

*Opšti pregledi/  
General reviews*

NEW PERSPECTIVES IN MULTIPLE  
SCLEROSIS TREATMENT

NOVE PERSPEKTIVE U LEČENJU MULTIPLE  
SKLEROZE

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*Key words*

multiple sclerosis, immunomodulatory  
therapy, monoclonal antibodies,  
Cladribine, Fingolimod, Fumaric acid  
(BG-12), Teriflunomide, Laquinimod

*Ključne reči*

multipla skleroza, imunomodulatorna  
terapija, monoklonska antitela,  
Kladribin, Fingolimod, Fumarna kiseli-  
na (BG-12), Teriflunomid, Lakvinimod

*Abstract*

Multiple sclerosis (MS) is a chronic inflammatory disorder of the central nervous system, traditionally considered to be an autoimmune, demyelinating, inflammatory and neurodegenerative disease. Based on this understanding, the initial therapeutic strategies were directed at immune modulation and inflammation control. Disease-modifying drugs (DMDs) require long-term, regular injection or monthly parenteral infusions, which may be uncomfortable and inconvenient for the patient. Thus, there is an important need for new therapeutic strategies, especially those that may offer greater patient compliance in order to optimize therapeutic outcomes. Researchers are currently investigating new drugs for the treatment of MS. Five oral therapies are in Phase III clinical trial development or have recently been approved for the treatment of relapsing-remitting MS (RRMS): Cladribine and Fingolimod, Fumaric acid (BG-12), Teriflunomide (A77126 or HMR1726) and Laquinimod (ABR-215062). Preliminary results indicate that oral medications are as effective as, or possibly more effective than, current injection agents. Future research into MS should focus on a combination of therapies and on the development of drugs directed against the remitting and progressive phases of the disease. The aim is to prevent of demyelination and a reduction of axonal loss.

Multiple sclerosis (MS) is the most common autoimmune inflammatory demyelinating neurodegenerative disease of the central nervous system (CNS). The treatment of MS has few aspects: immunomodulatory therapy (IMT) for the underlying immune disorder, inflammation control and therapies to relieve or modify symptoms. IMT is directed toward reducing the frequency of relapses and slowing progression. Currently, most disease-modifying agents have been approved for use only in relapsing forms of MS [1]. Currently available MS therapies have shown significant efficacy throughout many trials, on the other hand they produce different side-effect in patients. They require regular and frequent parenteral administration and are associated with limited long-term treatment adherence. This will pave the way for an optimized treatment approach, which will likely need both to target inflammation and to focus on promotion of neuroprotection and repair [2,3].

Oral agents as Fingolimod, Teriflunomide, Laquinimod, Cladribine, are possibly more effective than, current injectable agents. It is believable that improved outcomes will translate into higher real and perceived efficacy rates and contribute to improved adherence. The decision to switch established patients from injectable to oral medications will be made on balancing the efficacy and tolerability of the patient's existing therapy and their compliance history, even though safety is likely to become the most important factor in the future development of anti-MS drugs [4].

Exactly for safety reasons, some of the currently used oral therapies are approved as a second line treatment, after the patient is not responding to first line treatment [Interferon- $\beta$ , Glatiramer acetate]. Given the wide spectrum of clinical manifestations that MS can produce, patients may require consultations with a variety of specialists. Indeed, patients with MS are often best served by a multidisciplinary approach [1].

Monoclonal antibodies (MAbs) may have great potential as therapies for autoimmune diseases. Their development as treatments for MS is promising. Partially effective immunomodulatory therapies have been effective for many MS patients; however, for patients failing these immunomodulatory treatments, MAbs are an important new treatment option. Currently, MAbs are approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for treatment of many conditions, including autoimmune diseases. This article reviews MAbs that have been investigated as potential treatments for MS. The first MAb, approved for treatment of MS is Natalizumab. Other MAbs (Alemtuzumab, Rituximab, and Daclizumab) are investigated as promising therapies in development for treatment of MS. Adverse effects are relatively mild for these MAbs; however, care in administration and management of these agents is emphasized. Overall, these MAb therapies have great promise in the treatment of MS [5].

Monoclonal antibodies have been used as experimental treatments of MS since the 1980s. Their advantage is high specificity for their target; their disadvantages are that they (usually) require intravenous administration, often are associated with infusion reactions and, as large foreign proteins, they are immunogenic.

Past experience with monoclonal antibodies has taught researchers to interpret results seen in animal models with caution. Anti-TNF $\alpha$  antibodies are successful in the treatment of rheumatoid arthritis and work done using the animal model of MS (experimental autoimmune encephalomyelitis, EAE) suggested a beneficial effect on the disease [6].

