Published by MSAA in April 2015

MS RESEARCH UPDATE

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MSAA's *MS Research Update* is published annually as a service to the MS community. This update provides 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 as well as MSAA's programs and services, please visit **mymsaa.org** or call **(800) 532-7667**.

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MS RESEARCH UPDATE

Published in April 2015, this update is a comprehensive overview of research findings on the FDA-approved disease-modifying therapies, as well as many experimental treatments

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INTRODUCTION

This year's expanded *MS Research Update* incorporates new information about the approved disease-modifying therapies (DMTs), as well as numerous experimental drugs currently under investigation for the long-term treatment of multiple sclerosis (MS). Many studies are limited to relapsing forms of MS, so for easier recognition, trials with progressive forms of MS have been highlighted in bold.

Please note that symptom-management drugs are not included in this report. For more information on the specific symptoms of MS, please visit **mymsaa.org**, go to "About MS," and select "Symptoms."

While this 2015 edition of the *MS Research Update* reflects the incredible diversity and scope of research progress in MS, space does not allow for all of this research to be covered. Therefore, this is not a complete list of study results.

The information provided is based on a wide range of sources, including the extensive journal literature on MS and its management, a review of ongoing clinical trials, and papers presented at major national as well as international conferences. These include the 2014 conferences hosted by the American Academy of Neurology (AAN), the Consortium of Multiple Sclerosis Centers (CMSC), and the American 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, the first disease-modifying therapy for MS, and the beginning of the MS-treatment era. This medication, and others that followed, continue to show effectiveness over the long term. Importantly, these medications have also demonstrated a proven long-term safety track record, which is crucial when considering that people with MS often require treatment for decades.

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 year 2014 saw the approval of a new formulation of Copaxone, dosed three times per week versus daily. The year also saw a new type of interferon called Plegridy, which is dosed once every two weeks. A new agent given by a series of infusions once yearly, Lemtrada, was approved by the FDA at the end of 2014, making it the third newly approved treatment for MS in less than one year.

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 paper will be updated as new treatments become available.

This professional paper, titled "The Use of Disease-Modifying Therapies in Multiple Sclerosis: Principles and Current Evidence," was published in August 2014 and has been distributed to thousands of MS medical professionals. In November 2014, a summary was published. This is written in a more reader-friendly style to better serve the broader MS community. It shares the same title, with the addition of the word "SUMMARY" at the end. Both of these papers are available on MSAA's website by going to **mymsaa.org**, selecting "News from MSAA," and then scrolling down to those two papers (listed in order of publication date).

Please note that in this *MS Research Update*, 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 available agent, 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, please note that references have only been cited for the newer study results.

For information on trial phases, please refer to the inside-back cover of this publication. For any other questions about MS, or to learn more about MSAA's vital services and support, please visit **mymsaa.org** or call **(800) 532-7667**.

Avonex® (interferon beta-1a)

Company: Biogen

- ***Taken via weekly intramuscular injections; dosage is 30 mcg (micrograms)***
- ***The FDA approved Avonex in 1996 for relapsing MS and more recently for individuals with clinically isolated syndrome (CIS)***

Avonex has been shown to reduce the number of relapses and lesions on an MRI, as well as slow the progression of physical disability. This drug has been shown to be both safe and effective.

Interferons appear to reduce inflammation by modulating a favorable balance between cells that increase inflammation and cells that decrease inflammation. They also reduce the transport of damaging lymphocytes into the brain. Lymphocytes are immune-system cells produced to fight infection and disease.

In 2012, Avonex became available with a single-use, prefilled autoinjector called the Avonex Pen. The Avonex Pen incorporates the current Avonex Prefilled Syringe. Its needle is 25 gauge (width) and 5/8ths of an inch in length. Rather than a manual injection, the Avonex Pen injects with a click, using a covered needle that's half the length of the standard needle used with the Avonex Prefilled Syringe. In a Phase IIIb study, 94 percent of patients preferred the Avonex Pen over the Avonex Prefilled Syringe. This new option has the potential to make the weekly intramuscular self-injection process less stressful for people using this medication.

Long-term studies of Avonex include the ASSURANCE study, which evaluated 15-year data and showed that early suppression of clinical disease activity by Avonex is a marker of treatment response. This is associated with significant long-term benefits for quality of life as compared to patients who had received placebo. These results support other accumulating evidence that short-term responders to Avonex are also inclined to experience beneficial long-term outcomes.

A 10-year analysis of data from the CHAMPS trial – which treated patients with CIS and MRI findings consistent with MS – showed that although some had characteristics of disease progression, there was evidence of improved disease course with early treatment. These results again emphasize the value of early treatment. This effect remained evident in both the CHAMPIONS five- and 10-year extension studies.

Betaseron® (interferon beta-1b)

Company: Bayer HealthCare Pharmaceuticals

- ***Administered by subcutaneous injection every other day; dose is 250 mcg***
- ***Approved for relapsing forms of MS in 1993, and more recently, for individuals with CIS***

Betaseron reduces the number and severity of relapses (attacks) of MS. It also stabilizes the total lesion area as measured by MRI, compared to those without treatment.

Interferons appear to reduce inflammation by modulating a favorable balance between cells that increase inflammation and decrease inflammation. They also reduce the transport of damaging lymphocytes into the brain.

Follow-up data after 21 years from Betaseron's initial Phase III trial of RRMS[1]

show continued effectiveness and safety, as well as increased longevity. Following 21 years after the enrollment of this pivotal trial, Goodin and colleagues examined the effect of randomization to Betaseron versus placebo in the group of 372 patients on mortality. They found that patients originally assigned randomly to Betaseron showed a 50-percent reduction in mortality over the 21-year period compared with placebo.

The researchers conclude that the study provides evidence that early treatment with Betaseron (versus no treatment or delayed treatment) is associated with longer survival in people with relapsing-remitting MS (RRMS). The results suggest that treatment was more effective when given early in the course of the disease, and a more favorable outcome can be seen for those patients who received the active drug in the very first trials when evaluated two decades later.

Improved effects of early treatment were also demonstrated in a group of 468 patients with CIS who were randomized to active treatment or placebo in the BENEFIT trial. In this trial, patients were treated with Betaseron or placebo for up to two years after a CIS event. After two years, all patients enrolling in the extension trial were treated with Betaseron moving forward. In this way, there was an "early-treatment group" and a "delayed-treatment group." In addition to the effect on reducing the risk of MS relapses and MRI lesions, by five years, the treated group showed greater improvement in scores on the Paced Auditory Serial Addition Test (PASAT), a measure of cognitive function. A follow-up BENEFIT trial extension study at eight years presented in 2013 showed both groups had stable or low disability levels, although the patients treated immediately with Betaseron following CIS had fewer relapses than those with delayed treatment.

The small START study of patients with RRMS was designed to identify immune markers of Betaseron therapy. Immune markers are tendencies or indicators observed across a population with a particular disease state. Immune markers in this study were compared in those patients with and without relapses during the first year of treatment.

The study revealed that the patients treated with Betaseron had significant changes in the levels of several immune-system markers. A trend toward higher levels of the pro-inflammatory cytokine interleukin-17 (IL-17) was found in patients who relapsed. (Cytokines are small proteins that may stimulate or inhibit the function of other cells, and can be studied in the blood.) Higher brain-derived neurotrophic factor (BDNF) levels were observed in the relapse-free group. (BDNF is a protein found in the brain that helps to support nerves and their development.)

The data suggest that the mode of action of the beta interferons may involve a shift in cytokines in favor of an anti-inflammatory/regulatory profile. Findings also suggest that elevated IL-17 may correlate with having relapses, while increased levels of another cytokine, BDNF, may be protective. These findings serve as a platform for further research of biomarkers predictive of responses to interferon therapy. More discussion on the potential role of biomarkers in the future of MS therapy is given later in this publication.

Copaxone® (glatiramer acetate)

Company: Teva Neuroscience, Inc.

- ***Given via daily (20 mg) or three-times-weekly (40 mg) subcutaneous injections***
- ***Approved for RRMS and CIS***

Copaxone has been shown to significantly reduce the annual relapse rate in RRMS and reduce the risk of people with CIS for developing clinically definite MS (CDMS) at two years.

Copaxone is a synthetic polypeptide that mimics myelin basic protein, a key component of the myelin sheath (the protective covering of the nerves) that is damaged in MS. This therapy appears to decrease immune-system T cells that damage myelin, and may decrease inflammation by favorably shifting the balance among T-cell subtypes as well as by affecting several interleukins. (Interleukins are a type of cytokine, which are small proteins that may stimulate or inhibit the function of other cells.) Copaxone may also induce lymphocytes (immune-system cells produced to fight infection and disease) to produce factors that enhance the survival of cells that produce myelin, and may have a neuroprotective action that prevents damage to axons (nerve fibers).

An international European study called PreCISe was conducted to determine whether immediate treatment with Copaxone is better than delayed treatment in preventing conversion to clinically definite MS (CDMS). This study has shown that early treatment with Copaxone reduced the risk of converting to CDMS. The five-year extension data from this study were presented recently. The delay in the development of CDMS (resulting from early initiation of Copaxone) over placebo was maintained in the extension study with a CDMS risk reduction of 41 percent at five years. These results establish the importance of initiating treatment with Copaxone as early as possible to protect patients from the accumulation of disease activity.

In 2013, results were reported from the COPTIMIZE study,[2] a two-year observational survey of 672 patients with RRMS switching to Copaxone – due to a lack of efficacy or treatment intolerability with a different disease-modifying therapy. Patients who switched to Copaxone from other disease-modifying drugs generally improved in measures of fatigue, cognition, quality of life, and depression; mobility remained stable, although the Expanded Disability Status Scale (EDSS) increased slightly from baseline. A total of 72.7 percent of the patients who switched to Copaxone remained relapse-free.

Several years ago, the PROMISE study of 943 patients with **primary-progressive MS (PPMS)** failed to show that Copaxone was effective in this population of people with MS. Approximately 10 percent of the MS population is diagnosed with PPMS, where individuals experience a steady worsening of symptoms from the start, and do not have the periodic relapses and remissions found with relapsing-remitting MS (RRMS).

