

New Highlights in the Treatment of Progressive Multiple Sclerosis

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Abstract

Multiple sclerosis is an inflammatory, demyelinating disease of the central nervous system. Most patients have a relapsing-remitting disease type, for which medicines are mostly dedicated. Clinical course of some patients will transition to secondary progressive multiple sclerosis and small portion of patients is classified as primary progressive multiple sclerosis from the beginning. The treatment of progressive multiple sclerosis has been limited for a long time, however, for a few years attention has been paid to the need for new disease modifying drugs that would focus on the treatment of progressive multiple sclerosis. The breakthrough was ocrelizumab, which is the first medicine registered in the treatment of primary progressive multiple sclerosis, while siponimod is planned to be approved soon in the treatment of secondary progressive multiple sclerosis. Numerous studies are currently underway on new substances with anti-inflammatory, neuroprotective or remyelinating effects such as high-dose biotin, ibudilast, simvastatin, alpha lipoic acid or clemastine. The first research results are very promising nevertheless, more accurate drug research is needed.

Keywords: Multiple sclerosis; Progressive multiple sclerosis; Treatment; Clinical trials.

Introduction

Multiple sclerosis (MS) is a chronic, demyelinating, inflammatory disease of the central nervous system which multifactorial etiology [1,2]. It affects approximately 2.3 million mostly young people leading to disability and cognitive impairment [3,4]. MS is defined as 4 clinical subtypes: clinically isolated syndrome (CIS), relapsing-remitting (RRMS), primary progressive (PPMS) and secondary-progressive (SPMS) [5]. Most patients have initially RRMS and 85% of them switch in turn to SPMS. The smallest portion of patients are classified as PPMS. Clinical analysis and magnetic resonance imaging (MRI) allows to determine the phenotype of the disease [6].

Treatment in Progressive Multiple Sclerosis

In the treatment of MS, disease-modifying drugs (DMDs) play a key role. Most of these drugs are dedicated to the treatment of relapsing-remitting disease. In turn, the treatment of PPMS and SPMS, referred to jointly as progressive MS, proved to be very difficult due to the poorly understood and multivariate pathophysiology of MS. Many DMDs that are effective in RRMS therapy have failed to be successfully used in progressive MS [4]. Progressive MS treatment has been for a long time limited to symptomatic medications [7]. However, numerous studies have been recently conducted on the effectiveness of new substances in the treatment of progressive MS. Among these substances we distinguish: ocrelizumab, siponimod, high-dose biotin, ibudilast, simvastatin, alpha-lipoic acid and clemastine.

New Substances Tested in the Treatment of Progressive Multiple Sclerosis

Ocrelizumab

Ocrelizumab is a humanized monoclonal antibody directed against CD20 antigen which is located on B lymphocytes. B lymphocytes participate in the production of proinflammatory cytokines that destroy myelin and help in T cell activation, that is why they play an important role in the pathogenesis of MS [8,9]. What is more, B cells serve as effective cells presenting antigen in the context of histocompatibility proteins to activate T cells, which in turn can attract other immune cells like neutrophils and macrophages into the central nervous system (Table 1) [10]. Anti-CD20 antibodies cause B-cells depletion through apoptosis and antibody-dependent cytotoxicity [11,12].

The efficacy of ocrelizumab in the treatment of PPMS was investigated

in the ORATORIO study, a randomized, placebo-controlled, double-blind clinical trial [13]. The study involved 732 patients of which 488 received ocrelizumab and 244 placebo every 24 weeks for 120 weeks. The results showed that ocrelizumab significantly reduces the risk of progression of disability assessed based on Expanded Disability Status Scale (EDSS) over 12 weeks compared to placebo. Progression was reported in 32.9% of 488 patients receiving ocrelizumab and 39.3% from 244 patients receiving placebo. After 24 weeks of observation, the corresponding results were 29.6% and 35.7%. Several studies evaluated on secondary factors have shown that there was 3.4% reduction in the number of MRI lesions in patients taking ocrelizumab, while patients taking placebo had an increase of 7.4% [14-16]. It is worth noting that the study excluded people with the duration of the disease above 10-15 years and those with more than 55 years of age. Because of that, people qualified for the ORATORIO study were younger and they had MS for a shorter time than in most other clinical trials. This study showed that the efficacy of ocrelizumab decreases with the increasing age and among patients with gadolinium-enhancing lesions in the MRI [17]. Based on the study results, the European Medicines Agency indicates that ocrelizumab should be used at an early stage of PPMS. Ocrelizumab was also tested in two equally designed studies OPERA I and OPERA II lasting 96 weeks. 1656 patients with relapsing multiple sclerosis participated in the study. The efficacy of ocrelizumab has been compared with interferon beta-1a. Patients received 600 mg of ocrelizumab every 24 weeks or subcutaneous injections of interferon beta-1a three times a week through 96 weeks. After 24 weeks of observation, lower risk of disability progression in ocrelizumab patients was found, while in 96 weeks the incidence of relapses per year was lower in patients treated with ocrelizumab. What's more, MRI research showed that the frequency of new changes was also much

