

MS RESEARCH UPDATE



This year's *MS Research Update* has been published jointly by the Multiple Sclerosis Association of America (MSAA), the Consortium of Multiple Sclerosis Centers (CMSC), and the International Organization of MS Nurses (IOMSN). MSAA greatly appreciates the support from the CMSC and IOMSN to assist with the production of this publication. 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 2016 conferences could not be included in this writing. Information in this publication includes data presented at the 2015 conferences, as well as any important updates that occurred in early 2016. Please visit MSAA's website at mymsaa.org for future summaries of 2016 conference highlights.

To learn about the Consortium of Multiple Sclerosis Centers (CMSC), please visit mscare.org. They may also be contacted via phone at **(201) 487-1050** or via email at info@mscare.org. For information about the International Organization of MS Nurses (IOMSN), please visit iomsn.org.

MS RESEARCH UPDATE

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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 streamlined *MS Research Update* has been refined to emphasize numerous experimental drugs currently under investigation for the long-term treatment of multiple sclerosis (MS). Entirely new clinical trial data on some of the approved disease-modifying therapies (DMTs) has also been included. Please note that in order to keep this annual Research Update current and up to date, historical background and completed trials of approved DMTs are no longer included. Background information on approved therapies can still be found in our 2015 edition of the *MS Research Update*. This may be accessed by going to the "Publications" section of MSAA's website, under "MS Information," at mysaa.org. **A chart giving an overview of the approved DMTs may be found on pages 40-43.**

This 2016 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. 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 2015 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).

More than 20 years have passed since the United States Food and Drug Administration (FDA) approved Betaseron® (interferon beta-1b), the first disease-modifying therapy for MS,

and the beginning of the MS-treatment era. 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.

Preferably, treatment is now often started when a person is diagnosed as having a clinically isolated syndrome (CIS). This is defined as a single attack (or the 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 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.

The past two years have seen the approval of a new formulation of Copaxone[®] (glatiramer acetate), dosed three times per week versus daily, as well as a new type of interferon called Plegridy[®] (peginterferon beta-1a), which is dosed once every two weeks. A new agent given by a series of infusions once yearly, Lemtrada[®] (alemtuzumab), 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 2014, experts from member organizations of the Multiple Sclerosis Coalition (MSC), including the Multiple Sclerosis Association of America (MSAA), collaborated to develop and write a paper summarizing 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 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.

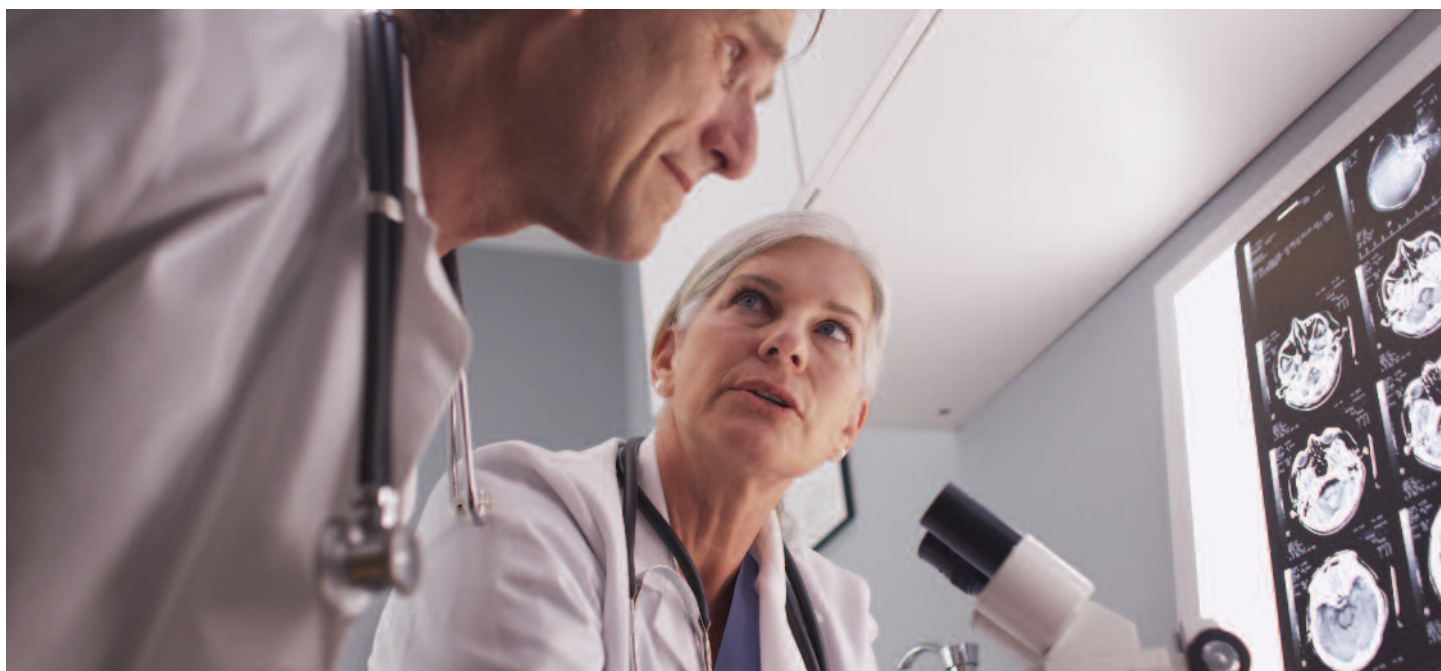
Please note that the authors have reported on the most recent study results available at the time of publication. While every effort has been made to provide meaningful, timely, and balanced information on each medication, keeping the length of information equal for each medication is not possible. Please 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.” For information on trial phases, please refer to pages 38 and 39.