A smaller number of individuals are diagnosed with progressive-relapsing MS (PRMS), which begins as PPMS, but subsequently develops relapses. PRMS is similar to PPMS as it steadily worsens from the onset, but symptom flare-ups (with or

without remissions) are also present. This is considered the least common form of MS. There has been some debate as to whether categorizing PRMS separately from PPMS – in terms of clinical course and prognosis – can be justified. A sub-study of the PROMISE data[3] evaluated differences in baseline characteristics and disability progression between patients with PPMS and PRMS.

In this PROMISE sub-study, 42 of the 943 PPMS patients ultimately developed relapses and converted to PRMS. Although the numbers of PRMS patients analyzed in this study were small, the results suggested that disease progression is more rapid in this clinical sub-group. **Since PRMS falls under the category of "relapsing forms" of MS, the use of disease-modifying therapies may be considered for individuals with this type of MS.**

The initial FDA-approved dose for Copaxone is 20 mg per day, given subcutaneously. The GALA trial was a randomized, placebo-controlled trial of Copaxone dosed at 40 mg given by subcutaneous injection three-times weekly versus placebo.

Data from this trial were first presented in Fall 2012.[4] This three-times weekly dosing strategy of Copaxone reduced relapse rates by 34 percent compared with placebo, and reduced new MRI lesions by 35 percent. This is comparable with the expected efficacy of Copaxone given at the standard dose of 20 mg injected daily, and no new safety concerns were identified.

In January 2014, the three-times per week dosing of Copaxone (at the new, 40-mg dose) was approved by the FDA. This new formulation enables individuals who take Copaxone to reduce their number of subcutaneous injections by 60 percent (from seven to three injections per week), once they are prescribed the new dosing regimen. In addition to the newly approved dose, daily Copaxone (at the 20-mg dose) will continue to be available.

Combination Studies

Although in MS the standard of care has been to use one disease-modifying therapy at a time, many other conditions from high blood pressure to cancer are often treated with combinations of medicines to achieve the best outcome. Combining medications safely and effectively requires careful long-term studies, as drug interactions can be complex and difficult to predict.

Results were presented in 2012 for the Combi-Rx trial,[5] designed to assess if the combination of Copaxone and Avonex is more effective at reducing relapse rates than either agent alone. This National Institutes of Health (NIH)-funded trial recruited 1,008 patients, who were randomized to three study arms: combination of Copaxone and Avonex; Copaxone alone; and Avonex alone.

Although all participants were on one or both of the active treatments, the trial was placebo-controlled. This means that for individuals not given the combination of Copaxone and Avonex, they would receive either Copaxone and a placebo, or Avonex and a placebo. This allowed researchers to compare all three treatment groups equally.

Interestingly, the combination of

Copaxone and Avonex taken together was not statistically superior to either therapy taken alone at preventing relapses. It is worth noting that these are the lowest relapse rates ever recorded in a clinical trial of these available agents, with the Combi-Rx trial continuing to support the excellent efficacy of these medicines, particularly when utilized early in the disease course. In this trial, the treatment group that received Copaxone alone had the lowest number of relapses.

Interestingly, in the Combi-Rx trial,[6] the combination was found to be superior to individual drugs for new MRI-lesion activity and the accumulation of total lesions. However, combination therapy failed to show an advantage on several other MRI outcomes.

A Phase II trial to study the effect of combining Copaxone and estriol (a naturally-occurring estrogen hormone) on relapse rate in women with RRMS finally reported preliminary results in 2014.[7] MS relapses are known to be significantly decreased during pregnancy.

This trial was designed to evaluate whether oral treatment with estriol, the major estrogen of pregnancy, would decrease relapses in RRMS when used in combination with injectable Copaxone. The preliminary results showed that the combination of Copaxone and estriol appeared safe over the two-year trial period, and there were no severe adverse events attributed to the treatment.

After the first year of the study, those on the combination of Copaxone and estriol had a significant reduction in relapse rates compared to those on Copaxone plus placebo, and cognitive testing suggested possible cognitive benefits of the estriol combination as well. However, the trial was designed to assess these outcomes at the end of two years.

Unfortunately, after the second year of the study, there was no statistical difference in relapse rates between those on Copaxone combined with estriol versus those on Copaxone combined with placebo. It is not clear if these results will justify continued investigation of estriol in a large clinical trial, but it is another example of the difficulty in proving that a combination strategy is both safe and effective.

Extavia ® (interferon beta-1b)

Company: Novartis Pharmaceuticals Corp.

- ***Administered by subcutaneous injection every other day; dose is 250 mcg***
- ***Approved for relapsing forms of MS and for individuals with CIS***

Extavia is an interferon beta-1b that is biologically identical to Betaseron and made in an identical process, but marketed by a different company. It was released in early 2010.

Extavia shares all prescribing, side effect, and safety information with Betaseron. The two pharmaceutical companies manage the patient-support programs differently; prices and copayments may also vary. The latest information is available through the patient-support programs at these two companies. For more information, visit **mymsaa.org**, and select "About MS," and "Prescription Assistance Programs."

Plegridy™ (PEGylated interferon beta-1a)

Company: Biogen

- ***Administered by subcutaneous injection once every two weeks at a dose of 125 mcg (micrograms)***
- ***Plegridy is approved for relapsing forms of MS***

PEGylation is a chemical modification that has been performed on the interferon beta-1a molecule that allows it to be given subcutaneously (under the skin) every two or four weeks, in contrast to the more frequent injections utilized by the currently approved forms of interferon. The goal is to reduce the number of injections, while maintaining the positive effect of the drug. Studies have tested this experimental therapy for safety and effectiveness. Approved by the FDA in the fall of 2014, this formulation of interferon gives patients the option of using a single-dose auto-injector with a prefilled syringe less frequently than the other self-injected DMTs.

The Phase III clinical trial (ADVANCE) enrolled patients with relapsing-remitting MS (RRMS) to determine the safety and efficacy of Plegridy as compared to placebo. Results were presented in 2013[8] from the first year of this Phase III study, where 1,512 patients were randomized to one of three groups: one group receiving placebo; a second group receiving Plegridy given by subcutaneous injection once every two weeks; and a third group receiving Plegridy by subcutaneous injection once every four weeks.

Plegridy dosed every two weeks significantly reduced MS disease activity versus placebo. Relapses were reduced by 36 percent, and new brain lesions by 67 percent, compared to placebo at one year. Disability outcomes were also positive in this one-year trial. In total, the proportion of disease activity-free patients over one year was significantly higher in the two treatment groups compared to placebo.

The overall incidence of serious adverse events (SAE) and adverse events (AE) was similar among the Plegridy and placebo groups. The most common serious adverse event was infection, which was balanced across all treatment groups (less than or equal to 1 percent per group). The most commonly reported adverse events with Plegridy treatment were redness at the injection site and influenza-like illness. Flu-like illness was reported in 47 percent of both treatment groups compared to 13 percent in the placebo group. These safety data are consistent with the established safety profile of interferon beta-1a therapies for MS.

After the first year, study participants who were taking the placebo were re-randomized to one of the two treatment groups (taking the active drug either once every two weeks or once every four weeks), and continued on their new treatment for the remainder of the second year in the study. Results of the second year of the ADVANCE study[9] were presented at the 2014 meeting of the American Academy of Neurology. Plegridy given every other week significantly reduced the risk of 12-week confirmed disability progression by 38 percent versus placebo, and significantly reduced the annualized relapse rate by 36 percent. Participants in the ADVANCE study were given the option to enroll in the ATTAIN open-label (no longer blinded) extension study.

Participants will be followed for up to four years in this second study.

In a subgroup of ADVANCE participants, up to 120 were enrolled in a sub-study that involves optical coherence tomography (OCT). This is a rapid, noninvasive, office-based imaging technique that allows objective evaluation of the thickness of the retinal axon (the nerve behind the eye) and nerve layers that atrophy (shrinking due to nerve cell death) in MS.

Preliminary evidence from other studies supports the use of OCT as an objective tool to monitor the effectiveness of a therapy as it is a direct way of visualizing loss of nervous system tissue, and it is expected that OCT may be used as an outcome measure in other future trials.

Rebif ® (interferon beta-1a)

Company: EMD Serono, Inc. and Pfizer Inc

- ***Administered by subcutaneous injection three times weekly; dosage is 22 or 44 mcg (the 44 mcg dose appears significantly more effective than 22 mcg, and 44 mcg is the dose most often used in the United States)***
- ***Approved for relapsing types of MS***

Rebif reduces the frequency of relapses and slows the progression of disability. It has also been shown to reduce MRI lesion area and activity compared to placebo.

Interferons appear to reduce inflammation by modulating a favorable balance between cells that increase inflammation and cells that decrease inflammation. They also reduce the transport of damaging lymphocytes into the brain. Lymphocytes are immune-system cells produced to fight infection and disease.

Two Phase IV observational clinical trials have been performed to evaluate ease of use and convenience of new injector devices for Rebif. These include The Multicenter, Open-label, Single-use Autoinjector Convenience Study of a device called Rebidose®,[10] and a multi-center, observational, 96-week Phase IV study of the RebiSmart™ self-injection system.[11] Rebidose is a single-use simplified autoinjector that provides ease of administration through a simple push-button injector. Rebidose became available in the United States in early 2013.

The RebiSmart device, not yet approved in the United States, is an electronic autoinjector that stores several doses of Rebif at a time. It provides an interactive interface to help make injections more tolerable and reminders to stay on schedule with the medication. In a German study, it was found to have a 97-percent adherence rate at three months from the initiation of auto-injector use. These two new injector devices may improve compliance with Rebif in people with relapsing forms of MS.

The REFLEX study[12] of 517 patients compared the efficacy of two dosing frequencies (once or three times per week) of Rebif versus placebo. The effect studied is the conversion to definite MS in patients with clinically isolated syndrome (CIS), which is also referred to as a "first demyelinating event." The primary endpoint was the time to confirmed MS using the McDonald criteria, which is a set of guidelines used to confirm a diagnosis of MS. The secondary endpoint was time to clinically definite MS (CDMS). CDMS is confirmed only when a second neurologic event (indicative of MS) occurs in a patient who previously had one

presenting symptom and was not yet diagnosed with MS.