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lower. The results indicated that ocrelizumab significantly reduced the development of MS compared to interferon beta-1a [14,16,18].

Ocrelizumab is administered intravenously. Next doses are given every 6 months. The first dose is divided in half and given in two injections with an interval of 14 days [12,13,18]. The effects of ocrelizumab therapy are visible after several months, which indicates that they are not achieved by the production of new antibodies in plasma cells [19]. Among the adverse effects of ocrelizumab, we distinguish an increased frequency of infusion-related reactions, upper respiratory tract infections, herpes infections and increased cancer incidence. Several cases of hepatitis B virus (HBV) reactivation were observed. This could later lead to fulminant inflammation, hepatic failure and to death, so it is necessary to register vaccinations against HBV and test the immunization status against HBV in patients treated with ocrelizumab [10,13,17,18]. There have also been reports of psoriasis in patients with MS treated with ocrelizumab [20]. Finally, ocrelizumab has been approved by the American Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) respectively in March and November 2017 [17]. This is the first drug for the treatment of not only RRMS but also PPMS.

Siponimod

Siponimod (BAF312) is a new selective modulator of sphingosine-1-phosphate receptor (S1P) type 1 and 5, which has immunomodulatory and neuroprotective effect. Table 1 it works through the sequestration of B and T lymphocytes in lymphoid organs [21-23]. Among the modulators of the S1P receptor, in addition to siponimod, we also include fingolimod, ponesimod, ozanimod and ceralifimod. An exploratory phase I trial of siponimod was carried out on a group of 48 healthy volunteers. It reveals that drug administration was safe at multiple doses. The only side effect was transient bradycardia, caused by the activation of G protein-coupled inwardly-rectifying potassium (GIRK) channels in human atrial myocytes. Pharmacokinetic studies have shown that the half-life of the siponimod is 30 hours, and the total elimination of the drug from the body takes 7 days [24]. A randomized, phase II trial known as BOLD, assessed the dosage, safety and efficiency of siponimod in patients with RRMS in comparison to placebo. Patients recruited from 72 centres, belonging to the first cohort (188 patients) received daily 10 mg, 2 mg and 0.5 mg of siponimod or placebo for 6 months. After three months of analysis, an additional 109 patients were treated with either 1.25 mg and 0.25 mg of siponimod or placebo for 3 months (second cohort). The first results showed a significant effect of the drug on the reduction of gadolinium-enhancing lesions in MRI after 3 months of treatment compared to placebo. Especially the 10, 2, 1.25 and 0.5 mg siponimod doses meaningfully reduced the number of new lesions in the brain. Siponimod in dose of 2 mg reduces the annual relapse rate compared to placebo after 6 months [25]. In addition to transient bradycardia, patients have a 20-74% reduction in total lymphocyte counts on day 7 of treatment that remained stable for 3-6 months and increased levels of alanine aminotransferases [26].