Data from clinical research trials has however given important insights in to the underlying disease mechanism and suggests that treating MS in the early inflammatory phase gives an opportunity to delay or prevent the onset of disease progression [7].

Natalizumab is a humanized monoclonal antibody that binds to the adhesion molecule alpha-4 integrin, inhibiting its adherence to its receptors. Natalizumab is indicated as monotherapy for the treatment of patients with relapsing-remitting forms of MS (RRMS), to delay the accumulation of physical disability and reduce the frequency of clinical exacerbations. It is generally used in patients who have not responded to a first-line disease-modifying therapy or who have very active disease [8].

Natalizumab has been associated with progressive multifocal leukocephalopathy (PML), an opportunistic infection of the brain that can lead to death or severe disability. The risk of PML seems to increase with a history of previous immunosuppression, duration of exposure to natalizumab beyond 2 years, and JC virus antibody positivity.

In 2008 early tests at Cambridge University suggest that alemtuzumab might be useful in treating and even reversing the effects of multiple sclerosis. Promising results were reported in 2011 from a phase III trial against Rebif. A combination trial with Copaxone (Glatiramer acetate) is being considered, and is expected to work synergistically [9].

Alemtuzumab is an anti-CD52 monoclonal antibody with remarkable efficacy in relapsing multiple sclerosis (MS). In clinical trials and off-label use in MS,

Alemtuzumab has been administered intravenously (IV). Alemtuzumab is approved for chronic lymphoid leukemia as IV. It has been granted fast-track status for FDA approval for use in relapsing-remitting MS. In a single-arm, open-label study in 45 patients with MS that was refractory to treatment with Interferon, Alemtuzumab effectively reduced relapse rates and improved clinical scores [4,10,11,12,].

The investigators report two patients with highly active relapsing MS who were treated with Alemtuzumab, had significant improvement and tolerated Alemtuzumab well without the typical infusion-associated adverse events. Alemtuzumab in MS warrants further studies as this may enhance patient convenience and minimize infusion-associated adverse events [13,14,15].

For patients with first-line treatment-refractory RRMS, Alemtuzumab could be used to reduce relapse rates and sustained accumulation of disability.

Currently, oral therapies with Teriflunomide and Fingolimod have been approved for the treatment of RRMS. Cladribine is an oral drug used to treat MS. In 2011 FDA has rejected cladribine for MS and requiring more data on its safety and risk-benefit. Fingolimod is a novel compound produced by chemical modification of a fungal precursor migration with unique immunological and neurobiological properties. It has reduced the rate of relapses in RRMS by over half, but has serious adverse effects. Its active metabolite, formed by in vivo phosphorylation, modulates sphingosine 1-phosphate receptors, which are a subset of a larger family of cell-surface, G protein-coupled receptors that mediate the effects of bioactive lipids known as lysophospholipids. Lysophospholipids are membrane-derived bioactive lipid mediators that can affect fundamental cellular functions, which include proliferation, differentiation, survival, migration, adhesion, invasion, and morphogenesis.

The mechanism of action of Fingolimod is incompletely understood but appears to be fundamentally different from other MS medications. Fingolimod-phosphate blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. Fingolimod promotes sequestration of lymphocytes within the lymph nodes, which may reduce lymphocyte Fingolimod is the first oral disease modifying treatment for relapsing forms of MS approved by FDA. Like other disease-modifying agents for MS, Fingolimod can reduce the frequency of clinical exacerbations and delay the accumulation of physical disability. The recommended dosage for Fingolimod is 0.5 mg once a day [11,16].

In 2012 Susan Jeffrey reports full results of the Teriflunomide oral use in people with RRMS. Results showed a significant but smaller annualized reduction in relapse rate but not in sustained accumulation of disability in the disease.

Mark S. Freedman, MD: Teriflunomide has been around for 10 years in one of the widest clinical development programs we have had, yet most people have not heard of it. It has been a bit of a „sleeper“. Teriflunomide derives from Leflunomide, which is used for treatment of rheumatoid arthritis. Unfortunately, Leflunomide has a black box warning because of potential liver dysfunction. This actually never panned out but the warnings were there. FDA also

placed Leflunomide into the „X” category for teratogenicity (contraindicated; benefit does not outweigh risk) [12].

Laquinimod is an experimental immunomodulator investigated as an oral treatment for MS. Additional oral agents are under development, including Laquinimod and Dimethyl fumarate. Most of these agents have completed phase 3 testing. Fumarate are salts and esters of Fumaric acid. It is found in fungi, lichen and moss in Iceland. It is used to treat psoriasis. Exposed to the sun, skin tones that produces acid. Fumarate be used in the treatment of patients with RRMS to significantly reduce relapses and disability progression. Here, Fumaric acid esters (FAE) are a new, orally available treatment option which had already been tested in phase II/III MS trials demonstrating beneficial effects on relapse rates and MRI markers [17].