Rebif, given at the standard dose of 44 mcg three times weekly, brought about a 51-percent reduction in the development of MS as compared with placebo. A 31-percent reduction in MS risk was seen with the once-weekly version of interferon beta-1a given subcutaneously, suggesting that the high-frequency interferon was more successful at prevention of disease activity in patients with CIS.

The Phase IV SKORE study evaluated cognition and fatigue in people with RRMS treated with Rebif. Its primary outcome measure was the percentage of patients with stable or altered cognition status; secondary outcome measures include the proportion with defined Expanded Disability Status Scale (EDSS) changes. The study had 300 participants; it was initiated in June 2009 and was reported at the Fall 2014 ECTRIMS conference.[13] After two years on Rebif, 61 percent had stable or improved scores on the PASAT, a measure of cognitive function. Similarly, 64 percent of patients on Rebif had stable fatigue scores, and 64 percent had stable or improved EDSS scores, indicating overall stability in cognition, fatigue, and disability in the majority of patients studied.

Effects of Disease-Modifying Therapies on Pregnancy

Because DMTs are not tested in pregnant women, information about the potential risks of fetal exposure is not available to guide decision-making by women who are pregnant or wish to become pregnant. Gathering as much information as possible on this important question is critical to women with MS during child-bearing years. Although women are advised to use birth control and to discontinue DMTs when they wish to become pregnant, fetuses are exposed during unexpected pregnancies or with the intentional use of DMTs during pregnancy.

Pregnancy outcomes with women on interferon beta-1b (Betaseron and Extavia) were examined in a large retrospective study presented in 2013.[14] The authors conclude that the data do not suggest an effect of interferon beta-1b on pregnancy outcomes after review of 1,045 pregnancy outcomes of women with an ongoing pregnancy at the time of reporting. Most pregnancies exposed to interferon beta-1b in utero resulted in healthy live births, and the spontaneous abortion rate was consistent with the rate seen in the general population. Final results from the Betaseron (interferon beta-1b) Pregnancy Registry[15] were also presented in 2013. Data were presented on 96 pregnancies, and no pattern was seen to suggest increased negative outcomes (such as fetal abnormalities) with Betaseron. Continued monitoring is recommended.

A German study looked at the effects of interferons and Copaxone on pregnancy and relapse rate. While these data support previous findings that the interferons and Copaxone do not present a major risk for birth

defects, anyone who is pregnant or plans on becoming pregnant should discuss the risks and the benefits with her doctor before starting or continuing any disease-modifying therapy. This study also reconfirmed the reduced MS-relapse rate seen during pregnancy and the increased relapse rate particularly in the first three months after birth. Exclusive breastfeeding seemed to have beneficial effects on postpartum relapse-rate reduction.

Despite a requirement for reliable contraception in Aubagio clinical trials, 83 pregnancies were reported in women who were either (A) taking Aubagio during clinical trials, or (B) partners of men taking Aubagio during clinical trials.[16] Upon learning of pregnancy, women were instructed to discontinue Aubagio and undergo a procedure that results in rapid elimination of the drug. Pregnancy outcomes were consistent with those in the non-MS population. No structural or functional problems have been reported in any of the infants exposed to Aubagio in the context of these clinical trials.

Women with RRMS planning to become pregnant are advised to discontinue treatment with Tysabri before conception. However, it is known that there is a risk of severe relapse following discontinuation of Tysabri and that high-dose steroid treatment is frequently required to manage these relapses. Results of a prospective controlled study of 97 women with RRMS who did not discontinue treatment during their pregnancy were reported.[17] When compared to both healthy and disease-matched control groups, the rates of major malformation, low-birth weight, and premature birth did not differ significantly. It will be important to weigh the risks and benefits of continuation of treatment with Tysabri against the risks and benefits of high-dose steroid treatment during pregnancy.

Editor's Note: While the data presented on pregnancy were encouraging, as a limited number of women who became pregnant on DMTs did not see abnormalities in their babies, individuals with MS need to be strongly cautioned. These studies look at small numbers of pregnancies and do not suggest that getting pregnant is considered safe while taking DMTs. Interferons in particular have been associated with spontaneous abortion (miscarriage) in animal models, and are not recommended for women who are pregnant or attempting to conceive. The recommendations of the FDA and MS experts still stand for women on DMTs to take preventative measures to avoid pregnancy.

Lemtrada® (alemtuzumab, formerly Campath)

Companies: Genzyme, a Sanofi company, and Bayer HealthCare Pharmaceuticals

- ***Administered in one course yearly by intravenous infusion over three-to-five consecutive days***
- ***Lemtrada is approved in relapsing types of MS***

Lemtrada is a humanized monoclonal antibody that targets a protein present on the surface of mature lymphocytes, resulting in a rapid depletion/suppression of T and B cells. This agent has been approved for the treatment of B-cell leukemia, although since 2012, it has been developed solely for MS.

A Phase II study of 334 individuals with early, active RRMS compared Lemtrada to high-dose Rebif (44 mcg) in RRMS. In this three-year safety and efficacy trial, Lemtrada was more effective than Rebif at reducing the relapse rate and the risk for six-month sustained accumulation of disability in patients with RRMS.

In a multi-year extension study of the 334 individuals who participated in the original Phase II study, Lemtrada yielded a 73-percent reduction in risk for sustained accumulation of disability. Additionally, 77 percent of Lemtrada-treated patients were relapse-free.

A five-year assessment showed that 87 percent were free of sustained disability accumulation, 72 percent were relapse-free, and 65 percent were free of clinical-disease activity. These data indicate that Lemtrada's treatment effect is durable; it halts clinical-disease activity in a significant proportion of RRMS patients through five years – even though many of those patients did not require subsequent re-treatment with the drug.

Lemtrada has since successfully completed two Phase III trials: CARE-MS I and II. The CARE-MS I study[18] compared the clinical and MRI results of treatment with Lemtrada, to treatment with subcutaneous Rebif (interferon beta-1a) in patients with RRMS who had not received prior treatment with any disease-modifying therapies. Rebif was given according to the regular dosing of three-times per week, while Lemtrada was given intravenously for five days, and then a second course one year later for three days. CARE-MS I was a multicenter international trial. Data were collected for each patient during a two-year period from the time of the first infusion.

The ARR (annual relapse rate) was 0.18 (or slightly less than one relapse every five years) for Lemtrada-treated patients. This was compared with 0.39 (or slightly less than one relapse every two-and-a-half years) for Rebif-treated patients. This means that Lemtrada reduced the ARR by 55 percent compared to Rebif. Individuals taking Lemtrada had a 59-percent reduction in severe relapses requiring steroid treatment. These clinical data were supported by MRI outcomes. Through year two, fewer Lemtrada patients developed new gadolinium-enhancing lesions (areas of active inflammation and myelin damage in the brain) than Rebif-treated patients (15.2 percent versus 27.2 percent).

CARE-MS II[19] is the third study to compare Lemtrada with Rebif. It was designed to evaluate the effect of Lemtrada on relapse and disability as compared to Rebif in people with RRMS who had relapsed on prior therapy –

people for whom a first-line injectible medication was insufficient. The study design was otherwise the same as that in CARE-MS I. The co-primary efficacy endpoints were the ARR and time to six-month sustained accumulation of disability as measured by the Expanded Disability Status Scale (EDSS).

Relapse data showed that 65 percent of patients treated with Lemtrada were relapse-free at two years, as compared to 47 percent with Rebif. These data also showed a 49-percent reduction in relapse rate as compared to Rebif. The group treated with Lemtrada showed a decrease in the mean disability score, versus a slight worsening of disability in those treated with Rebif. Approximately 29 percent of patients treated with Lemtrada experienced a six-month sustained improvement in disability, as compared to 13 percent with Rebif.

In addition to the new goal of identifying improvement in disability achieved by some participants in clinical trials, looking at the percent of patients who are "disease-activity free" (also referred to as having "no evidence of disease activity," or NEDA) during a clinical trial is another important aspirational goal of our increasingly powerful therapies for MS. Along these lines, subsequent analyses of the Lemtrada clinical trial data were presented in 2013.[20]

In a subset of patients with highly active disease in the CARE-MS II trial (patients with multiple relapses and enhancing MRI lesions in the year prior to enrolling in the trial), 24 percent of individuals treated with Lemtrada were free of disease activity at the end of the two-year study, while none of these study participants treated with Rebif (interferon beta-1a) achieved that outcome.

Three-year follow-up data from the CARE-MS II extension study presented in 2014 demonstrated[21] that Lemtrada has a durable treatment effect. Eighty percent of individuals with RRMS who received two yearly courses of the drug in the CARE-MS II trial did not need to receive a third course of treatment. Seventy percent of EDSS scores were stable or improved at year three, compared to the baseline measurement upon entry into the trial.

Several safety concerns have been raised by the above studies, including infusion reactions to the medication, and an increased risk of infection and emergent autoimmune diseases in patients treated with Lemtrada. All three studies showed a modest increase in the incidence of infections, though no opportunistic infections occurred. (These types of infections are a result of micro-organisms found in the body that only infect a person when the immune system has been weakened.) No treatment-related fatalities were reported in the Phase III studies.

In the CARE-MS I and II studies respectively, approximately 18 percent and 16 percent of Lemtrada patients developed an autoimmune thyroid disorder. At the 2014 American Academy of Neurology meeting, further data was presented: Four-year follow-up data from the ongoing CARE-MS extension study found that in years zero to four, 35 percent of individuals receiving Lemtrada experienced a thyroid adverse event. None of these events resulted in discontinuation of treatment with Lemtrada, and most of the

thyroid-related adverse events were treated with conventional treatment. The incidence of events peaked at month 36 and decreased thereafter.

