis B infection or a history of life-threatening infusion-related reactions to Ocrevus. Other rare adverse events, including cancer and progressive multifocal leukoencephalopathy (PML), could potentially occur, but these risks are still being investigated; as of the time of approval, no cases of PML had occurred.
Tysabri® (natalizumab); humanized monoclonal antibody; inhibits adhesion molecules; thought to prevent damaging immune cells from crossing the blood-brain barrier	300 mg dose given via IV infusion every four weeks; side effects include headache, fatigue, depression, joint pain, abdominal discomfort, and infection	Risk of infection (including pneumonia) was most common serious adverse event during studies. The TOUCH Prescribing Program monitors patients for signs of PML; risk factors include: the presence of JC virus antibodies, previous treatment with immunosuppressive drugs, and taking Tysabri for more than two years.

ORAL MEDICATIONS

NAME AND TYPE OF MEDICATION	HOW ADMINISTERED AND SIDE EFFECTS	ADDITIONAL NOTES
Aubagio® (teriflunomide); immunomodulator affecting the production of T and B cells; may also inhibit nerve degeneration	7 or 14 milligram tablet taken orally, once per day; side effects include headache, elevations in liver enzymes, hair thinning, diarrhea, nausea, neutropenia (a condition that reduces the number of certain white blood cells), and paresthesia (tingling, burning, or numbing sensation)	More severe adverse events include the risk of severe liver injury and the risk of birth defects if used during pregnancy. A TB test and blood tests for liver function must be performed within six months prior to starting Aubagio, and liver function must be checked regularly. If liver damage is detected, or if someone becomes pregnant while taking this drug, accelerated elimination of the drug is prescribed.
Gilenya® (fingolimod); S1P-receptor modulator, which blocks potentially damaging T cells from leaving lymph nodes	0.5 milligram capsule taken orally once per day; side effects include headache, flu, diarrhea, back pain, abnormal liver tests, and cough	Adverse events include: a reduction in heart rate (dose-related and transient); infrequent transient AV conduction block of the heart; a mild increase in blood pressure; macular edema (swelling behind the eye); reversible elevation of liver enzymes; and a slight increase in lung infections (primarily bronchitis). Infections, including herpes infection, are also of concern. A six-hour observation period is required immediately after the first dose, to monitor for cardiovascular changes.*
Tecfidera® (dimethyl fumarate); immunomodulator with anti-inflammatory properties; may have neuroprotective effects, potentially protecting the nerves and myelin covering	240-milligram tablet taken twice daily; side effects include flushing and gastrointestinal events; reduced white blood cell (lymphocyte) counts; elevated liver enzymes in small percentage of patients	Adverse events include mild or moderate upper respiratory infection, pruritus (chronic itching), and erythema (skin redness or rash). Gastroenteritis (an inflammation of the lining of the intestines) and gastritis (an inflammation of the stomach lining) have also occurred. Reduced white-blood cell counts were seen during the first year of treatment. Liver enzymes were elevated in 6 percent of individuals taking Tecfidera, compared to 3 percent on placebo.*

**Progressive multifocal leukoencephalopathy (PML), a potentially fatal, viral infection of the brain, has occurred in a few patients taking either Gilenya or Tecfidera. The Tecfidera cases have been associated with low counts of lymphocytes, a type of white blood cell.*

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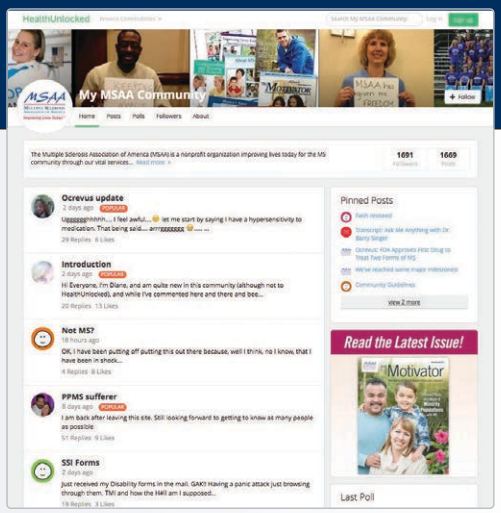

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