Finally, in the year 2012, in the 31 countries, the third phase of clinical trial called EXPAND for siponimod in SPMS began. It was a double-blind, randomized trial with placebo. Qualified patients were between 18 and 60 years old, had a progression of disability registered for the last 6 months and the initial disability score according to EDSS from 3 to 6.5. Number of 1651 patients was included in the study, 60% of which were women. They were randomized 2:1 and received siponimod at an increasing dose of up to 2 mg or placebo [27]. The most important efficacy factor was the time to 3-month progression of disability as measured by EDSS. Of all patients, 1363 (86%) completed

the study. The average duration of the study was 18 months. 87% of patients participated in the study at least 12 months. 449 events of disability progression were confirmed among the examined patients. The use of siponimod was associated with a 21% reduction in the risk of disability progression after 3 months of follow-up and 26% after 6 months, compared with placebo. Therefore, siponimod treatment also showed a beneficial effect on the annual indicator of relapses, the number of gadolinium enhancing lesions, the volume of T2 lesions and the new T2 lesions. As in the ocrelizumab trial, greater efficacy of siponimod treatment has been observed in younger people and with gadolinium-enhancing lesions at the start. In the EXPAND study side effects occurred at a similar rate of 88.7% compared to that observed in the BOLD study, leading to discontinuation of treatment in 7.6% of patients. The most frequent complaints were headaches, urinary tract infections, hypertension, nasal and pharyngeal infections [28]. Siponimod and fingolimod belong to the same group of drugs, however, the first one as a selective drug for the S1P and S5P receptor, differs from the second one with a slightly fewer side effects. Generally, siponimod is most often associated with the risk of bradycardia, hypertension, cough, dyspnoea, diarrhoea or macular oedema [21]. However, there was a higher rate of seizures recognized in patients treated with siponimod, which has also been observed with fingolimod. The therapeutic effect of these drugs is similar, but fingolimod is used in the treatment of RRMS and is ineffective in progressive MS. Thanks to proven clinical effectiveness, siponimod is planned to be approved soon in treatment of SPMS [29].

High-dose biotin (MD1003)

Biotin, also known as vitamin B, is a cofactor of five enzymes involved in the production of energy and fatty acids [30]. This substance has good bioavailability, fast absorption and excretion. It is eliminated mainly by urinary excretion [31]. Two mechanisms are proposed as a beneficial effect of biotin in multiple sclerosis. The first is the increased energy production in demyelinated axons. The second mechanism is the enhancement of myelin synthesis in oligodendrocytes by acting as a cofactor for acetyl-CoA carboxylase-1 and -2, which intensifies fatty acid production and myelination (Table 1) [32]. Furthermore, biotin affects cellular energy production and reduces hypoxia that affects the pathogenesis of MS [31,33]. MD1003 is an oral form of biotin at a very high dose of 300 mg per day, which is 10,000 times higher than the daily dose of 30 µg recommended by the US Food and Nutrition Board. MD1003 has shown encouraging efficiency in progressive MS treatment in recent studies [34,35]. The first pilot, open-label, unblinded study using high-dose biotin included 23 patients with progressive MS. Patients received biotin at a dose of 300 mg daily for 2-36 months, an average of 9.2 months. More than 90% of patients reported some degree of clinical improvement, including a 22% reduction in EDSS, visual acuity improvement, MR spectroscopy, P100 latency on visual evoked potentials, clinical examination and neurological symptoms [35].

The next was MS-SPI, a double-blind, placebo-controlled, randomized study lasting 12 months. It was conducted in sixteen French MS centers and included 154 patients aged 18-75 years, with PPMS or SPMS in a 2:1 ratio. 103 patients received MD1003 at a dose of 100 mg three times a day and 51 received placebo for 12 months. The study was followed by a 12-month extension period where all patients received MD1003 open-label. The percentage of patients with improvement in MS-related disability in month 9, confirmed at 12 months was the primary endpoint. The improvement was defined as a decrease of 0.5 point in EDSS with an output result of 6-7, or by 1 point with a score of 4.5-5.5. At least a 20% decrease during a 25-foot walk (TW25) was also recorded, compared to the best TW25 value during

screening or randomization visit. Subgroup analysis also revealed that patients with a lower EDSS score had a better chance of getting to their first endpoint. The first endpoint was not achieved by any of the patients receiving placebo. Nevertheless, at the 24th month of the study, a reduction in disability in relation to baseline was observed in both 14 out of 91 (15.4%) patients who received MD1003 all the time, as well as in 5 out of 42 (11.9%) patients receiving placebo in the first year. Several secondary endpoints were also investigated in this study, such as percent of patients with EDSS improvement, EDSS change and Clinical Global Impression Scale, where significant improvement was noticed during the placebo-controlled phase. Generally, MD1003 was well tolerated by patients. A multicentre phase 3 study is conducted based on the promising results of this study [36].