In the CARE-MS studies, approximately 1 percent of subjects developed a potentially severe bleeding disorder called immune thrombocytopenic purpura (ITP). With ITP, the blood does not clot as it should, and this can result in internal bleeding. It is important that patients treated with Lemtrada commit to monthly lab and self-monitoring because, if not detected and treated, ITP can have grave consequences. When addressed promptly, ITP caused by drug treatments such as Lemtrada, responds readily to treatment. A program to monitor for the development of thyroid issues and immune thrombocytopenia was successful in early detection of these known complications from Lemtrada in the clinical trials.

With the side effects and adverse events in mind, the significant reduction in relapses with Lemtrada compared with Rebif was a deciding factor in the FDA's consideration of Lemtrada as an addition to the available treatment options for RRMS. In June 2012, the parent company announced that Lemtrada was submitted to both the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for approval.

In September 2013, the EMA granted marketing authorization for Lemtrada for the treatment of multiple sclerosis. In Europe, the drug is indicated for the treatment of adult patients who have relapsing-remitting MS with active disease defined by clinical or imaging features.

In November 2013, the FDA held a meeting to discuss Lemtrada. Despite raising concerns over the drug's safety as well as study design, the FDA's advisory committee voted to recommend the drug for approval. Unlike the EMA's decision, the committee recommended that the treatment be approved only as a second-line therapy, when other disease-modifying therapies fail or are not tolerated well by a patient.

However, in December 2013, Lemtrada was initially denied FDA approval. After a period of detailed reconsideration of the data, the FDA decided to approve Lemtrada for use in the United States in November 2014. Because of its safety profile, the FDA indicated that use of Lemtrada should generally be reserved for people who have had an inadequate response to two or more MS therapies.

The prescribing information for Lemtrada includes a boxed warning about the potential for serious, sometimes fatal, autoimmune conditions based on the data described earlier, including thyroid conditions, immune thrombocytopenia (ITP), and an immune condition that impacts the kidneys. Patients need to be aware of the potential for serious and even life-threatening infusion reactions on the days the medication is administered, and an increased risk of malignancies in the long-term.

Patients electing to be treated with Lemtrada need to take preventative antiviral medications and undergo careful monitoring, including blood and urine tests every month for 48 months after the last dose is given, as well as annual skin exams, as part of the Lemtrada REMS (Risk Evaluation and Mitigation Strategy) program.

Novantrone® (mitoxantrone)

Company: EMD Serono, Inc.

- ***Given via intravenous infusion, the dose varies according to an individual's weight. It is administered once every three months for a maximum of two-to-three years. The total dose is limited to avoid risking damage to the heart.***
- ***Approved for use in SPMS, PRMS, worsening RRMS, and people who are not responding favorably to standard therapies.***

Novantrone is an immunosuppressant that has been used for many years to treat cancer. It targets rapidly dividing cells, including those believed to be involved in MS. Side effects may include cardiac disease and leukemia; patients must be closely monitored to minimize these risks. The risks of cardiotoxicity and leukemia limit the use to a maximum of two-to-three years and have dramatically reduced the use of Novantrone in the United States.

This drug appears to delay the time to a first-treated relapse, reduce the number of relapses, delay the time to disability progression, and decrease the number of new lesions that can be detected by MRI. It also appears to stabilize disease activity in some individuals with SPMS.

In June 2013, the FDA released a message regarding the potential harm that Novantrone can have on the heart's pumping action. Individuals who have or will be taking this drug must have their heart tested before treatment and every year thereafter, even after discontinuing with Novantrone. To view the full message, please visit **mymsaa.org/novantrone-fda**.

Tysabri® (natalizumab)

Company: Biogen and Elan Pharmaceuticals, Inc.

- ***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 drug was originally recommended for patients who have not responded adequately to, or who cannot tolerate, another treatment for MS, although its use is evolving through new study findings as specified in the FDA's label changes, described later in this section.

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).

A pivotal trial of Tysabri showed that this agent substantially reduces clinical and MRI activity in relapsing MS. Recent studies with Tysabri indicate that the drug may achieve a sustained improvement in disability for individuals with relapsing-remitting MS (RRMS). At 18 months and up to 24 months of treatment with Tysabri, 87 percent of RRMS patients previously treated with Avonex showed stable or improved MRI scans. In this same group, disability scores as measured by the Expanded Disability Status Scale (EDSS) were stable or improved in 59 percent of patients.

A Phase IV trial, The Randomized Treatment Interruption of Natalizumab (RESTORE)[22] study, evaluated the impact of

stopping Tysabri and switching to other disease-modifying therapies. This study enrolled 175 patients and found a high rate of recurrence of MS disease activity, both in terms of relapses and new lesions on MRI, beginning about three months after Tysabri was stopped. This study provides important information, especially for people on Tysabri who are weighing the risks and benefits of stopping this drug – particularly in light of PML risk.

Progressive Multifocal Leukoencephalopathy (PML)

Tysabri has been increasingly utilized as a disease-modifying therapy in RRMS, though clinical use of this drug has been limited from the outset by the risk of progressive multifocal leukoencephalopathy (PML). PML is a viral brain infection caused by the JC virus, which, when not discovered and treated early, can typically lead to severe disability or death. Many people are exposed to the JC virus (JCV), which typically remains dormant; however, it may become activated and infect the brain when one's immune system becomes weakened, a condition that may result from immunosuppressive drugs.

Once projected as a universal risk of approximately 1 in 1,000, based on Tysabri's pivotal trial data, new data presented and published in 2012 allow for the risk of Tysabri-associated PML to be estimated for each individual with increasing precision.

Three risk factors for Tysabri-associated PML have since been identified, allowing for the classification of individuals according to their relative risk of PML.[23] The most important risk factor is the presence of JC-virus antibodies. Roughly 50-to-60 percent of adults carry the JCV antibodies, which can now be determined by a simple blood test.

The JCV Antibody Program (STRATIFY-2) began in April 2010, enrolling more than 30,000 people with MS, and will continue for several more years. Testing for JCV antibodies was added to the FDA label for Tysabri in 2012. The JCV antibodies assay is available through Quest Diagnostics, at no charge to patients if ordered with the "STRATIFY JCV™" test form (available from Quest and Biogen). People testing negative for JCV antibodies are at risk for becoming JCV-positive by approximately 2-to-3 percent per year. Current recommendations are to re-test JCV antibodies status every six months in JC-virus negative people on Tysabri therapy. Some neurologists may opt to test JC-virus status more frequently, though this goes beyond the current FDA guidance.

The second risk factor for the development of Tysabri-associated PML is the duration of Tysabri treatment. Risk for PML in JCV-positive people increases the longer Tysabri is used. The risk is small in the first year of treatment with Tysabri, likely less than 1 in 1,000. In the second year, this increases to approximately 1 in 500, and beyond two years on Tysabri, the risk increases further.

The third risk factor for the development of Tysabri-associated PML is prior treatment with immune-suppressing medications such as Cytoxan® (cyclophosphamide), Novantrone (mitoxantrone), or other chemotherapy agents. Standard injectable MS disease-modifying therapies (interferons and Copaxone, listed

earlier) are not considered immune suppressants, and use of these prior to Tysabri does not increase the risk of PML.

As of Fall 2014, approximately 517 cases were reported of PML[24] with Tysabri, while more than 130,000 people have been treated with this medication. The FDA labeling of Tysabri has been updated to further quantify the risk. The new labeling also notes the increased risk from previous use of immunosuppressive medications.

Although PML is always serious, it is no longer always fatal. Early recognition and the quick removal of Tysabri using a procedure called plasmapheresis have improved the outcomes. Early PML diagnosis and treatment increases the survival rate to 80 percent (although often with disability).

In December 2013, the FDA approved a label change for Tysabri. Some of the more notable changes include: indications of approval for first, second, and third-line therapy are the decision of the provider; updated data includes patients on treatment for up to six years; an increased risk of developing herpes encephalitis and meningitis – patients need to be instructed by the provider to immediately report if they experience fever, headache, or confusion; and one patient with acute liver failure is noted.

Current Study Information

As the use of Tysabri in early MS has not been widely studied, 300 individuals with early RRMS who are JC virus antibody-negative will be followed over the course of four years while undergoing treatment with Tysabri.[25] One purpose of the study is to find out how effective Tysabri is at keeping patients who are in the early stages of RRMS free of disease. This study is expected to run through the end of 2016.

Final results of the Tysabri 24 PLUS study were presented in 2013. In this observational study, the clinical course of patients with RRMS receiving Tysabri for more than two years was assessed. Patients experienced reductions in relapse rates of more than 90 percent compared to their status before treatment. Eighty percent of patients experienced no relapses during the entire observation period after baseline. The mean EDSS scores remained stable at the level observed before the start of treatment. Safety data, including the number of cases of progressive multifocal leukoencenphalopathy (PML) were consistent with the known safety profile of Tysabri.

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 **PPMS** and **secondary-progressive MS (SPMS)**.[26] 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 provides encouraging evidence that Tysabri may have beneficial effects in progressive forms of MS.

To continue this line of investigation, a large, randomized trial of Tysabri in **SPMS** called **ASCEND**[27] is ongoing, and will evaluate the effects on the accumulation of disability in people with SPMS. As of Fall 2013,[28] all 889 SPMS patients have been enrolled. This trial is

expected to conclude in 2015.

A small study of 20 individuals with RRMS[29] is evaluating the role of Tysabri on cognition and neurodegeneration (the breakdown or cell death of nerve cells). Its objective is to further establish the role of Tysabri in preventing neurodegeneration in MS and to establish new markers for such damage. This study is expected to conclude in 2016.

Other studies are exploring the effects of Tysabri on ambulation (walking and mobility), cognition, fatigue, depression, bladder function, sexual function, disability, and health-related quality of life. Some of these studies are completed with generally favorable results. One study indicated that Tysabri-treated patients had fewer MS-related hospitalizations and emergency-room visits over one year of treatment, suggesting that it may reduce the economic burden of MS.

