

October 2019 Newsletter



Progressive MS – Emerging New Treatment Frontiers

Significant progress has been made in the treatment of relapsing remitting MS (RRMS) over the past 25 years, with more than a dozen [disease modifying therapies](#) (DMTs) available for this form of the disease. Treatment of progressive MS has been a major focus in MS research but has remained a mystery until recently. New milestones have been reached in the past year, with a first-ever treatment for primary progressive MS (PPMS) now available, and new treatment options for secondary progressive MS (SPMS). Efforts to better understand and treat progressive MS continue with more novel treatments in the pipeline.



The DMTs used to treat RRMS typically work by decreasing inflammation and reducing the number of relapses an individual may have. These drugs are not usually effective in treating PPMS because this form of the disease does not involve significant inflammation. They may be effective in people with SPMS who still experience relapses however there is [evidence](#) that DMTs don't work for those whose symptoms just get gradually worse.

New treatments for progressive MS

In March 2017, the U.S. Food and Drug Administration (FDA) approved [Ocrevus](#) (ocrelizumab) as the first and only treatment for PPMS. This approval was based on results of the [ORATORIO trial](#), in which 732 subjects with PPMS received either ocrelizumab or placebo. Results showed ocrelizumab treatment slowed disability progression, reduced brain lesion volume and brain atrophy, compared to treatment with placebo. Ocrevus is a first-line treatment, which means that there are no recommendations for people to try other MS therapies before taking it. It is taken by infusion every 6 months. Ocrevus reduces nerve degeneration by lowering the number of a certain type of white blood cell ([lymphocytes](#)) in the blood that cause the immune system to attack the protective coating that surrounds nerves (the myelin sheath). While the approval of this medication opens up new possibilities for adults with PPMS, it's important to note that Ocrevus has not yet been tested in children.

There are two new treatment options for those living with SPMS. [Mavenclad](#) (cladribine) was approved for RRMS and active SPMS in March 2019. [Research](#) shows it decreases the number of MS relapses, slows the progression of physical disability, and reduces disease activity as seen on MRI. Cladribine is an oral treatment, taken in two treatment courses, twelve months apart. It targets lymphocytes without suppressing the immune system continuously. It's important to note that Mavenclad, like many DMTs, has significant risks. Serious side effects include an increased risk of cancer, fetal harm, decrease in white blood cells, as well as an increased risk of infections and liver injury. As a result, it is generally recommended in people with MS who have had an inadequate response to, or are unable to tolerate, another MS therapy.

[Mayzent](#) (siponimod) also gained FDA approval in March 2019 as a first-line treatment for adults with RRMS (including [clinically isolated syndrome](#)) and active SPMS. Siponimod acts by retaining lymphocytes in the body's lymph nodes, keeping them out of circulation and out of the central nervous system (the brain and spinal cord). The effectiveness of this oral treatment was demonstrated in the [EXPAND study](#) (the largest phase III clinical trial in SPMS), involving 1,651 participants with SPMS. Subjects taking Mayzent had significantly less progression of disability and fewer relapses than those taking placebo. Of note, this benefit was not seen in study participants with non-active SPMS.

Chemotherapeutic agents are used to stop the multiplication of rapidly growing cells, either by killing the cells or by stopping them from dividing. These drugs are typically used in the context of cancer, however they are also used to treat autoimmune conditions, such as rheumatoid arthritis and MS. In MS, chemotherapy works by killing or inhibiting lymphocytes (which drive the immune system attack).

