

# Treatment of Multiple Sclerosis

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Received 16 September 2014; accepted 19 June 2016; published 22 June 2016

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## Abstract

**Background:** A new method of immune-based therapies has been made and applied on multiple sclerosis patients in last decades. Some of these treatments have a high efficacy and reasonable side effects. In slowing disease progression, present treatments have significant limitations, but often associated with significant adverse effects of immunosuppression, with having a bit low capability to counter the disability. **Methods:** This is a review meta-analysis of treatment of multiple sclerosis. **Results:** Thus a valuable aim for multiple sclerosis clinical research is to introduce more effective therapies. **Conclusion:** It is absolutely necessary to increase the individualized therapy planes development in respect to make better planes to disease-modifying treatments.

## Keywords

**Immune Sequestration, Multiple Sclerosis, Non-Specific Immune Modulation, Lymphocyte-Targeted Therapy**

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## 1. Introduction

Current progress of the immunopathogenesis of multiple sclerosis (MS) has made the development of promising and novel neurotherapeutic strategies. This review meta-analysis study summarizes Phase II and phase III clinical trials updated data explaining the clinical safety and efficacy promising therapeutic interventions in MS patients (Pt). But adverse effects may get to our knowledge with more Pt studies and increase use of the drugs (**Table 1**).

**Table 1.** Selected MS therapies.

Lymphocyte-targeted therapy	Mechanism of action	Route/Dose	Results	Status	AEDs
Alemtuzumab	Anti-CD52	IV 12 mg dose/y	75% ↓ SAD (12 mg dose), 74% ↓ RR	Phase III	ITP (3 pts), Graves disease (20%)
Rituximab	Anti-CD20	IV (1 gram dose, Q2w, × 2)	91% ↓ CEL in RRMS	Phase II	Infusion reaction, allergies
Cladribine	Purine nucleoside analog	Oral (3.5 and 5.25 mg/kg total dose)	58% ↓ RR, 43% disease free	Phase III	HZV, lymphopenia, HA, nasopharyngitis, lymphopenia
Daclizumab	Anti-CD25/anti-IL2	SQ 2 mg/kg (Q2w)	72% ↓ CEL in RRMS patients	Phase II	Skin rash, chest discomfort, headaches, lymphopenia
CTLA4Ig	Prevents T cell activation	IV (2, 10.0, 20.0, or 35.0 mg/kg)	No significant changes	Phase I	Lymphadenopathy, urinary tract infections, headaches, blurred vision, and upper respiratory tract infections
<b>Immune sequestration</b>					
Fingolimod	Sphingosine-1-phosphate (S1P) analog	Oral (1.25 and 5 mg)	80% ↓ CEL, 50% ↓ RR	Phase III	Bradycardia, nasopharyngitis, dyspnea, headaches, diarrhea, nausea, encephalitis, skin cancer
SB-683699	Alpha-4 integrin antagonist	Oral (150 - 1200 mg Twice Daily)	No data available	Phase II	No data available
<b>Unspecific immune suppression</b>					
Laquinimod	Antiinflammatory	Oral 0.6 mg/d	40% ↓ CEL	Phase III	LFT elevation, Budd Chiari
Fumaric acid (BG12)	Antiinflammatory/ Neuroprotective	Oral (120 - 240 mg TID)	69% ↓ CEL	Phase III	Diarrhea, cramps, nausea and flushing
Teriflunomide	Inhibition of immune cell proliferation	Oral (7 and 14 mg dose)	61% ↓ CEL	Phase II	Nasopharyngitis, alopecia, nausea, limb pain, diarrhea, and arthralgia

## 2. Lymphocyte-Targeted Therapy

### 2.1. Cladribine

It is a purine nucleoside analogue with lymphotoxic effects when combined into the deoxyribonucleotide acid (DNA) of dividing and resting cells having increased deoxycytidine kinase activity (lymphocytes and monocytes), and subsequent stopping of DNA replication, DNA damage, and cell death [1]. In computing to its lymphotoxic effects, by inhibiting S-adenosyl homocysteine hydrolase and DNA methylation, it possesses epigenetic properties [2]. In the 1980s, FDA approved it for treatment of hairy cell leukemia.

It parenterally (total dose 2.8 mg/kg) significantly decreased the volume and number of T<sub>1</sub> gadolinium-enhancing lesions, accumulation of T<sub>2</sub> lesion volume, disability progression and relapse rate in Pt with progressive and relapsing forms of MS [3]-[5]. Because of dose-dependent increase in side effects was observed, as oral tablet formulation, we are going to selection of low doses for use in an ongoing clinical development program.

Using it orally in Pt with relapsing-remitting MS (RRMS), a recent placebo-controlled Phase III trial, showed a 58% reduction in annualized relapse rates (3.5 mg/kg daily for 4 to 5 days, with two courses in the first year) at two years compared with placebo [44]. In addition, compared with 61% of Pt in the placebo group, 80% of Pt remained relapse-free ( $P < 0.001$  for both dose regimens). Relative to Pt in the control group, Pt in the active drug group experienced a 30% reduction in the risk of disability progression [6]. Side effects included headaches, nausea, upper respiratory tract infections, and nasopharyngitis. Lymphopenia occurred more frequently in the active drug group (22%). Pt treated with it, 2.3% reported herpes zoster virus (HZV) infections, although these were localized to the skin and were responsive to preventative treatment. For Pt with relapsing MS, it has

the potential to be the first orally administered disease-modifying therapy available [44].