FDA-APPROVED MEDICATIONS: ADMINISTERED ORALLY

Aubagio® (teriflunomide)

Companies: Genzyme, a Sanofi company

- ***Oral medication (tablet form) taken daily; two doses approved: 7 mg and 14 mg***
- ***Approved for relapsing forms of MS***

Aubagio (teriflunomide) contains the same active ingredient as leflunomide, which has been used in the treatment of rheumatoid arthritis since 1998. This drug is an immuno-modulator that affects the production of T and B cells. It inhibits rapidly dividing cells, including activated T cells, which are thought to drive the disease process in MS. Unlike some drugs that modulate the immune system, Aubagio is thought to leave the immune system's response to infection intact, so it may still fight against infection while a patient is taking this drug. It may also inhibit nerve degeneration by reducing the production of free radicals. (Free radicals can damage cells in the brain and other organs.)

Aubagio was the second oral medication to be FDA-approved for relapsing forms of MS, and became available in October 2012. Both a 7-mg and 14-mg daily dose were approved, although the 14-mg dose proved to be more effective in clinical trials.

People taking Aubagio are advised to be checked for exposure to tuberculosis (TB) prior to starting this medication, as several cases of TB occurred in trials. Liver function tests must be performed monthly for the first six months while on Aubagio, and periodically thereafter. Hair loss is another potential side effect, although this can be transient.

Aubagio is considered Pregnancy Category "X," and both men and women of child-bearing potential should use effective birth control while taking Aubagio. As the drug can remain in the body for up to two years, this is an important consideration to plan in advance. If pregnancy is contemplated, a rapid decrease of Aubagio levels in the blood can be induced by taking cholestyramine or activated charcoal. The process takes 11 days.

Prior to approval, Aubagio successfully completed several large clinical trials. The TEMSO trial for RRMS compared 7 mg and 14 mg of Aubagio in 1,088 individuals. Both doses significantly reduced the annualized relapse rate by approximately 31 percent. The 14-mg dose also reduced the risk of sustained disability progression by 29.8 percent relative to placebo. Aubagio (7-mg dose) resulted in a 39.4-percent reduction in brain-lesion volume on MRI compared with placebo; the 14-mg dose resulted in a 67.4-percent reduction. The number of gadolinium-enhancing lesions were also reduced with both doses compared with placebo, and a trend toward a greater effect was observed with the higher dose. No difference in the rate of serious infection, opportunistic infection, or malignancy was found.

A Phase III extension study TEMSO is ongoing. Patients who completed the original study and who received the drug are being maintained on the same dose; those who received placebo are randomized to Aubagio 7 mg or 14 mg. The study remains double-blinded, and will evaluate safety and efficacy. Preliminary data presented in 2013[30] found no new or unexpected adverse events (AE) associated with long-term (up to nine years) exposure to Aubagio. Adverse events were consistent with the two-year core trial, and incidence of adverse events generally decreased and remained low.

Results of the TOWER study of 1,169 individuals with RRMS were reported in the fall of 2012.[31] The results showed a 36.3-percent reduction in ARR with Aubagio (14 mg), versus placebo. There was also a significant 37-percent risk reduction in the number of patients who were relapse-free during the trial and a 31.5-percent reduction in the risk for 12-week sustained accumulation of disability versus placebo. Results for the 7-mg dose showed a significant but smaller reduction in relapse rate but not in sustained accumulation of disability.

A third Phase III study called TENERE[32] compared the two oral doses of Aubagio to Rebif. The primary endpoint was time to the first occurrence of confirmed relapse or permanent treatment discontinuation for any reason, whichever came first. In the study, 48.6 percent of patients receiving the 7-mg dose of Aubagio and 37.8 percent of those on the 14-mg dose relapsed or discontinued treatment, compared to 42.3 percent of patients on Rebif. However, the rate of permanent treatment discontinuation was lower with Aubagio (18.3 and 19.8 percent) than Rebif (28.8 percent).

The Phase III TOPIC study[33] of 618 individuals with clinically isolated syndrome (CIS) reported data in 2013. This study also compared 7-mg and 14-mg doses of Aubagio versus placebo. The study's primary endpoint was the time to conversion to clinically-definite MS (CDMS) after CIS. The study was ended early as revised diagnostic criteria have enabled earlier diagnosis of MS.

The 14-mg dose of Aubagio reduced the risk of second MS relapse (and thus reduced the risk of conversion from CIS to "clinically definite MS") by 43 percent. Safety and efficacy were consistent with the other Phase III Aubagio studies. This highlighted the ability of early treatment with this disease-modifying therapy to delay the onset of MS attacks.

Gilenya®

(fingolimod, formerly known as FTY720)

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. Gilenya blocks potentially damaging T cells from leaving lymph nodes, lowering their number in the blood and tissues. It may reduce damage to the central nervous system (CNS) and enhance the repair of damaged nerves within the brain and spinal cord. Study data suggest that Gilenya may have neuro-protective effects.

Some adverse events with Gilenya include: an initial reduction in heart rate; infrequent changes in the conduction of electricity in the heart (atrioventricular [AV] block); macular edema (a condition that can affect vision, caused by swelling behind the eye); and infections, including reactivation of herpes infections. Following the death of a patient within 24 hours after taking a first dose of Gilenya in November 2011, the FDA conducted an investigation, and in April 2012, updated the prescribing guidelines for Gilenya.

Other deaths from cardiac causes have been reported from among the many thousands of people in several countries who have been treated with this medication. Contraindications now include a history or presence of cardiac conditions (such as myocardial infarction or stroke in the previous six months, second-and third-degree atrioventricular block, or other serious cardiac rhythm disturbances) or in patients treated with certain antiarrhythmic drugs.

The updated prescribing information recommends that all patients starting treatment should undergo electrocardiography immediately before the first dose and at the end of the initial six-hour observation period, along with hourly measurement of blood pressure and heart rate. Continuous cardiac monitoring must be performed in some cases. This "First Dose Observation" is part of a set of monitoring requirements that need to be completed when Gilenya is prescribed.

Study Information

The FREEDOMS Phase III study compared Gilenya with placebo and showed the drug to be safe and well tolerated. Gilenya reduced the risk of confirmed disability progression by 30 to 32 percent versus placebo, and significantly increased the proportion of patients who were disease-free over two years. It also resulted in a 30-percent reduction of brain-volume loss as compared with placebo at one and two years, suggesting a possible direct neuroprotective effect. A second Phase III study, FREEDOMS II, compared Gilenya with placebo, and reported similar results.

Two deaths from herpes virus infections occurred in the FREEDOMS trials; both of these individuals received a higher dose of fingolimod that is not FDA-approved or prescribed. No deaths from infections were reported in those individuals treated with the FDA-approved lower dose, which is the only

dose available for MS patients.

The TRANSFORMS Phase III trial was a 12-month study of the efficacy of Gilenya as compared to Avonex in individuals with RRMS. In summary, Gilenya was more effective in reducing the annual relapse rate, resulted in less deterioration in the ability to independently perform daily activities, was associated with a lower rate of brain atrophy, and showed a greater effect on reducing MRI measures of lesion activity. No difference in progression of disability was demonstrated in this 12-month study.

In both the FREEDOMS and TRANSFORMS studies, Gilenya significantly reduced the frequency of severe relapses and the number of individuals who required intervention (steroids or hospitalization), along with reducing the number of relapses with no or only partial recovery. In the TRANSFORMS trial, Gilenya also consistently reduced the annualized relapse rate in patients with highly active MS as compared to Avonex.

Interim data were presented in 2013 from LONGTERMS,[34] a single-arm, open-label extension study that began in June 2010 and will continue through June 2016. Clinical disease activity remained low for up to five years in patients treated with Gilenya, an interim data analysis indicates. Most patients remained relapse-free and disability remained stable for up to five years. Approximately 70 percent of patients continuing on Gilenya were relapse-free. As with many extension trials, individuals dropping out may have caused a "selection bias" favoring long-term use.

Several analyses[35] of Gilenya's clinical trials have demonstrated that Gilenya has significant effects on slowing brain atrophy in MS. In the TRANSFORMS trial, Gilenya significantly reduced brain volume loss over one year compared with Avonex, and in the FREEDOMS trials, Gilenya reduced brain volume loss over two years compared with placebo.

Intriguingly, in new research presented in 2013,[36] patients on Gilenya who remained disease-free over 48 months were shown to have less brain-volume loss over the four-year study than those who were not disease-free. In addition, reduced brain-volume loss was associated with better clinical outcomes at month 48. These data suggest that the effect of Gilenya on slowing brain atrophy may have a clinical impact on preventing disability.

An Italian study[37] confirms that the first dose of Gilenya is generally safe and well-tolerated; these results are consistent with results from previous trials. Data were collected from 812 Italian patients who were undergoing the required six-hour First-Dose Observation period following administration of Gilenya. Most patients (95.2 percent) did not have any adverse events during the six hours. Cardiovascular adverse events occurring in 18 patients were all self-limiting, and did not require intervention.

The six-month Phase IV EPOC[38] study also presented data in 2013. This study was designed to evaluate: patient-reported outcomes; physician assessment of a change; as well as safety and tolerability in patients with relapsing MS, who had also been previously treated with other DMTs and are now receiving Gilenya. This study found that, based on the Treatment Satisfaction Questionnaire for Medication (TSQM), people

with relapsing multiple sclerosis (MS) reported greater treatment satisfaction after starting the oral treatment Gilenya versus switching to, or staying on, one of the injectable DMTs (one of the interferons or Copaxone).

Although Gilenya was approved for 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 medication for PPMS, this is 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 by press release in December 2014[39] 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. Detailed data will be presented at the 2015 American Academy of Neurology meeting, and it is hoped that these data will yield further insight into the pathogenesis of PPMS.

Another ongoing Gilenya clinical trial is a Study Evaluating Safety and Efficacy of Two Doses of Fingolimod Versus Copaxone.[40] 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 preventing relapses. This study is expected to report data in 2015.

Tecfidera™ (dimethyl fumarate)

Company: Biogen

- ***Oral medication; 240 mg pill taken twice daily (taking Tecfidera only once daily has not been demonstrated to be effective in MS)***
- ***Tecfidera is approved for relapsing forms of MS***

The United States Food and Drug Administration (FDA) announced in March 2013 that it had approved Tecfidera (dimethyl fumarate or DMF, formerly known as BG-12) as a first-line therapy for the long-term treatment of relapsing forms of multiple sclerosis (MS). Tecfidera is an oral fumaric acid ester, related to a medication called Fumaderm®. This latter medication was previously shown to be effective in patients with psoriasis and was used for this indication in Germany for many years. The mechanism of action in MS is still under investigation; however, Tecfidera may have a distinct dual mechanism of action.