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 of the 13 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.

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.



This *MS Research Update 2016*, covering information from the year 2015 and early 2016, must begin with a sobering note in regard to the failure of two highly anticipated clinical trials in progressive MS. 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 below, success in relapsing MS does not always predict similar efficacy in those with progressive disease. We begin with some of the unsuccessful studies of 2015 before moving on to the numerous positive avenues of ongoing MS research in both relapsing and progressive forms of MS.

Tysabri® (natalizumab)

Company: Biogen

- *Administered via intravenous infusion every four weeks in TOUCH program-authorized infusion centers; dose is 300 mg*
- *Approved for individuals with relapsing types of MS*

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 migration 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)**.¹ 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 ASCEND² 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 primary endpoint of the study was the percentage of patients with confirmed progression of disability according to several standardized measures. Biogen reported in a press release in October 2015 that the study did not meet its primary or secondary endpoints that relate to preventing the accumulation of disability. The data have not yet been presented in detail, but this is anticipated in 2016. It is hoped that detailed analyses of this trial may yield insight into particular groups or types of patients with progressive MS who may respond favorably to this available therapy.

Gilenya® (fingolimod)

Company: Novartis Pharmaceuticals Corp.

- *Oral medication; 0.5 mg capsule taken once daily*
- *Approved for relapsing forms of MS*

Gilenya is the first in a class of immunomodulatory drugs called “S1P-receptor modulators.” It is similar in structure to a naturally occurring component of cell-surface receptors on white blood cells. (White blood cells are produced by the immune system to fight infection and disease.) Gilenya blocks potentially damaging T cells from leaving lymph nodes, lowering their number in the blood and tissues. It may reduce damage to the CNS and enhance the repair of damaged nerves within the brain and spinal cord.

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**. As there is presently no FDA-approved medicine for PPMS, this was an important study for the field. 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.

Unsurprisingly, given this agent’s success in reducing relapses and new MRI lesions in RRMS patients, there were fewer new MRI lesions seen in the Gilenya-treated patients. The safety results were generally consistent with this medication in prior MS trials. 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.³ 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. This study is expected to report data in 2016.

Laquinimod (also known as Navenra®)

Company: Teva Neuroscience, Inc. and Active Biotech

- *Oral medication taken once daily; dosing is still under investigation*
- *Laquinimod is 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 there was a trend 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.⁴

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 (CONCERTO⁵), was designed to compare two

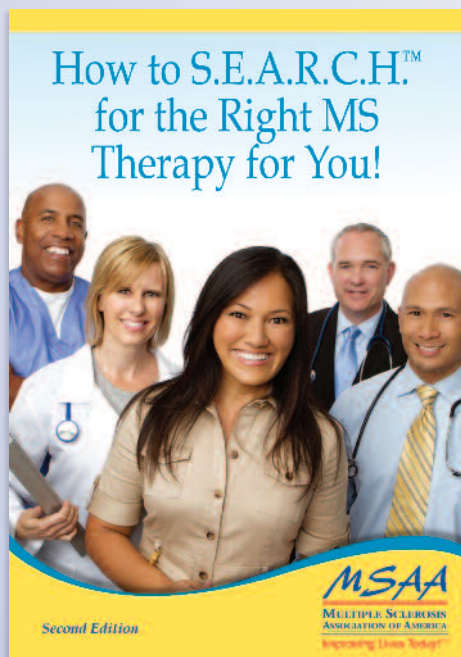
doses of laquinimod (including a 1.2 mg dose, which was higher than that tested in prior Phase III studies) with placebo, looking at confirmed disease progression as the primary outcome. This is the first modern RRMS trial to prioritize prevention of disability over prevention of relapses. The trial 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 2015.⁶ 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. Several cardiovascular side effects had occurred in patients receiving the higher dose, so the decision was made to continue only the lower, 0.6 mg dose in which no such events had occurred. The safety of patients enrolled in these studies will continue to be monitored closely as the trials utilizing the lower dose continue.

New S.E.A.R.C.H.™ Booklet Now Available



MSAA's SEARCH booklet has been updated! This new booklet details MSAA's SEARCH program, which is designed to assist individuals with learning about the approved disease-modifying therapies (DMTs) for the long-term treatment of MS. It provides information on the DMTs, along with important questions to ask your healthcare provider when looking to begin a medication or make a change in your present therapy... questions such as, "What are the side effects?" and "Will I have access through insurance?"

Designed as a memory aid, the SEARCH acronym represents the key areas that should be considered when "searching" for the most appropriate MS treatment.

Safety
Effectiveness
Access
Risk
Convenience
Health Outcomes (overall wellness)

MSAA offers a SEARCH "toolkit," which includes this detailed booklet, along with a wallet-size reference card, and more. For more information, please visit mymsaa.org or call **(800) 532-7667, ext. 154**.

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 natalizumab (Tysabri) and alemtuzumab (Lemtrada), which are already approved for MS. Several other monoclonal antibodies have shown promise in MS, and these are reviewed in this section.