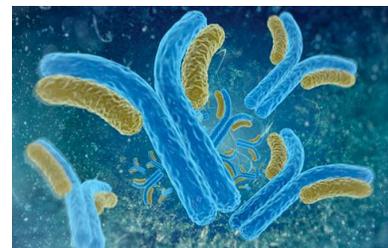


Chemotherapy treatments for progressive MS

[Novantrone](#) (mitoxantrone) is used for worsening RRMS and SPMS. It is administered intravenously by an infusion once every three months. There is [evidence](#) to suggest mitoxantrone reduces the number of MS relapses and disability progression. However, it has serious side effects, including heart problems and leukemia. As a result, individuals taking it require regular cardiac monitoring and there's a limit to how much one can take. Specifically, an individual can receive a total maximum dose of no more than 140 mg over the course of their lifetime (which covers about 2 years of MS treatment). It's usually used to treat people with disease that gets worse quickly when other treatments don't work.

[Methotrexate](#) is often used to treat rheumatoid arthritis. It has also been proven effective in the treatment of people with SPMS. Two clinical trials, a [2001 study](#) and a [2004 study](#), show it reduces disability in subjects with progressive MS. Methotrexate has fewer side effects and is less expensive than other treatments. It may be considered as a therapeutic option in people with comorbid rheumatological disorders, those who have financial constraints, or individuals not willing to take a more aggressive treatment.

[Antibodies](#) are protective proteins produced by the immune system in response to the presence of a foreign substance, called an [antigen](#). [Monoclonal antibodies](#) are pure antibodies, which are made in the lab to mimic the body's immune system. Scientists can design antibodies that specifically target a certain antigen, and then make copies of that



antibody in the lab. They are used to treat many diseases, including rheumatoid arthritis and cancer. Researchers are studying their effectiveness in treating progressive MS.

Monoclonal antibody treatments for progressive MS

The [ASCEND trial](#) looked at the ability of [Tysabri](#) (natalizumab) in slowing disease progression in subjects with SPMS. While subjects in this study showed improvement in upper limb disability as compared to lower limb, researchers concluded it did not reduce disease progression. Longer-term trials are needed to assess its benefit in SPMS.

[Rituximab](#) was tested in two trials, [one](#) of which was terminated early and the [other trial](#) failed to show any effect in this regard. However, the recent approval of ocrelizumab in PPMS suggests that Rituximab (an antibody with a similar mechanism of action) may be useful and warrant further research.

A [recent study](#) of 15 subjects with SPMS showed treatment with [Lemtrada](#) (alemtuzumab) resulted in improvement in disability and cognition. This suggests that alemtuzumab may be a treatment option for SPMS patients. Additional larger scale studies are needed to confirm these results.

Researchers are evaluating a number of other agents for the treatment of progressive MS, with promising results that warrant further study.



New treatment possibilities for progressive MS

Statins are a group of drugs that act to reduce levels of fats, including triglycerides and cholesterol, in the blood. There is evidence they may be a promising treatment for progressive MS. The [Multiple Sclerosis - Simvastatin Trial](#) (MS-STAT) investigated treatment with high-dose [Zocor](#) (simvastatin) versus placebo in 140 subjects with SPMS. Results showed simvastatin reduced the rate of whole-brain atrophy compared with placebo and was well tolerated and safe.

[Tyrosine kinases](#) play a role in many cell functions, including cell signaling, growth and division. They are a type of [targeted therapy](#), often used to treat cancer. In a small

[clinical trial](#) of 35 subjects with PPMS and relapse-free SPMS, subjects were given [masatinib](#) (an oral tyrosine kinase inhibitor) or placebo. Subjects taking masatinib had improved [Multiple Sclerosis Functional Composite](#) (MSFC) scores (suggesting less impairment), compared to worsening scores in subjects on placebo and treatment was well tolerated. This improvement was seen as early as 3 months into therapy and was sustained at 18 months. These data suggest that masitinib may have therapeutic benefit for those with PPMS and relapse-free SPMS and could therefore represent an innovative avenue of treatment for progressive forms of the disease.

Ibudilast is an anti-inflammatory drug that has been used in Japan to treat asthma for almost twenty years. More recently, it has been found to have anti-inflammatory activity in the central nervous system, which is of potential use in the treatment of MS. A phase II clinical trial, known as [SPRINT-MS](#), recently investigated treatment with ibudilast in subjects with progressive MS. The trial was conducted at the Cleveland Clinic and 27 other sites across the U.S. and enrolled 255 people with PPMS or SPMS. The results suggest that Ibudilast is well tolerated and significantly slows the rate of brain atrophy compared to placebo.