First, it is an immunomodulator with anti-inflammatory properties. This induces anti-inflammatory cytokines (small proteins that may stimulate or inhibit the function of other cells) and appears to suppress damaging macrophage cell activity. Macrophages are a type of white blood cell that can damage both myelin in the central nervous system and the nerves themselves.

Second, Tecfidera may also have neuroprotective effects. This is due to its activation of a substance that is critical for resistance to cellular damage (from what is termed "oxidative stress") as well as for normal immune function.

Completed Studies with Tecfidera

Two large Phase III trials were conducted with Tecfidera; both showed positive outcomes. The Phase III DEFINE study, which compared two doses of Tecfidera against placebo in 1,200 patients, was completed in February 2011. The Phase III CONFIRM study, which enrolled 1,232 patients, tested two dose levels against placebo, and also compared Copaxone against the same placebo group; the study was completed in September 2011.

In the DEFINE study, 240 mg of Tecfidera was given either twice or three times daily versus placebo for two years. The study met its primary endpoint with a 49-to 50-percent reduction in the proportion of patients who relapsed during the study period. In addition, each of the two doses reduced the risk of sustained disability progression (for at least 12 weeks) by 34-to-38 percent.

The CONFIRM study compared the same two dosing frequencies of Tecfidera with placebo for two years and also compared the same placebo group to a group receiving daily subcutaneous injections of Copaxone. (Please note that the study was not designed to compare the effectiveness of Tecfidera to Copaxone.) The study met its primary endpoint with a reduction in relapse rates of 44 to 51 percent for Tecfidera compared to placebo. No statistically significant difference was observed in the remaining clinical endpoint of confirmed disability progression, possibly due to the unexpectedly low rate of progression in the placebo group. In both studies, compared to placebo, individuals given Tecfidera had significantly reduced disease activity as shown on magnetic resonance imaging (MRI) scans.

Continuation Studies

A continuation study of 1,736 patients who participated in the DEFINE and CONFIRM studies, called ENDORSE, is evaluating the long-term safety profile of Tecfidera and efficacy on clinical outcomes, MRI scans, and quality-of-life. The study continues as of 2015.[41]

In 2014, PML occurred in one patient in the ENDORSE study who had taken Tecfidera for four years. Because of this event, the FDA revised its label for Tecfidera with new precautions and recommendations.

The label points out that the patient who developed PML had experienced prolonged lymphopenia while taking Tecfidera. Lymphopenia is a reduction in circulating lymphocytes, which are white blood cells aimed at fighting disease and infection. In general, the label now explains that Tecfidera may decrease lymphocyte counts, and states that 2 percent of patients experienced low lymphocyte counts for at least six months.

The revised labeling includes instructions that lymphocyte counts should also be obtained after six months of treatment, and every six–to-12 months thereafter. Neurologists should consider if Tecfidera should be discontinued if lymphocytes remain low.

Other medical safety issues continue to be followed through the ENDORSE study. Although malignancies have been observed in this patient population, at an incidence of less than 1 percent, it was not apparent that these were directly caused by Tecfidera. Additional data from ENDORSE is anticipated at national meetings in 2015.

Side Effects and Adverse Events

In studies, flushing and gastro-intestinal (GI) events – such as diarrhea, nausea and vomiting, and abdominal pain – were the most commonly reported side effects. Flushing and gastrointestinal events occurred in approximately 30-to-40 percent of patients and occurred more often at the beginning of treatment, decreasing in frequency after the first one to two months on this medication.

A small study presented at the 2014 American Academy of Neurology meeting evaluated four individuals who took the oral asthma medication montelukast, 10 mg once daily (while continuing treatment with Tecfidera)[42]. The study found that GI symptoms decreased within 72 hours and the improvement persisted for 30 days on montelukast. Symptom severity, as measured by the Gastrointestinal Symptom Rating Scale (GSRS), decreased by 81 percent.

Other adverse events, which were mild or moderate in severity, included upper respiratory infection, pruritus (chronic itching), and erythema (skin redness or rash). The only serious adverse events (aside from MS relapses) to occur in two or more patients taking Tecfidera during these large studies were gastroenteritis (an inflammation of the lining of the intestines) and gastritis (an inflammation of the stomach lining).

During the first six months of therapy in the DEFINE study, liver enzymes were elevated in 6 percent of individuals taking Tecfidera, compared to 3 percent of the placebo group. No cases of liver failure were reported in either study. Excess protein in the urine (proteinuria) was observed slightly more often in the treated groups versus the placebo group of the DEFINE study. No cases of kidney failure were reported in either study.

Pregnancy outcomes are known for 25 of the 35 pregnancies exposed to Tecfidera. To date, pregnancy data indicate no increased risk of fetal abnormalities or adverse pregnancy outcomes associated with exposure to Tecfidera during the first trimester. Further data regarding pregnancies will be collected through a pregnancy registry. As with DMTs discussed previously, the recommendations of the FDA are for women on DMTs, including Tecfidera, to take preventative measures to avoid pregnancy.

Ongoing Studies

The Phase II EXPLORE trial is evaluating oral Tecfidera as a combination therapy with an injectable medication. It will determine the safety and tolerability of Tecfidera when administered in combination with interferons or Copaxone, in 100 people who continue to have evidence of disease activity despite receiving consistent treatment for at least one year. Efficacy endpoints that will determine the effectiveness will also be assessed in a subset of participants. Although the study concluded in 2012, the results have not been published as of early 2015.

Please see MSAA's online chart of long-term treatments at
mymsaa.org/DMTchart

Laquinimod (also known as Nerventra®)

Companies: Teva Neuroscience, Inc. and Active Biotech

- ***Oral medication taken once daily; dosing is still under investigation***
- ***Laquinimod is being studied in RRMS and Progressive MS***

Although its exact mechanisms of action are unknown, laquinimod is an immunomodulator, apparently through its effects on cytokines 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 central nervous system (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.[43] The first analysis compared the expected risk of disability progression (given a particular relapse rate) with that seen in the pooled data. In this analysis, the effect of laquinimod on reducing the risk of disability progression was larger than predicted. The second analysis examined the relationship between relapses and disability by looking at disability progression in both relapsing and relapse-free patients in the two trials. About one third of the patients who progressed were relapse-free, suggesting that these two outcome measures are mediated through different pathways.

Since laquinimod may have more of an effect on disability than on relapses, a new trial looking primarily at laquinimod's disability-preventing impact was designed. This 24-month trial, The Efficacy and Safety and Tolerability of Laquinimod in Subjects With Relapsing Remitting Multiple Sclerosis (CONCERTO)[44], is comparing two doses of laquinimod (including a 1.2-mg dose, which is 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 will be studied at higher doses in a **primary progressive MS trial** beginning in 2015.[45] This trial will primarily evaluate the effect of laquinimod on brain atrophy, and secondarily on clinical outcomes. It is designed to enroll approximately 375 people, and is anticipated to run through the end of 2017.

EXPERIMENTAL MEDICATIONS: MONOCLONAL ANTIBODY MEDICATIONS

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 injections***
- ***Daclizumab is being studied in both RRMS and secondary-progressive MS (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: 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. These results were all for the low- and high-dose

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 whose protein sequences have been modified to increase their similarity to antibodies produced naturally in humans. Monoclonal antibodies are an important type of medication, as they can be specifically targeted to perform a particular action, which is 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.

groups respectively. 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 presented[46] in 2012. Patients who were on placebo and began treatment with DAC HYP in the extension trial had a 59-percent reduction in annualized relapse rate compared to the year prior, while patients who continued on DAC HYP saw their low relapse rate from the prior year maintained.

In 2013, further data from this trial was presented;[47] 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,[48] a Phase III study of 1,841 participants with relapsing MS, comparing DAC HYP to Avonex. DAC HYP was administered subcutaneously once every four weeks for 96 to 144 weeks in 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.[49] Treatment 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 in 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 side effects will be closely evaluated in further analyses of the Phase III trial.

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: 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 **low-inflammatory SPMS**, sponsored by the National Institute of Neurologic Diseases and Stroke, is testing Rituximab versus placebo (RIVITaLISe). The study is recruiting participants[50] and expected to run until 2016. The primary outcome measure will be the progression of brain atrophy after two years of treatment, unless predetermined analysis shows that the secondary outcome measures of MRI and clinical assessment are more reliable measures of effectiveness than brain atrophy.

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 (discussed on next page).

Ocrelizumab

Companies: Genentech and Roche Pharma AG

- ***Administered via intravenous infusion***
- ***Ocrelizumab is being studied in RRMS and in primary-progressive MS (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.

In a Phase II study of ocrelizumab[51] in 220 individuals with RRMS, reductions in the total number of brain lesions detected by MRI scans were highly significant at 96 percent for 2,000-mg ocrelizumab and 89 percent for 600 mg compared to placebo. The annualized relapse rate was significantly lower versus placebo at week 24, with a reduction of 73 percent for ocrelizumab 2,000 mg, and 80 percent for ocrelizumab 600 mg. Ocrelizumab's effectiveness was maintained through week 72; the proportion of relapse-free patients at week 72 was 84 percent for the 600-mg group, and 82 percent for the 2,000-mg group.

Infusion-related symptoms, which were generally mild to moderate, were seen in the ocrelizumab-treated groups. The number of serious adverse events was small and similar among the groups. However, one patient in the ocrelizumab 2,000-mg group died of a systemic inflammatory response of unknown etiology. Although Phase III trials in rheumatoid arthritis had significant rates of serious and opportunistic infections, none were identified in this trial of 220 people with MS. Please note that the number of MS patients studied in this Phase II trial is small in comparison to the number of rheumatoid arthritis patients studied in the larger Phase III studies that have already been completed.

Several Phase III trials of ocrelizumab are now underway. OPERA I[52] and II[53] are comparing ocrelizumab (600 mg) to Rebif in RRMS and plan to enroll approximately 800 patients in each study. These trials are anticipated to run through mid-2015.