Another open-label trial observed the effect of biotin on clinical symptoms and MR imaging in MS patients. It included 43 patients, of whom 7 suffered from PPMS, 26 from SPMS, and 10 from RRMS. Patients received 300 mg of biotin per day for one year [37]. However, it was not MD1003, but biotin from a compounding pharmacy. All subjects underwent laboratory evaluation and EDSS assessment every 3 months, as well as MRI at baseline and after 1 year. The first year of treatment with biotin was completed only by 24 out of 43 patients (56%). High-dose biotin was safe and well tolerated, but no benefits were observed in the study. It is worth noting that the patients taking part in this study were older (mean age is 61 years), whereas in previous studies, where the therapeutic benefits of biotin were noted, patients were on average 50.7-52.8 years [35,36]. Biotin is considered safe and well-tolerated by patients. However, it may interfere with laboratory testing of biotinylated assays used for detection of proteins such as troponin, creatine kinase and thyroid-stimulating hormone. This is important information for both the patient and the doctor, especially in the case of urgently-placed tests. Patients taking high doses of biotin should inform the doctor or laboratory technician, so that the test results can be properly interpreted [38,39].

Ibudilast

Ibudilast is an oral drug used to treat asthma and ischemic stroke in Asian countries [40]. It inhibits macrophage migration factor (MIF), phosphodiesterase-4 (PDE-4) and -10 (PDE-10), toll-like-receptor-4 (TLR4), suppresses production of tumor necrosis factor- α (TNF- α), pro-inflammatory interleukin IL-1 β and IL-6 [40,41]. Ibudilast is thought to act neuroprotectively through inhibiting the production of IL-10 and other neurotrophic factors and through the reduction of neuronal cell death induced by microglial activation (Table 1) [42,43]. Ibudilast crosses the blood-brain barrier with potential beneficial effects in multiple sclerosis [44]. The efficacy of neuroprotective properties of ibudilast was investigated in the phase II trial in patients with RRMS. The results showed that the drug reduced the progression of brain atrophy depending on the dose and the proportion of gadolinium-enhancing lesions. However, it did not reduce the appearance of new lesions on MRI [45]. The efficacy of ibudilast in patients with progressive MS has been studied in a recently completed phase II double-blind clinical trial called NeuroNEXT 102 (NN102) or Secondary and Primary Progressive Ibudilast NeuroNEXT Trial in Multiple Sclerosis (SPRINT-MS). The study involved 255 patients with PPMS and SPMS, randomized 1:1, who had progression of disability in the last two years; 129 patients received ibudilast up to 100 mg if tolerated and 126 patients received placebo for 96 weeks. The primary efficacy endpoint was the rate of brain atrophy measured by the brain parenchymal fraction (BPF). The main secondary endpoints included pyramidal tracts changes, the magnetization transfer ratio in the brain tissue, the retinal nerve fibre layer thickness and the cortical atrophy. Eighty-six percent of patients

completed the study that lasted 96 weeks. Ibudilast was associated with 48% slower brain atrophy progression than placebo. However, it was also associated with a higher percentage of gastrointestinal side effects such as diarrhoea, nausea, vomiting, headache and depression [46,47].

Alpha-lipoic acid

Alpha-lipoic acid (ALA) is a natural endogenous antioxidant produced in the liver. It is also provided by numerous food products. ALA has a potentially neuroprotective character thanks to the downregulation of inflammatory cytokines, T-cell infiltration into the central nervous system, repair of oxidative damage and metal chelation (Table 1) [48,49]. It causes side effects such as headaches, rashes and gastrointestinal problems [50]. Several pilot studies on the impact of ALA in MS have already been carried out. One of these studies shows that ALA has a positive effect on MS activity and T-cell migration by reducing matrix metalloproteinase 9 (MMP-9) and soluble intercellular adhesion molecule-1 (sICAM-1) factors [50]. Another placebo-controlled study in patients with RRMS shows that ALA also reduces interferon- γ (INF- γ), transforming growth factor- β (TGF- β), IL-4 levels and oxidative stress [51,52].