Other experimental agents under intense investigation for use in MS include Daclizumab (anti-CD25 antibody) and Ocrelizumab (anti-CD20 antibody). Both of these agents have shown promise in early clinical development trials [18].

Fumaric acid is found in fumitory (*Fumaria officinalis*), bolete mushrooms (specifically *Boletus fomentarius* var. *pseudo-igniarius*), lichen, and Iceland moss. Fumarate is an intermediate in the citric acid cycle used by cells to produce energy in the form of adenosine triphosphate (ATP) from food. Human skin naturally produces fumaric acid when exposed to sunlight. Fumarate is also a product of the urea cycle.

BG-12 is a tablet version of the drug dimethyl fumarate. It is being developed for RRMS, who have submitted an application for the drug to be licensed in Europe. Current phase of trial: completed phase III BG-12 is a tablet taken by mouth two or three times a day. BG-12 is an oral version of the drug dimethyl fumarate (a form of fumaric acid). It is not known exactly how BG-12 works but studies have demonstrated that it has an anti-inflammatory effect. This may be helpful in preventing the inflammation that causes damage in the brain and spinal cord of people with MS.

BG-12 is able to affect the immune system. There is also some evidence to suggest that BG-12 may have a neuroprotective effect on people with MS, but this has not been tested directly in clinical trials to date. Two phase III clinical trials of BG-12 have been completed for RRMS. These trials included more than 2,000 people with MS worldwide. Studies evaluated the effect of BG-12 on relapse rate, the progression of disability, and various MRI brain scan meas-

ures of the damage caused by MS. Two years trial investigating the benefits and safety of BG-12 compared with glatiramer acetate.

The most common side effects reported were flushing, gastro-intestinal disorders and headache. BG-12 was more successful at reducing the annual relapse rate than glatiramer acetate. It has not been compared with any other therapies for MS. The manufacturers of BG-12, have submitted an application for Europe. If this application is successful a licence may be granted during 2013 [19].

Oxidative stress plays a crucial role in many neurodegenerative conditions such as Alzheimer's disease, amyotrophic lateral sclerosis and Parkinson's as well as Huntington's disease. Inflammation and oxidative stress are also thought to promote tissue damage in MS. Recent data point at an important role of anti-oxidative pathways for tissue protection in chronic-progressive MS [19].

There are clinical studies focused on the effects of insulin-like factor-1 on the course of MS. This cytokine decreases blood brain barrier permeability. Studying the possibility of replacement therapy with stem cells is at an experimental stage. So far, stem cell researches are not positive.

Combined therapy in MS targets simultaneously using more than one drug or successive application. Good experimental effect in MS patients is derived from the combination of Statins with Glatiramer acetate, while the combination of Statins with Interferon provides significant side effects [20,21]. The studies that we have now are all single-agent studies, other than this one. There are hardly any combination trials. But, moving forward and thinking about what we have learned from this design, it would be of interest to take an anti-inflammatory agent and combine it with a neuroprotective agent, so you cover more of the pathologic spectrum of multiple sclerosis.

### Sažetak

Multipla skleroza (MS) je hronično zapaljenjsko oboljenje centralnog nervnog sistema, uobičajeno se smatra da je autoimunsko, demijelinizaciono, zapaljenjsko i neurodegenerativno oboljenje. Na tome se zasnivala prvobitna strategija lečenja, usmerena na imunomodulaciju i kontrolu zapaljenja. Lekovi koji modifikuju bolest zahtevaju dugotrajno i redovno davanje injekcija ili parenteralno, u infuziji mesečno, što može biti nekomforno i neprijatno za pacijenta. Zbog toga postoji značajna potreba za novim terapijskim pristupima, posebno onim koji omogućavaju optimalan ishod lečenja i pristanak većeg broja pacijenata. Istraživači neprekidno istražuju i otkrivaju nove lekove za MS. Pet lekova za oralnu primenu su trećoj fazi kliničkih istraživanja ili je u skorije vreme odobrena njihova primena za lečenje relapsno-remitentne MS (RRMS): Kladribin i Fingolimod, Fumarna kiselina (BG-12), Teriflunomid (A77126 ili HMR1726) i Lakvinimid (ABR-215062). Preliminarni rezultati ukazuju da su današnji lekovi za oralnu primenu jednako efikasni, ili čak efikasniji od lekova koji se daju u injekcijama. Buduća istraživanja MS bi trebalo da se usmere na kombinovanje terapija i na razvoj lekova za faze remisije i progresije bolesti. Cilj je da se spreči demijelinizacija i da se smanji gubitak aksona.

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