In addition, because subgroup analysis of Rituxan in the OLYMPUS study suggested a benefit to younger PPMS patients and those with gadolinium-enhancing lesions, ocrelizumab is also being studied in **primary-progressive MS (PPMS)**. The Phase III ORATORIO[54] safety and efficacy study of ocrelizumab in 630 patients with PPMS is currently recruiting participants.

Patients will receive either ocrelizumab (300 mg given intravenously in two infusions, separated by 14 days in each treatment cycle) or placebo. The study is scheduled to run through late 2017. The primary outcome measure is time to onset of sustained disability progression (for at least 12 weeks); secondary outcome measures include the time to sustained disability progression (for at least 24 weeks), change in the total volume of T2 lesions (as seen on MRI), as well as safety, tolerability, and adverse events.

Ofatumumab (also known as Arzerra®)

Companies: GlaxoSmithKline and Genmab

- ***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 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.[55] 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.

Vatelizumab

Companies: Genzyme and Glenmark Pharmaceuticals

- ***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. This is similar to the mechanism of action of natalizumab (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 their involvement in areas of inflammation, and thus potentially reducing inflammatory events in MS.

The EMPIRE study,[56] 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, and it is expected to enroll 168 patients at 55 sites in 10 countries. The study 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 that have a mechanism similar to that of Gilenya (fingolimod). These agents have been well tolerated and reduced lesions related to RRMS. It is hoped that these agents, RPC1063, siponimod (BAF312), ponesimod, and ONO-4641, will maintain or 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).

RPC1063

RPC1063 is a selective modulator of one type of S1P receptor, S1P1. 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 RPC1063 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 RPC1063 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 RPC1063. The drug is moving into a larger, Phase III version of the RADIANCE trial[57], where it will be compared with Avonex in 1,200 subjects with RRMS. This trial is expected to run through the end of 2017.

Siponimod (BAF312)

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 in which the goal was 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, as compared to those taking one of the two lower doses or the placebo. Additionally, MRI findings indicated that treatment with siponimod was associated

with a reduction in active lesions on MRI. 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 **secondary-progressive MS (the EXPAND trial)**[58] 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

Ponesimod is another selective S1P receptor modulator that completed a Phase II trial; results were reported in 2012.[59] 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 new lesions were seen for all treatment groups as compared with 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[60] over two years presented in 2013 demonstrated continued efficacy and no new safety issues emerged. A decision regarding the continued development of ponesimod in a Phase III trial in RRMS is expected in early 2015.

ONO-4641

In the Phase II DreaMS trial, 407 RRMS patients were randomized to placebo or one of three different doses of ONO-4641 (0.05 mg, 0.10 mg, or 0.15 mg once daily for 26 weeks).

All three treatment groups showed a substantial decrease in MRI disease activity as measured both by gadolinium-enhancing lesion numbers and new or enlarging T2 lesions. Compared to placebo, lesion counts were reduced by 82 percent in the 0.05 mg/day group; 92 percent in the 0.10 mg/day group, and 77 percent in the 0.15 mg/day group. The study was not designed to evaluate relapse rates or disability progression, but there was a statistically significant decrease in relapse rate (with the 0.10-mg dose). Adverse events were similar to those seen with Gilenya, including bradycardia and lymphopenia (a reduction in circulating lymphocytes) in some patients. These were dose-related and did not result in drug discontinuation.

As of early 2015, the companies developing ONO-4641 have decided not to continue investigations of this drug. It remains to be seen if this agent will proceed to a Phase III trial.

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. 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. Mast cells are involved in the immune response, in the recruitment of lymphocytes to the brain, and also in inflammatory processes associated with MS. A small Phase II trial of masitinib in **progressive MS**[61] showed a trend toward benefit; however, the results were not

statistically significant.[62]

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 trial[63] 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; results are expected in 2015.

Ibudilast

Ibudilast (MN-166) is an oral agent with novel immune modulating and potential neuroprotective properties that is being studied in progressive 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 ibudilast had a primary neuroprotective role independent from a substantial effect on overt inflammation, the **Phase II Secondary and Primary Progressive MS Ibudilast NeuroNEXT trial (SPRINTMS)**[64] was launched in Fall 2013. It will include 28 enrolling clinical sites across the United States.

The trial is designed to evaluate the safety, tolerability, and efficacy of MN166 (ibudilast) administered twice daily to individuals with **primary- or secondary-progressive MS**. 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 trial is expected to require approximately three years for enrollment, treatment, and data analyses, and will run through the end of 2016.

Tcelna™ (formerly Tovaxin®)

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 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**.[65] 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 is planned to enroll 180 patients and is expected to run through the end of 2015.

Amiloride

It is hypothesized that accumulation of salt and potassium within the cells of MS lesions may contribute to cellular injury and neurodegeneration (the breakdown of nerves). This hypothesis would suggest that by blocking certain channels in these cells, the buildup of these molecules can be prevented and neurodegeneration can be prevented. This strategy was tested and data presented in 2013,[66] looking at the use of amiloride – a potassium-sparing diuretic approved for the treatment of high blood pressure and congestive heart failure – that may have 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 dose used for high blood pressure) for a period of three years.

Researchers found a significant reduction in the development of brain atrophy, and a slowing of the development of disability during the treatment phase, suggesting that amiloride may exert neuroprotective effects in patients with progressive MS. Because amiloride does not readily cross the blood-brain barrier, it is not clear the precise mechanism for the results. This pilot study was the first translational study 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 neuritis[67] was initiated in 2013 and is expected to run through 2015.

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 if patients with early forms of MS 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 European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) Annual Meeting in fall 2012, Chataway and colleagues presented the results of the **MS-STAT trial**.[68] This Phase II study evaluated whether high-dose simvastatin can slow the rate of whole-brain atrophy, and/or disability, in **secondary-progressive MS (SPMS)**.

In this study, 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, and the rate of brain atrophy was 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 a tantalizing possibility.

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 at ECTRIMS in the fall of 2012,[69] and disappointingly, minocycline did not provide significant improvement to either clinical or MRI outcomes.

Another Phase III trial with 200 participants looking at minocycline is still ongoing. This trial will evaluate the effect of 100 mg of oral minocycline twice daily on the conversion of clinically isolated syndrome (CIS) to a diagnosis of MS at six and 24 months. It began in January 2009 and is scheduled for completion in December 2015. It will determine whether 100 mg of oral minocycline twice daily reduces the conversion of CIS to clinically active MS and if any treatment benefit seen after six months is maintained at two years.

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, including new data presented in 2013.[70] 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.

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. IL-17 appears to be a major inflammatory component in MS. This study also demonstrates that Vitamin D increases suppressive T cells that combat inflammation.

An important longitudinal cohort study presented in 2012 by Mowry and colleagues[71] 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, as discussed above, studied the effects of interferon beta-1b (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.[72] 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 December 2016.

A Phase II study that has completed recruiting[73] participants is investigating whether Vigantol® oil, a form of Vitamin D hormone supplement (cholecalciferol), provides any added benefit when given in conjunction with Rebif. The study will have

348 participants; it began in February 2011 and is scheduled for completion in May 2015. 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, the proportion of subjects free from disease activity at 96 weeks, and changes in cognitive function.

The French CHOLINE Phase II study[74] of 250 individuals with RRMS who are receiving ongoing treatment with Rebif began in January 2010 and is scheduled for completion in June 2015. The aim of this study is to evaluate the efficacy and safety of supplementary treatment with Vitamin D3 in people with RRMS treated with Rebif.

The study participants will be divided into two groups, one receiving Vitamin D3 100,000 IU twice monthly along with Rebif treatment, and the other group will be on 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.

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.

Salt

An array of recent research ranging from molecular studies to animal models and even some preliminary human data, has implicated levels of dietary salt – sodium chloride, or NaCl – as potentially affecting MS outcomes. In research presented in 2013,[75] high dietary salt was found to increase autoimmune neuro-inflammation by markedly boosting a Th17 helper T-cell driven autoimmune response in EAE (an experimental disease used to simulate MS in mice).

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,[76] 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.

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.

Chronic Cerebrospinal Venous Insufficiency (CCSVI)

From approximately 2009 through 2013, the Chronic Cerebrospinal Venous Insufficiency (CCSVI) theory of MS pathogenesis received considerable attention. The evidence continues to increase that occlusions/obstructions of the vascular system in cerebrospinal veins (certain veins located in the head and neck), imaged with ultrasound and magnetic resonance venography, do not appear to be related to MS.

Reports from an ongoing study at the University of Texas Health Sciences Center in Houston showed that people with and without MS had abnormalities consistent with CCSVI, and that this abnormality was not found to be more common in people with MS. The group used strict ultrasound criteria definitions, and concluded that their tests – using neurosonography and magnetic resonance venography – did not support the concept that CCSVI is causally involved in MS.

Several vascular-intervention procedures to address the reported venous narrowing in MS are being studied. However, these procedures have also been offered in clinical practice, outside of the safety oversight inherent in clinical trials. Shortly after the American Academy of Neurology's (AAN) meeting in mid-2012, the FDA issued an alert about risks, including death, associated with these surgical treatments of CCSVI.

The FDA Safety Communication regarding CCSVI treatment in MS stated that the FDA believes there is no reliable evidence from controlled clinical trials that this procedure is effective in treating MS. Data to support CCSVI as a clinical entity on its own or its relationship with MS are inconclusive and at times, contradictory. The FDA believes that using these medical devices in CCSVI treatment procedures poses a risk to patients for several reasons.

First, there is no clear diagnostic evidence that CCSVI exists as a distinct clinical disorder or is linked to MS. Second, the venous stenoses seen on imaging tests may be normal variants and not related to a disease process. Furthermore, the safety and effectiveness of using balloon angioplasty devices or stents in the internal jugular or azygos veins have not been established, and that major risks, including death, have been associated with these procedures.