Finally, the effect of alpha-lipoic acid on patients with SPMS was examined in the phase II randomized, double-blind clinical trial with placebo. The study included 51 patients who received 1200 mg ALA per day for 2 years. The primary challenge was the annual percent change of brain volume (PCBV) on brain MRI. Secondary outcomes included changes in disability (EDSS), safety and quality of life, rates of brain atrophy, retinal substructures and spinal cord. Studies have shown a 68% reduction in brain atrophy in patients taking ALA in comparison to placebo. There were no differences in clinical outcomes, brain substructures and optical coherence tomography metrics between ALA and placebo patients [53]. During the study, patients tolerated ALA very well. Predictably, patients receiving ALA experienced gastrointestinal problems more often than patients taking placebo. One of the patients taking ALA developed proteinuria caused by membranous glomerulonephritis. Two other patients receiving ALA have elevated levels of alkaline phosphatase. In turn, another patient receiving ALA was disqualified from the trial after developing renal failure because of elevated creatinine level and died several months later [53]. Despite this, alpha lipoic acid seems to be a promising drug in the prevention of brain atrophy in MS, however its clinical application requires additional research.

Simvastatin

Simvastatin belongs to a group of substances known as 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA) inhibitors, which are useful in the treatment of hyperlipidaemia. They are used in high-risk patients with coronary artery disease. Among the statin mechanisms of importance in MS, the production of anti-inflammatory Th2 lymphocytes, decreasing of T-cell proliferation and inhibition of presentation of major histocompatibility complex (MHC) class II to antigen is distinguished (Table 1) [54]. In addition, statins decrease adhesion molecule expression and have a protective role for cells [55]. Some studies on the use of simvastatin in the monotherapy treatment of RRMS have shown a positive effect on disease activity [56]. The study with the combination of simvastatin and INF- β treatment did not show benefits in the progression of disability and frequency of relapses [57]. The effect of high doses of simvastatin on brain atrophy in patients with SPMS was examined in the phase II double-blind, placebo-controlled clinical trial called MS-STAT. This study was performed at three UK centres and included 140 patients with SPMS who were randomized 1: 1. For 2 years 70 patients received simvastatin 80 mg per day and the

Drug	Mechanism of action	Overall effect
Ocrelizumab	Monoclonal humanized antibody against CD20 antigen	Anti-inflammatory
Siponimod	Selective modulator of sphingosine -1- phosphate receptor type 1 and 5	Immunomodulatory, Neuroprotective
High-dose biotin	Cofactor for acetyl-CoA carboxylase-1 and -2, energy production in demyelinated axons	Neuroprotective, Remyelination
Ibudilast	Inhibition of macrophage migration factor, phosphodiesterase 4 and -10, toll-like-receptor-4, suppression of tumour necrosis factor- α , interleukin-1 β and -6	Neuroprotective
Alpha-lipoic acid	Anti-oxidant, downregulation of inflammatory cytokines, repair of oxidative damage and metal chelation	Anti-inflammatory, Neuroprotective
Simvastatin	3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors, production of Th2 lymphocytes, decreasing of T-cell proliferation, inhibition of presentation of major histocompatibility complex class II	Anti-inflammatory, Neuroprotective
Clemastine	H1 and a M1 / M3 receptor antagonist, differentiation of oligodendrocytes and remyelination	Remyelination

Table 1: The mechanism of action and the overall effect of the new and potential disease-modifying drugs in progressive multiple sclerosis treatment.

remaining 70 patients received placebo. The primary result was a 43% reduction of the brain atrophy in patients taking simvastatin versus placebo, with additional positive effects for the clinical and patient reported measurement results, mainly Extended Disability Status Scale and MS-Impact Scale-29. No difference was found in several secondary outcomes, such as new or enlarging T2-hyperintense lesions on MRI, relapse rate and immunological markers. The number of observed adverse effects was similar in both groups [58]. The MS-STAT study was re-analysed for the effect of simvastatin on cognitive, neuropsychiatric and health-related quality-of-life measures in secondary progressive multiple sclerosis. Evidence has been found for the positive effect of simvastatin on the frontal lobe function and the physical measure of quality of life. Although the effects of simvastatin on other factors have not been found, these potential effects underline the importance of assessment of quality of life in progressive multiple sclerosis studies [59].