Daclizumab (Zinbryta; known in other formulations as Zenapax®)

Companies: Biogen and AbbVie

- *Administered via intravenous infusion every four weeks; also studied when given in subcutaneous (under the skin) injections*
- *Daclizumab is being studied in both RRMS and SPMS*

Daclizumab 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. Daclizumab 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 intravenous infusion.

Participants in the Phase II CHOICE study had either RRMS or SPMS, with worsening disease activity while taking one of the

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.

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, the number of new gadolinium-enhancing lesions was reduced by 69 percent and 78 percent; the number of new or newly enlarging T2-hyperintense lesions

was 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 with the lower dose and 43 percent with the higher dose.

Participants who completed this trial were enrolled in an extended trial called SELECTION to evaluate long-term safety and efficacy. One-year results of the SELECTION trial were presented⁷ at theECTRIMS meeting in the fall of 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 was presented;⁸ patients who received two years of treatment with DAC HYP in the SELECT trial and its one-year extension study, SELECTION, were evaluated to determine the rate of brain atrophy (brain-volume loss). During the second year of treatment, brain-volume loss 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 in people with MS may be consistent with neuroprotection.

DAC HYP was further studied in the DECIDE trial,⁹ 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. Outcome measures included relapse rate, functional decline, and disability progression, as well as quality of life.

Initial results of the DECIDE trial were presented in 2014. Treatment¹⁰ 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 of the Phase III trial.

In abstracts presented at the 2015ECTRIMS 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 and tolerability profile has been well characterized in clinical studies for periods up to six years. As of spring 2016, this agent is

under review by the FDA and a decision on approval is anticipated by the middle of the year.

Rituxan® (rituximab)

Companies: Genentech and Biogen

- *Administered via intravenous infusion*
- *Rituxan is 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. At 48 weeks, the number of active lesions was reduced by 91 percent and relapses were reduced by 58 percent.

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 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 that were free of gadolinium-enhancing activity at baseline. There was an 88-percent reduction in the average number of these lesions.

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)(into the spinal fluid) rituximab versus placebo (the RIVITaLISE¹¹ 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 patients 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 patients (14 on active drug and nine on placebo) who had received at least two doses of the drug. Though 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 there are multiple reasons that 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. 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 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 ocrelizumab, as discussed in the following entry.

Ocrelizumab

Companies: Genentech and Roche Pharma AG

- *Administered via intravenous infusion*
- *Ocrelizumab is being studied in RRMS and in PPMS*

Like Rituxan, this drug is an anti-CD20 monoclonal antibody. It has the potential advantage of being a more humanized antibody than Rituxan. As noted in the introduction to this section, 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. "More humanized" refers to a protein sequence that is more similar to antibodies produced in humans, compared to another humanized monoclonal antibody (Rituxan in this instance).

In a Phase II study of ocrelizumab¹² 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 (roughly one year and five months); 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 ocrelizumab group.

The findings of three important studies of ocrelizumab in MS were announced in 2015.¹³ 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. Patients 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. The incidence of adverse events associated with ocrelizumab was similar to placebo; the most common adverse events were mild-to-moderate infusion-related reactions. 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.

The number of serious adverse events in the ORATORIO, OPERA I, and OPERA II studies were small and similar among the groups. Although Phase III trials in rheumatoid arthritis

had significant rates of serious and opportunistic infections, and one patient died of a systemic inflammatory response of unknown etiology (e.g., the reason why this response occurred), no opportunistic infections were identified in these trials. Serious adverse events included infusion reactions and the occurrence of several malignancies, which will be carefully reviewed to assess if this represents a safety concern with this agent. It should be noted that in February 2016, the FDA granted “Breakthrough Therapy Designation” for ocrelizumab for the treatment of **PPMS**, which will potentially expedite the review process.

Ofatumumab (also known as **Arzerra**[®])

Company: Novartis

- ***Administered via intravenous infusion and will also be studied via subcutaneous injection***
- ***Ofatumumab is being studied in RRMS***

Like Rituxan and ocrelizumab, this drug 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 patients 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.

Results from MIRROR, a 12-week Phase II study comparing several doses of ofatumumab in RRMS, were reported in 2014.¹⁴ In the MIRROR study, 231 patients 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 2015¹⁵ demonstrated continued suppression of new MRI lesions at week 48 and a dose-responsive effect on B cells. These data will guide future clinical trials of this agent, expected to be initiated in 2016.

Vatelizumab

Company: Glenmark Pharmaceuticals and Sanofi Genzyme

- *Administered via intravenous infusion*
- *Vatelizumab is being studied in RRMS*

Vatelizumab is a humanized monoclonal antibody that targets VLA-2, a collagen-binding integrin expressed on activated lymphocytes (immune-system cells produced to fight infection and disease). This is similar to the mechanism of action of Tysabri, although with a different molecular target. The precise mechanism of action of vatelizumab in MS is not known, although it is hypothesized to block VLA-2 on activated immune cells, preventing the penetration of inflammatory lymphocytes from crossing into the brain, thus potentially reducing inflammatory events in MS.

The EMPIRE study,¹⁶ initiated in 2014, is a global Phase IIa/IIb double-blind, randomized, placebo-controlled study assessing the efficacy, safety, and dose-response of vatelizumab in patients with active RRMS. The study duration is 12 weeks for the MRI portion and two years for the safety follow-up. It is expected to enroll 168 patients at 55 sites in 10 countries.