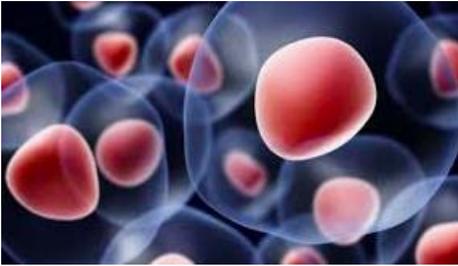
Results from initial studies are encouraging enough for two new agents to advance to larger MS clinical trials.



Emerging progressive MS treatments

[Researchers](#) in France found that treatment with high-dose biotin (a water-soluble B vitamin) resulted in sustained reversal of disability in subjects with progressive MS, and treatment was well tolerated. As part of this study, 154 subjects with worsening disease in the previous 2 years received high-dose biotin (100 mg) or placebo for 12 months. Biotin treatment reduced EDSS scores by more than 1 point and decreased the time for subjects to walk a distance of 25 feet by more than 20 percent (both indicators of improvement in MS-related disability). This benefit was sustained for the duration of the study. A larger [clinical trial](#) is underway to confirm these results.

Lipoic acid is a naturally occurring antioxidant in the body. A [2017 study](#) looked at lipoic acid treatment compared to placebo in 51 subjects with SPMS. Subjects taking lipoic acid had significantly less brain atrophy over a 2-year period (which suggests a sustained clinical benefit in SPMS) and it was well tolerated. A multi-site [clinical trial](#) is currently enrolling subjects to further document these findings.



As discussed in our [July 2018 newsletter](#), stem cell therapy is a restorative therapy that has shown substantial benefit in patients with RRMS. A number of studies suggest this type of therapy may hold promise for those with progressive forms of the disease. A small Phase II [study](#) in which 10 subjects with SPMS received IV administration of mesenchymal stem cells (MSCs) showed subjects experienced better visual acuity and improved evoked potentials as a result of treatment. A [pilot study](#) conducted at the Tisch MS Research Center of New York found intrathecal administration of MSCs (injection into the spinal cord) resulted in clinical improvement in 4 out of 6 subjects with progressive MS. Researchers in the United Kingdom are conducting the [ACTiMUS trial](#) to compare the effectiveness of autologous hematopoietic stem cell transplant (HSCT) in PPMS and SPMS. They recently completed a phase I trial of this treatment in progressive MS with favorable results and hope the ACTiMUS trial will confirm these findings.

A wide variety of [medications](#) are used to treat specific symptoms of progressive MS. These include, but are not limited to, bladder and bowel problems, erectile dysfunction, fatigue, pain, and spasticity. Maintaining healthy lifestyle habits can also make a difference. For example, people with progressive MS may be able to relieve some symptoms with exercise and stretching. This can preserve mobility, control weight gain, and increase energy levels. Eating a nutritious diet and staying on a regular sleep schedule may also be beneficial. Some people find that massage, meditation, or acupuncture help to relieve stress and ease pain. Physical and occupational therapy can also teach strategies for increasing mobility and managing symptoms. As discussed in our [June 2019 newsletter](#), assistive devices can help people with progressive MS function and help maintain their independence. Accessibility accommodations and services, such as special parking permits, may also be helpful in this regard.

People living with progressive MS face the possibility of gradually losing function with each passing day, potentially losing the ability to do the things they enjoy. Accelerating research efforts focused on finding effective treatments for progressive MS is of prime importance. With new knowledge gained from current and future studies, there's hope the quality of life for those living with progressive forms of the disease can be improved and the uncertainty they face can be minimized. ACP is dedicated to facilitating research into topics like this that impact the MS community.