Clemastine

Clemastine is an H1 and a M1/M3 receptor antagonist with antihistaminic activity. It's supposed positive effect on the pathogenesis of MS is based on the differentiation of oligodendrocytes and remyelination depending on the M1 muscarinic receptor [60,61]. Recently, phase II of a double-blind, placebo-controlled, cross-over trial called ReBUILD with clemastine fumarate has been successfully completed. The study included 50 patients with relapsing-remitting MS with chronic optic neuropathy. The study lasted for 150 days. Patients were randomly assigned to either clemastine fumarate in dose 5.3 mg received orally twice daily for 90 days, followed by placebo for 60 days or vice versa. All participants underwent a test for visual evoked potentials (VEPs) at the beginning of the study, after a month, after the end of taking the first drug and at the end of the trial. Changes in latency of potential P100 in VEP were observed; it is a wave with a positive peak at approximately 100 ms following stimulus onset. The primary result was the shortening of the P100 time delay for potentials with full field of view. This is the first attempt to determine the effectiveness of drug remyelination in the treatment of chronic demyelinating lesions (Table 1) [62].

Future Perspectives

There are still many potential therapies that can be used in the treatment of progressive MS, and their effectiveness and safety is being studied. Therapy using hematopoietic stem cell transplantation is very promising, however, its benefits are limited to the highly active inflammatory disease [63]. In turn, mesenchymal stem cells (MSC) therapy remain of interest in the progressive MS because of repair-promoting and neuroprotective functions [64]. By now, some early-phase studies of MSC transplantation in progressive MS have been

carried out [65,66]. There are many differences in the methods of transplantation, which is why further research is needed to find the best transplantation technique and to get better results. There is currently ongoing Assessment of Bone Marrow-derived Cellular Therapy in Progressive MS (ACTiMuS) trial whose aim is further investigation of the efficacy of autologous bone marrow intravenous infusion without myeloablation in progressive MS [67].

Amiloride, fluoxetine and riluzole are other drugs whose use in progressive MS is currently being tested in phase II four-arm trial with placebo, called MS-SMART [68]. Amiloride is a diuretic. Fluoxetine is a selective serotonin reuptake inhibitor. Both drugs have a probable neuroprotective effect [69]. In turn, riluzole is an inhibitor of sodium channel with anti-glutamatergic properties. So far, it is the only disease-modifying drug registered by EMA (FDA approved also edaravone) to treat amyotrophic lateral sclerosis (ALS), but its effectiveness is negligible [70]. However, a one-step preliminary clinical trial of 16 patients with SPMS receiving 50 mg of riluzole twice daily for a year of observation showed that it may have a beneficial effect on brain atrophy and reduction of T1 hypointense lesion accumulation in cervical spine [68]. Another drug tested is masitinib. It is a tyrosine kinase inhibitor that has anti-inflammatory activity [71]. The effectiveness of its use in progressive MS was initially confirmed in pilot trial, and a phase III clinical trial involving patients with PPMS and SPMS is in progress [67]. A promising method of multiple sclerosis treatment is antigen-specific T cell tolerization. It involves the inhibition of self-reactive T cells under the influence of antigen-specific immunological tolerance. Various application methods are tested based on myelin peptide, T-cell and DNA vaccination, or antigens coupled with cells or nano-particles [72,73].

Conclusion

Treatment of progressive forms of MS is still a big challenge due to the unclear pathogenesis of this process. There are reports that a causative agent in the pathogenesis of MS is HHV-6 that causes first roseola, then CIS and finally adult MS through the induction of infected oligodendrocytes to withdraw their myelinating processes. A fight between viral activation and clearance by the immune system induces RRMS. The disease course becomes increasingly more autoimmune and progressive after oligodendrocyte debris becomes sufficient to induce a strong anti-myelin immune response. Nevertheless, HHV-6 as an etiological agent of MS is not accepted by the entire medical community [74]. However, recent years have brought a lot of research into spectrum of drugs that can be used to treat progressive MS. Great hopes are associated with ocrelizumab, which is the first drug registered in the treatment of PPMS, and siponimod, which has been preregistered for the use in SPMS in the USA and is waiting for the

approval by EMA. Studies are also ongoing on the other substances that have potentially neuroprotective, remyelinating and anti-inflammatory effects. Preliminary results of the research are very promising. The final confirmation of the efficacy and safety of these drugs in progressive multiple sclerosis is only a matter of time.

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