Although no clinical data had been made public, Sanofi announced in a press release in fall 2015 that a pre-planned interim analysis revealed the primary efficacy endpoint was not met. The principal developer of this agent, Glenmark, planned to continue the EMPIRE study, which is expected to be completed in mid-2016.

New S1P Receptor Modulators

Data have been presented on several investigational oral agents, now in ongoing clinical trials, which have a mechanism similar to that of Gilenya, by isolating lymphocytes (that damage myelin) in the lymph nodes. These agents have been well-tolerated and reduced lesions related to RRMS. It is hoped that these agents, ozanimod (RPC1063), siponimod (BAF312), and ponesimod, will maintain or potentially improve on the efficacy and safety of Gilenya. However, researchers continue to remain vigilant with regard to cardiovascular side effects, such as bradycardia (slowed heart rate).

Ozanimod (formerly RPC1063)

Company: Celgene

- *Oral medication being studied at several doses*
- *Ozanimod is 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 RRMS patients were studied in this trial, which began with a seven-day gradual titration of ozanimod up to the full dose under investigation. The double-blind study then 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, headache, and urinary tract infections, as well as mild elevations in liver enzymes in some participants. Notably, no serious cardiac events were reported in the subjects receiving ozanimod.

In February 2016, the 72-week extension data of the RADIANCE trial were presented. These showed a continued reduction in relapses and gadolinium-enhancing lesions for those patients 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 version of the RADIANCE trial,¹⁷ where it is being compared with Avonex in 1,200 subjects with RRMS. This trial is expected to run through the end of 2017.

Siponimod (BAF312)

Company: Novartis

- *Oral medication studied at several doses*
- *Siponimod is being studied in SPMS*

Data from a Phase II dose-finding study of siponimod in people with RRMS were also reported in 2012. 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 this will minimize cardiac issues.

The trial had a complex design, with the primary goal to determine the most appropriate dosing regimen. One group of 188 patients received placebo or once-daily siponimod in doses of 10 mg, 2 mg, or 0.5 mg for six months. A second group of 109 patients were given one of two additional intermediate doses of 1.25 mg or 0.25 mg for three months.

At six months, the proportion of relapse-free patients as compared to placebo was 84 percent for the 10 mg group, 92 percent for the 2 mg group, and 77 percent for the 0.5 mg group. In the placebo group, 72 percent were relapse-free. After six months, the ARR (annual relapse rate) was lower for the individuals who were taking one of the three higher doses. Additionally, MRI findings showed a reduction in active lesions. The 2 mg dose reached statistical significance versus placebo, with a reduction in active lesions of approximately 80 percent.

A Phase III trial of siponimod in **SPMS** (the EXPAND trial)¹⁸ began recruitment in 2013 and is expected to run through fall 2016. This is the first S1P receptor modulator to be studied in SPMS.

Ponesimod

Company: Actelion

- *Oral medication being studied at a dose of 20 mg per day*
- *Ponesimod is being studied in RRMS*

Ponesimod is another selective S1P 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® (oral teriflunomide) 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.

Masitinib

(also known as Kinavet® and Masivet®)

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**²¹ showed a trend toward benefit; however, the results were not statistically significant.²²

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 patients treated with masitinib showed a response to treatment versus none of those receiving a 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 trial²³ 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 patients 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 forward.

Ibutilast

Company: MediciNova

- *Oral medication*
- *Ibutilast is being studied in progressive MS*

Ibutilast (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 addicts. Based on early MS-trial evidence that ibutilast had a primary, neuroprotective role, independent from a substantial effect on overt inflammation, the **Phase II Secondary and Primary Progressive MS Ibutilast NeuroNEXT trial (SPRINTMS)²⁴** 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 ibutilast 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. The NIH and National MS Society are supporting the study along with a commercial partner, MediciNova. The trial is expected to require approximately three years for enrollment, treatment, and data analyses, and will run through the end of 2016.

In March 2016, ibutilast 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 drug 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

- *Administered as five subcutaneous injections per year*
- *Tcelna is being 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 was found to be safe, but did not achieve statistical significance in the primary endpoint, which was a reduction in the cumulative number of gadolinium-enhancing lesions.

The placebo group did, however, experience an annualized relapse rate (ARR) of 0.34 per year (or one relapse roughly every three years), while the Tcelna group had an ARR of 0.21 per year (or roughly one relapse every five years), representing a 37-percent decrease. The drug was well tolerated with mild skin reactions in some patients; no serious safety concerns were raised by this study. In a subgroup of 70

patients 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.

After re-branding this agent as Tcelna, a new clinical trial initiative was launched in 2012. Tcelna is being studied in a **Phase II trial in SPMS** in the Abili-T study.²⁵ This is a placebo-controlled two-year trial, evaluating brain atrophy on MRI as the primary outcome, and delay in accumulation of sustained disability as the secondary outcome. The trial has fully enrolled 190 patients and data is expected in the second half of 2016. Tcelna has been granted Fast Track designation by the FDA in SPMS.

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.

In a larger study of 305 patients called RECYCLINE, minocycline was used as an add-

on to Rebif in people with RRMS. Patients being treated with Rebif were randomized to oral placebo or minocycline 100 mg twice daily for 96 weeks. Data were presented atECTRIMS in the fall of 2012,²⁶ 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 individuals with a first clinical demyelinating event, i.e., 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 patients with early forms of MS who were

taking atorvastatin (Lipitor®). However, a three-year Danish study of patients 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.