The largest CCSVI study to date was presented at ECTRIMS in the fall of 2012. In the CoSMo study, Comi and Italian colleagues studied nearly 2,000 people with MS and other neurological diseases, as well as healthy controls. Differences in CCSVI between MS and other neurologic conditions and healthy participants were not statistically different, and the study group concluded that the data did not support that CCSVI is a disease connected to MS.

For more information on CCSVI and the FDA's warning, please refer to MSAA's online news articles, "FDA Issues CCSVI Treatment Warning" and "CCSVI Update." These may be accessed by visiting MSAA's website at **mymsaa.org** and selecting "News from MSAA" under "MS News," and then scrolling down to the articles on CCSVI.

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 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 cellular "checks and balances," tissues could grow without restraint, as seen in some malignancies. Anti-LINGO-1 (BIIB033) is an agent with potential remyelinative 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[77], 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.

The first Phase II trial of anti-LINGO, called RENEW, launched in 2013.[78] The study recruited patients with newly-diagnosed MS involving the visual pathways (optic neuritis) to evaluate the drug's effect on remyelination.

Anti-LINGO-1 demonstrated an improvement in the study's primary endpoint, which was the extent of recovery of the optic nerve after optic neuritis as compared to placebo. This was measured by full field visual evoked potential (FF-VEP), an electrical test of the speed that the optic nerve sends visual signals to the brain.

The study showed no effect on secondary endpoints, including change in thickness of the retinal layers (optic nerve neurons and axons). Anti-LINGO-1 was generally well tolerated in this study, noting that two patients had hypersensitivity 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.

To that end, a second, larger Phase II trial (SYNERGY)[79] is looking at this drug in combination with Avonex. **The study will recruit approximately 400 individuals with either RRMS or SPMS.** It 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.

For a detailed review of the science behind anti-LINGO-1, please see the article in *CNS Drugs*, "Blocking LINGO-1 as a Therapy to Promote CNS Repair: From Concept to Clinic," Mi et al, 2013.[80]

Other agents under investigation to potentially foster remyelination or myelin repair include agents in early stages of development – and still with experimental names – such as GSK239512[81] and rHIgM22.[82] Proof of principle data are expected for both of these agents in 2015.

Erythropoietin: Erythropoietin is a hormone produced by the kidneys that promotes the formation of red blood cells in the bone marrow. It has shown neuro-protective effects in animal studies. A German Phase I/IIa pilot study suggests that high-dose treatment, but not a lower-dose regimen, leads to clinical improvement of motor function. Cognitive performance was also improved. Studies are ongoing, and these include one that is evaluating erythropoietin as an adjunct treatment for optic neuritis.[83]

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.

A double-blind, placebo-controlled Phase I/II clinical trial of idebenone,[84] sponsored by the National Institute of Neurological Disorders and Stroke, is currently recruiting **participants with PPMS** with little to moderate disability. It began in July 2009 and is scheduled for completion in September 2016.

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. It 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 study[85] in **secondary-progressive MS** is enrolling, with completion planned for late 2016.

Transdermal Administration of Peptides: A small Polish study of 30 individuals[86] 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 controls. 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. Additionally, progression as measured by the Expanded Disability Status Scale (EDSS) was slightly lower, indicating that disability did not worsen, and may have slightly improved, plus 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.

Other Agents in Development

A number of other agents have shown some encouraging immunomodulatory effects and have been studied in humans. These agents are under investigation for possible future use in MS and include the following:

Secukinumab (AIN457) is a humanized monoclonal antibody to IL-17. A preliminary study[87] administered AIN457 to a very small number of patients with psoriasis, rheumatoid arthritis, and uveitis with variable results. A proof-of-concept trial in RRMS[88] enrolled 73 patients and showed a reduction in gadolinium-enhancing MRI lesions compared with placebo.[89] A larger, Phase II trial has been planned to enroll approximately 380 patients with relapsing MS; the design of the study was presented at ECTRIMS in Fall 2013.

RTL1000 is a protein that inhibits the activation of myelin-reactive T cells, preventing the release of inflammatory cytokines and causing the release of anti-inflammatory cytokines. This molecule is related to the pathways studied transdermally (through the skin), as discussed earlier with peptides. A preliminary safety/tolerability dose-finding study of RTL1000 was reported in 2012.[90]

SB-683699 (firategrast) 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 placebo-controlled Phase II trial[91] 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 falls into a class of "antisense oligonucleotides" not previously used in MS. The results of a Phase II trial were published in 2014,[92] 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.

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 **secondary-progressive MS (SPMS)**. In a Phase I/II study of 18 patients with aggressive disease presented in 2014,[93] pixantrone was as effective as Novantrone with less cardiotoxicity. According to the study abstract, pixantrone is structurally similar to Novantrone and both drugs have similar immunosuppressive properties in animal studies, but may be 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,[94] 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, and the mean 9-Hole Peg Test (9-HPT). Larger, longer-term studies are warranted given these promising results.

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). This form of stem-cell therapy first requires a wiping out or "ablation" of the immune system, typically with high-dose chemotherapy. This intensive course of chemotherapy destroys most blood cells as well as the bone marrow, where blood cells are formed. Then a patient's own hematopoietic stem cells can be transplanted, in an effort to completely reset the immune system in 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 multiple sclerosis. The HALT Phase II study was conducted in 25 patients with highly active RRMS who had failed conventional therapy. The two-year follow-up results of the HALT study were reported in 2013.[95] 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 reported in 2014.[96] A total of 78 percent of subjects had no new disease activity. Treatment failed in five subjects, and two deaths occurred. There have been 130 adverse events that were severe or life-threatening, most relating to low blood counts induced by the treatment approach. 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.

A study in Sweden[97] found a high proportion of patients with aggressive, relapsing forms of MS, were free from disease activity following hematopoietic stem-cell transplantation (HSCT). A group of 41 patients participated, with a mean annualized relapse rate of 4.1 in the year preceding treatment, which means that on average, each was 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 the participants were relapse-free and 77 percent of the 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.

A second type of stem-cell therapy utilizes mesenchymal stem cells, which 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 study,[98] 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. There were no serious adverse events or deaths. Although the mechanism by which mesenchymal stem cells exert their

beneficial effects has not been fully worked out, 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.

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 trial[99] announced in fall 2013. This single-center trial plans to enroll 20 patients with **progressive MS**, and will infuse 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, ascertain the 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 has been reported by the media.

Biomarkers

In medicine, the term "biomarker" refers to 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 that are 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 other factors that may indicate 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 and how effective the drug will be. 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 identify 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 that can be measured in the blood. Another study was designed to evaluate 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.

A genetic study, with results reported in 2012, also suggested that multiple genetic markers may predict a favorable response to Copaxone. A further study of genetic predictors of response to Copaxone was presented at ECTRIMS in fall 2014.[100] This assay is to be evaluated in further studies in 2015.

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.

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 therapeutic intervention in MS.
- A study using gene expression analysis of whole blood showed significant differences in expression profiles of patients with optic neuritis compared with 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 trial is studying more than 1,000 people with RRMS participating in the CombiRx study (described on page 8); this includes patients on interferon 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 will identify biomarkers and link them to clinical- and MRI-based outcomes, such as the extent of inflammation and rate of disease progression. It will examine how the biomarkers may be related to disease development, progression, differences among symptoms, and response to treatment. Based on these genetic biomarkers, likely best-responders to either form of therapy can be identified.

Genetic Studies

As discussed in this article in previous years, 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. 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, 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 known to be associated with other autoimmune diseases such as Crohn's disease and type 1 diabetes; MS is believed to be an autoimmune disease as well.

These and other genetic 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. It is also hoped that they will enhance our ability to design better treatments for early MS.

Neuroprotective Agents

The term "neuroprotection" refers to strategies designed to prevent irreversible damage from a variety of cell types in the central nervous system (CNS), as well as to promote regeneration after MS-related damage has occurred. These have the goal of preventing the development of disability. A variety of neuroprotective strategies are now being studied.

- One that seems especially promising is to identify the role that the neurotoxic transmitters glutamate and nitric oxide play in the development of neuronal damage, with the goal of preventing this process.
- At the same time, studies are focusing on stimulating growth factors that promote neural function, such as brain-derived neurotrophic factor (BDNF).

This combination – decreasing factors that cause damage, while at the same time increasing factors that stimulate growth – holds significant potential for preventing MS-related damage and stimulating neuronal function.

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. And ongoing clinical trials in 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, including FDA-approval of new agents since the previous edition of this *MS Research Update* was published. 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. The new generation of MS medications will undoubtedly enhance both the benefits, and the complexity, of the MS therapy decision-making process.

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**.

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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.

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 the pharmaceutical company and the FDA information about the relative safety of the new drug, and its effectiveness. 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 several 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.

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.

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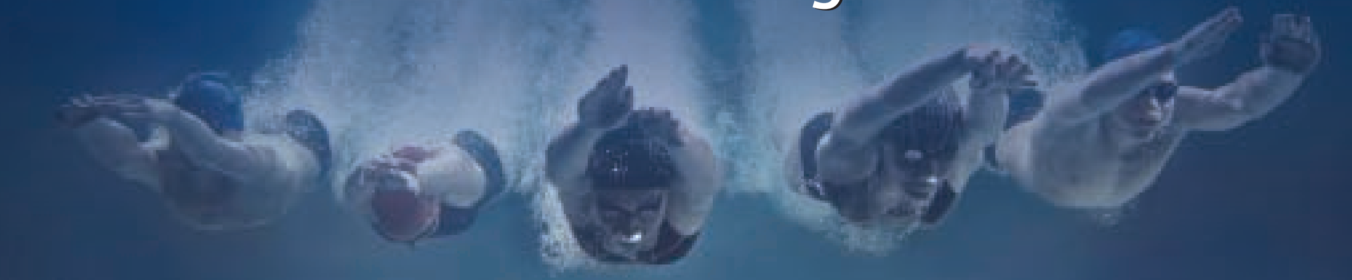

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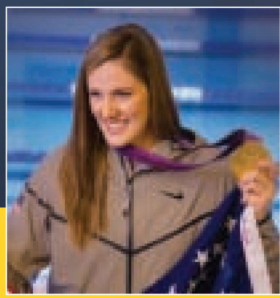

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