At the ECTRIMS Annual Meeting in fall 2012, Chataway and colleagues presented the results of the MS-STAT trial.²⁷ This Phase II study evaluated whether high-dose simvastatin can slow the rate of whole-brain

atrophy, and/or disability, in **SPMS**.

In the MS-STAT trial, 140 patients were randomized, and the simvastatin group had a statistically significant benefit over the placebo group 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 drugs, this is an exciting possibility.



Ways to Stay Informed

Please visit MSAA's recently redesigned and mobile-friendly website at mymsaa.org to access important and timely information about MS, including treatments and symptom management, as well as MSAA's programs and services.

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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: LINGO-1 itself is a protein in the central nervous system whose role is to halt myelination and prevent the survival of neurons. The cells making up all organs in the body receive such “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 malignancies. Anti-LINGO-1 (BIIB033) is an agent with potential remyelination properties, after animal studies showed that it blocks this protein responsible for stopping the growth of myelin. It was shown to promote spinal cord remyelination and axonal integrity in the animal model of MS (EAE).

The first trials of experimental anti-LINGO to stimulate myelin repair – human Phase I trials,²⁸ involving 64 healthy adult volunteers and 42 people with relapsing or **secondary-progressive MS** – have been completed. In these trials, intravenous (IV) doses of anti-LINGO were well tolerated, and there were no serious adverse events; headache was the most frequent adverse event reported.

The first Phase II trial of anti-LINGO, called RENEW, launched in 2013.²⁹ The study recruited patients with newly-diagnosed MS

involving the visual pathways (optic neuritis) to evaluate the drug’s effect on remyelination. Results were presented in spring 2015. 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.

Patients 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.

The study showed no effect on secondary endpoints, including change in thickness of the retinal layers (optic nerve neurons and axons) as measured by optical coherence tomography (OCT), or on visual function, measured by a test of vision called low-contrast letter acuity. Anti-LINGO-1 was generally well-tolerated in this study, noting that two patients 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 provide an encouraging indication that anti-LINGO-1 appears safe and may facilitate remyelination, though meaningful clinical

outcomes will need to be assessed in larger trials.

To that end, a second, larger Phase II trial (SYNERGY)³⁰ is looking at this drug in combination with Avonex. The study will recruit approximately 400 patients with both RRMS and SPMS, and will examine the degree to which patients have an improvement in disability with anti-LINGO. Since this agent does not reduce relapses or prevent new MRI lesions, further studies with anti-LINGO, and other potential remyelination therapies, will need to utilize new endpoints to prove efficacy. These include measurements of recovery or improvement on physical, visual, cognitive, and other functional assessments of the effects of MS.

Results will provide clinical information about this drug's efficacy for neuroprotection or repair within the central nervous system (CNS). The results will also address two fundamental questions: 1) Are the effects seen in the optic neuritis study replicable in other areas of the nervous system? And 2) Does this translate to improved function in patients with MS either in the short or long term?

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**³¹ and **rHlgM22**.³² Proof-of-principle data are expected for both of these agents in 2016.

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 2013,³³ 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 was studied in 14 people with **PPMS** using MRI markers of neurodegeneration as outcome measures of neuroprotection. Patients with PPMS 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. This suggests that amiloride may exert neuroprotective effects in patients with PPMS. 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.

A Phase II trial studying this agent in optic neuritis³⁴ was initiated in 2013 and data is expected in 2016. This study is similar in principle to the RENEW study of anti-LINGO-1 as discussed above, as the attempt is to foster

protection and repair in the optic nerve in the acute phase after optic neuritis.

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 neuritis³⁵ (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 patients, 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.

Idebenone (Catena® 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,³⁶ sponsored by the National Institute of Neurological Disorders and Stroke, recruited participants with **PPMS** who had little to moderate disability. The trial began in July 2009 and is 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 patients with SPMS who were treated with MIS416 for 12 weeks showed some improvement. A further Phase II study³⁷ in **SPMS** is planned to be completed in late 2016.

Transdermal Administration of Peptides: A small Polish study of 30 individuals³⁸ 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. A preliminary study³⁹ administered AIN457 by intravenous infusion to a very small number of patients with psoriasis, rheumatoid arthritis, and uveitis with variable results. A proof-of-concept trial in RRMS⁴⁰ enrolled 73 patients and showed a reduction in gadolinium-enhancing MRI lesions compared with placebo.⁴¹

A larger, Phase II trial was planned to enroll approximately 380 patients with relapsing MS; the design of the study was presented atECTRIMS 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 atECTRIMS in the fall of 2015. To date, no individuals with MS have received this experimental treatment.

SB-683699 (finategrast) is an oral agent thought to reduce the number of active white blood cells entering the brain. It works via a similar mechanism to Tysabri. It had positive results in a Phase II trial⁴² using gadolinium-enhancing lesions as the primary outcome.

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 2014⁴³, noting that ATL1102 decreased the emergence of new active brain lesions as compared with placebo, after only two months of treatment in approximately 70 RRMS patients. As of 2015, the development path for this agent is still being considered.

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 patients with aggressive disease, results presented in 2014⁴⁴ showed that pixantrone was as effective as Novantrone, but with less cardiotoxicity. Although via a different mechanism of action than rituximab and ocrelizumab, pixantrone was shown in this study to reduce B cells by 95 percent. According to the study abstract,⁴⁵ pixantrone is structurally similar to Novantrone

and both drugs have similar immunosuppressive 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 2014,⁴⁶ 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.⁴⁷ 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 colleagues⁴⁸ 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 an individual 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

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 colleagues⁴⁹ 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.

Mowry and colleagues at Johns Hopkins have initiated a multi-center clinical trial in which patients 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.⁵⁰ Patients 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.

A Phase II study⁵¹ investigated whether Vigantol[®] oil, a form of Vitamin D hormone supplement (cholecalciferol), provides any added benefit when given in conjunction with Rebif. The study had 348 participants and began in February 2011. Primary outcome measures are the mean change from baseline in the total volume of T2 lesions at week 48 and the proportion of relapse-free subjects at week 96. Secondary outcome measures include sustained disability progression, MRI measures of disease progression, proportion of subjects free from disease activity at 96 weeks, and changes in cognitive function. Although this study was completed in 2015, results are not yet available.

The French CHOLINE Phase II study⁵² 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 patients 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.

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.

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 patients were

randomized to high-dose biotin or placebo.

The primary endpoint of the study was defined as the proportion of patients 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 patients in the MD1003 arm showing an improvement of EDSS or T25FW at nine months and confirmed at 12 months, compared to none of the patients 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 drug.

These results suggest a possible therapeutic effect of high-dose biotin in progressive MS, and merit further study. Noting that the dose of biotin studied would require taking hundreds of commercially available vitamin pills, it is not generally recommended that patients begin such a regimen at the present time. Studies also need to determine if any toxic effects could result from taking such high doses of this vitamin.

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 2013⁵³, 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,⁵⁴ 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.⁵⁵ Kremmentsov 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.⁵⁶

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.

Stem Cells

Based on encouraging results from a variety of studies, clinical trials are now starting to enroll patients 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 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, in an effort to completely “reset” the immune system with the hopes of abolishing the autoimmunity responsible for MS.

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 is being conducted in 25 patients with highly active RRMS who have failed conventional therapy. The two-year follow-up results of the HALT study were

reported in 2013.⁵⁷ The treatment induced profound immune suppression and a high rate of sustained remissions at two years.

Further interim results covering three years of the study were published in early 2015.⁵⁸ The trial found that 78 percent of the study subjects had no new disease activity. Treatment failed in five subjects, and two deaths occurred; one attributed to MS progression and one secondary to asthma. There have been 130 adverse events that were severe or life-threatening, most relating to low blood counts induced by the treatment approach. There were two suicide attempts, neither completed, both in patients reported to have an unremarkable history before the HSCT, meaning that neither had a history of psychological problems that might lead to suicide attempts. Study participants will be followed for five years in total to see how long the benefits of this treatment may continue, and if the safety profile proves to be manageable.

Another study in Sweden published previously⁵⁹ found a high proportion of patients with aggressive, relapsing forms of MS, were free from disease activity following HSCT. A group of 41 patients 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 patients 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 patients with RRMS and 28 patients with **SPMS** who underwent HSCT over a 10-year period.⁶⁰ The study was open-label, meaning that everyone in the study received the treatment and thus there was no 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, there was also a significant *improvement* in disability scores for those patients in which long-term data were available.

While the data from this study is 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 a patient 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. These cells can be derived from tissues other than bone marrow and do not require a “wiping out” of the immune system for their use. In a Phase IIa study⁶¹, 10 patients with **SPMS** with involvement of the visual system were infused with self-derived (autologous) mesenchymal stem cells.

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.⁶² 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 commonsense 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 a patient’s stem cells; grow and multiply them; administer them to the patient; 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 is being investigated in an open-label Phase I clinical trial⁶³ announced in fall 2013. This small, single-center trial of 20 patients with progressive MS has fully enrolled. The study design involves 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 patients 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 continued to be 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 patients 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. We already utilize one type of blood test 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 patient 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 2014⁶⁴ 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 patients 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 patients on Avonex only, Copaxone only, or a combination of both. Samples of serum and white blood cells are being obtained from each patient 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 patients' symptoms and response to treatment. Based on these genetic biomarkers, likely best-responders to either form of therapy can be identified.

Genetic Studies

There has been a growing body of evidence 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.⁶⁵ 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.

The study involved nearly 10,000 people with MS and more than 17,000 controls without MS, taking place in 15 countries. The research was carried out by approximately 250 investigators. The results are now to be confirmed and expanded in a second, large-scale study. The team found that a large number of these genes are related to T-cell function; they were mainly associated with T-cell activation and proliferation. This was particularly important because these are the cells believed to be the major mediators of the early immune attack on the brain and spinal cord in MS. Two of the genes are linked to Vitamin D, and low Vitamin D levels have already been implicated as a risk factor for developing MS. As noted earlier, more than one-third of the genes are associated with other autoimmune diseases such as Crohn's disease and type 1 diabetes; MS is believed to be an autoimmune disease as well.

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 MS patients. 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, 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.

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 patients at the highest risk for MS may lead to opportunities for intervention before the condition becomes clinically apparent.

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

The vast collection of organisms that inhabit the human gut, the microbiome, has been demonstrated to influence immune responses and modulate susceptibility to chronic diseases. Recent studies have related gut dysbiosis (an imbalance of bacteria) to Crohn's disease, type 1 diabetes, obesity, and autism. Additionally, animal model work suggests an important role in MS.

The Multiple Sclerosis Microbiome Consortium (MSMC) is a multi-disciplinary collaboration composed of two translational MS Centers (Mount Sinai and UCSF). Together, they have initiated a microbiome-oriented basic/experimental program and sequencing/bioinformatics program. The MSMC is currently analyzing hundreds of samples by bacterial DNA sequencing aimed at identifying group differences at the genus-level (a genus is a group of related animals or plants that includes several or many different species⁶⁶). Tracked variables include demographics, body mass index (BMI), medical history, MS clinical

course and phenotype, disease-modifying therapy, and diet. The MSMC has successfully implemented IRB-approved protocols to recruit MS patients and controls, as well as to process and analyze their blood and stool samples.

Initial results show significant genus-level differences in the microbiomes of patients treated with Copaxone compared to untreated subjects. Female patients 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 MS patient 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.

CLOSING NOTES

In summary, the future of 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 if we are to truly know that our medications are globally effective in MS.

Despite the setback of unsuccessful trials in progressive MS, ongoing clinical trials in both **PPMS** and **SPMS**, as well as investigations into neuroprotection, remyelination, and repair, offer great promise for the treatment of progressive MS and the goal of reversing the damage caused by this disease. 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.

As clinicians have more numerous and more complex treatment options to offer patients, 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 more information about MS and its treatments, please contact MSAA at **(800) 532-7667**, or visit mymsaa.org.

Trial Phases for Investigating Drugs and Treatments

Every approved treatment for MS has undergone extensive study prior to receiving approval by the United States Food and Drug Administration (FDA). The process of testing a new drug therapy for MS is time-consuming, and all drugs must undergo several phases of investigation in order to be deemed both safe and effective.

Before a pharmaceutical company can initiate testing in humans, it must conduct extensive preclinical or laboratory research. This research typically involves years of experiments in animal and human cells, to develop compounds that have the desired biological effect. Once such a drug is developed, it is often tested on animals before human studies can even begin. The clinical testing of experimental drugs is normally done in three phases, with each successive phase involving a larger number of people. Sometimes fourth-phase trials are conducted after approval for additional data on effectiveness and adverse events over a longer period of time.

MS poses a specific set of challenges for clinical research. It is a highly-variable condition that affects everyone differently. Choosing the correct population of MS patients to study poses formidable challenges to clinical research, and is a major reason why accurately comparing the results of different MS drug trials (in order to answer the question “which drug is

better?”) is impossible.

In addition, MS varies over time, even within the same person. He or she may experience “good days” and “bad days,” as well as actual MS relapses that last for days to weeks and even months. Symptoms may persist from previous relapses, and other effects, such as fatigue, stiffness, and pain, are difficult to study.

Choosing what outcome to study is another challenge to MS research design. Some of the most commonly studied include: number of relapses; time to next relapse; number of new lesions seen on MRI; and cumulative disability (as measured by the EDSS). “EDSS” refers to the Kurtzke Expanded Disability Status Scale, which uses numbers from one to 10 to measure degree of disability, largely in terms of mobility.

All of these variables take time to assess. In general, several years of research are needed for an MS drug to even begin Phase III testing. Once begun, Phase III trials require several months to enroll, often two years to conduct, and another year for the results to be fully analyzed and published. Obtaining FDA approval after studies are complete usually takes the better part of a year as well. The standards for proving that a drug is safe for patients and proven effective against MS are incredibly high, and many years of work are necessary to meet these standards.

PHASE I: 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.

Phase I trials are referred to as “open label” and “unblinded,” because everyone – the patient, medical staff, and investigators – knows the drug and dose that each participant is receiving. A Phase I study will investigate side effects that occur as dosage levels are increased. Phase I trials can take several months to one year to complete.

PHASE II: 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.

These studies are also “randomized,” so that participants are assigned to treatment groups (or “treatment arms”) based on chance. One group of patients receives the experimental drug, while a second “control” group will receive a standard treatment or placebo. In this manner, the study can provide information to the pharmaceutical company and the FDA about the relative safety of the new drug, and its effectiveness.

In multiple sclerosis (MS), Phase II trials frequently use disease-activity measurements determined through MRI scans (such as new lesions or gadolinium-enhancing lesions) as the primary outcomes. MRI scans are used because this sort of data can be obtained more quickly and with fewer patients versus determining clinical outcomes, such as relapse rates or permanent disability. Only about one-third of experimental drugs successfully complete both Phase I and Phase II studies.

PHASE III: 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. This large-scale testing provides the pharmaceutical company and the FDA with a more thorough understanding of the drug's effectiveness, benefits, and the range of possible adverse reactions.

Most Phase III studies are randomized and blinded trials. Only after a Phase III study is successfully completed can a pharmaceutical company request FDA approval for marketing the drug.

PHASE IV: 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.

Self-Injected Medications

NAME AND TYPE OF DRUG	SIDE EFFECTS	HOW ADMINISTERED	ADDITIONAL NOTES
Avonex® (Interferon beta-1a) immune system modulator with antiviral properties	Flu-like symptoms and headache, blood count and liver test abnormalities	30 micrograms taken via weekly intramuscular injection	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	Flu-like symptoms, injection-site skin reaction, blood count and liver test abnormalities	250 micrograms taken via subcutaneous injection every other day	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 (immune system modulator that blocks attacks on myelin)	Injection-site skin reaction as well as an occasional systemic reaction - occurring at least once in approximately 10 percent of those tested	20 (daily) or 40 (three times weekly) milligrams taken via subcutaneous injection	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 a dose of 20 milligrams daily, but in January 2014, a new dose of 40 milligrams three times weekly was approved by the FDA. The original 20-milligram daily dose remains available, so patients and their doctors may now choose their preferred dosing regimen.
Extavia® (Interferon beta-1b) immune system modulator with antiviral properties	Flu-like symptoms, injection-site skin reaction, blood count and liver test abnormalities	250 micrograms taken via subcutaneous injection every other day	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.

Self-Injected Medications

NAME AND TYPE OF DRUG	SIDE EFFECTS	HOW ADMINISTERED	ADDITIONAL NOTES
<p>Glatopa™ (glatiramer acetate) As a generic version of Copaxone, Glatopa is a synthetic chain of four amino acids found in myelin (immune system modulator that blocks attacks on myelin)</p>	<p>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</p>	<p>20 milligrams taken daily via subcutaneous injection</p>	<p>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.</p>
<p>Plegridy® (Interferon beta-1a) immune system modulator with antiviral properties</p>	<p>Flu-like symptoms, injection-site skin reaction, blood count and liver test abnormalities</p>	<p>125 micrograms taken via subcutaneous injection once every two weeks</p>	<p>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.</p>
<p>Rebif® (Interferon beta-1a) immune system modulator with antiviral properties</p>	<p>Flu-like symptoms, injection-site skin reaction, blood count and liver test abnormalities</p>	<p>44 micrograms taken via subcutaneous injection three times weekly</p>	<p>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.</p>

Infused Medications

NAME AND TYPE OF DRUG	SIDE EFFECTS	HOW ADMINISTERED	ADDITIONAL NOTES
<p>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 central nervous system (CNS).</p>	<p>Common side effects include rash, itching, headache, pyrexia (increase in temperature), nasopharyngitis (inflammation of the nose and throat), nausea, diarrhea and vomiting, insomnia, numbness/tingling, dizziness, pain, flushing, and infection.</p>	<p>Lemtrada is given for a course of five days via intravenous (IV) infusion and followed one year later by a second three-day course.</p>	<p>Adverse events from Lemtrada can include infusion reactions to the medication, an increased risk of infection, emergent autoimmune diseases, a potentially severe bleeding disorder called immune thrombocytopenic purpura (ITP), and an increased risk of malignancies including thyroid cancer, melanoma and lymphoproliferative disorders. For early detection and management of these risks, Lemtrada is only available through a restricted distribution program, the Lemtrada REMS (Risk Evaluation and Mitigation Strategy).</p>
<p>Novantrone® (mitoxantrone) Antineoplastic agent (immune system modulator and suppressor)</p>	<p>Side effects include nausea, thinning hair, loss of menstrual periods, bladder infections, and mouth sores; additionally, urine and whites of the eyes may turn a bluish color temporarily</p>	<p>IV infusion once every three months (for two to three years maximum)</p>	<p>Novantrone carries the risk of cardiotoxicity (heart damage) and leukemia; it may not be given beyond two or three years. People undergoing treatment must have regular testing for cardiotoxicity, white blood cell counts, and liver function. Because of the potential risks, Novantrone is seldom prescribed for individuals with MS. Anyone taking Novantrone now or given Novantrone previously needs to have annual evaluations of his or her heart function, even if no longer receiving this medication.</p>
<p>Tysabri® (natalizumab) Humanized monoclonal antibody (inhibits adhesion molecules; thought to prevent damaging immune cells from crossing the blood-brain barrier)</p>	<p>Headache, fatigue, depression, joint pain, abdominal discomfort, and infection</p>	<p>IV infusion every four weeks</p>	<p>Risk of infection (including pneumonia) was the most common serious adverse event during the studies (occurring in a small percentage of patients). The TOUCH Prescribing Program monitors patients for signs of PML, an often-fatal viral infection of the brain. Risk factors for PML include: the presence of JC virus antibodies, previous treatment with immunosuppressive drugs, and taking Tysabri for more than two years.</p>

Oral Medications

NAME AND TYPE OF DRUG	SIDE EFFECTS	HOW ADMINISTERED	ADDITIONAL NOTES
<p>Aubagio® (teriflunomide) Immunomodulator (affecting the production of T and B cells; may also inhibit nerve degeneration)</p>	<p>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)</p>	<p>7- or 14-milligram tablet taken orally, once per day</p>	<p>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.</p>
<p>Gilenya® (fingolimod, FTY720) S1P-receptor modulator (blocks potentially damaging T cells from leaving lymph nodes)</p>	<p>Headache, flu, diarrhea, back pain, abnormal liver tests and cough</p>	<p>0.5-milligram capsule taken orally once per day</p>	<p>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 (a condition that can affect vision, caused by 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.</p>
<p>Tecfidera® (dimethyl fumarate) Immunomodulator with anti-inflammatory properties; may have neuroprotective effects, potentially protecting the nerves and myelin covering from damage</p>	<p>Flushing and gastrointestinal events; reduced white-blood cell (lymphocyte) counts; elevated liver enzymes in small percentage of patients</p>	<p>240-milligram tablet taken twice daily</p>	<p>Other adverse events include mild or moderate upper respiratory infection, pruritus (chronic itching), and erythema (skin redness or rash). In studies, the only serious adverse events to occur in two or more patients taking Tecfidera was gastroenteritis (an inflammation of the lining of the intestines) and gastritis (an inflammation of the stomach lining). Reduced white-blood cell (lymphocyte) 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.</p>

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