## 2.2. Alemtuzumab

It is a humanized monoclonal antibody (Ab) directed against CD52, a cell surface receptor expressed on monocytes, natural killer cells, lymphocytes, and macrophages. It binds to T- and B- lymphocytes, resulting in Ab-dependent cell lysis, and subsequent elimination from the blood and bone marrow, with the effect lasting up to 16 months. As a matter of interest, immune cells (IC) regeneration capacity remains intact after repetitive drug therapies, in the course of immune reconstitution, premature forms of B-cells (transitional type I cells) possibly activated by high B-cell activation factor levels are seen early. This event could bring into light the development and association of Ab-mediated autoimmune disorders seen in the course of its treatment. It is currently FDA-approved to treat B-cell chronic lymphocytic leukemia (CLL).

Its studies in the treatment of Pt with secondary progressive MS (SPMS) relapsing-remitting (RR) have suggested efficacy in the suppression of annualized relapse rates, but depending on stages of the disease, with variable results in preventing progression of disability. Its intravenous (IV) recent Phase II randomized blinded clinical trial at 12 or 24 mg per day for five consecutive days during the first month and on three consecutive days at 12 and 24 months, compared with IFN  $\beta$ -1a in Pt with early RRMS, it decreased the rate of sustained accumulation of disability by 71%, with a 74% reduction in the annualized rate of relapse significantly. About 80% of Pt receiving it remained relapse-free at 36 months [44]. Decrease in total brain volume and T<sub>2</sub> lesion volume analysis was greater in the Pt receiving it. Side effects in the Pt receiving it included thrombocytopenic purpura, autoimmune thyroid disorders and infections. About one-third of Pt develops Ab against the thyrotropin receptor and subsequently develops autoimmune hyperthyroidism [7].

## 2.3. Rituximab

It is a chimeric Ab directed against human CD20 phosphoprotein present on all B-cell lineages except for plasma cells, stem cells and pro-B cells. It acts by binding to B-cell lymphocytes, initiating a series of events that leads to B-cell lysis and subsequent depletion. The benefit of decrease of B-cell in controlling the course of the disease supports the recently recognized active role of B-cells in the pathogenesis of MS. The standard dose of it is 375 mg/m<sup>2</sup> given weekly for four weeks, or a fixed dose of 2 g divided into two infusions of 1 g each two weeks apart. Following 2 g of it IV administration, CD20 positive B-cells are rapidly decreased and remain undetectable for up to six months longer.

It has shown efficacy in the treatment of Pt with RRMS. A 91% decrease in the number of gadolinium-enhancing lesions on (magnetic resonance imaging (MRI) scans, as well as a significant decrease in the number of clinical relapses is demonstrated by a recently completed randomized clinical trial using a standard dose of it in RRMS Pt. Mild infusion-related side effects were seen in most Pt, but serious side effects were rare [8]. In a recent trial of Pt with primary progressive multiple sclerosis (PPMS), it appeared to have efficacy only in young Pt with signs of active inflammation on MRI scans [9]. Five cases of progressive multifocal leukoencephalopathy [45] (PML) have been recently reported in Pt receiving it for the treatment of rheumatoid arthritis (RA) and systemic lupus erythematosus. However, these Pt were receiving other immunosuppressants [44].

Ocrelizumab, a humanized monoclonal Ab against human CD20, is currently under investigation in a Phase II trial evaluating its safety and efficacy in Pt with RRMS [10]. Given the functional similarities between it and rituximab, it is unclear which of these will be developed for use in MS [44].

## 2.4. Daclizumab

It is a humanized mouse monoclonal Ab that binds to the alpha-subunit of the interleukin (IL)-2 receptor. This receptor is present on activated B- and T-cells but not on natural killer (NK) cells, and is important for T-cell activation and proliferation. The clinical benefit of it has been linked to significant expansion of immunoregulatory CD56 NK cells, and subsequent down regulation of adaptive T-cell responses (CD8 and CD4 positive T-cells) [11]. Compared with baseline, in an initial open-label study with IV of it 1 mg/kg, five Pt with SPMS and six Pt with RRMS demonstrated a reduction in number of contrast-enhancing lesions by 78% and in relapse rate by 81% [12]. Compared with Pt receiving IFN  $\beta$  alone, a recent open-label Phase II trial using subcutaneous (SQ) of it 2 mg/kg in MS Pt with inadequate response to IFN  $\beta$  therapy, demonstrated a 72% reduction in the

number of new or enlarged contrast-enhancing lesions at week 24. Because Type I IFN is also known to enhance NK cell function, the question of possible synergism between IFN and its treatment is raised [13] [44]. Chest discomfort, generalized lymphadenopathy, lymphopenia, headaches, skin rash, and transient elevation of bilirubin levels and liver function tests have been reported. It is already in clinical use to prevent rejection of kidney transplants. A multicenter Phase II trial investigating a SC formulation of its monotherapy is ongoing.

## 2.5. CTLA-4 Ig

It is a chimeric fusion protein that inhibits T-cell activation by binding the B7-1 and B7-2 costimulatory molecules on antigen-presenting cells. A recent Phase I clinical trial showed that IV administration of it was well tolerated in Pt with MS, and most side effects were rated as mild. Headaches, lymphadenopathy, upper respiratory tract infections, urinary tract infections and blurred vision were most frequently reported. Immunologic assessment of the Pt showed a decrease in myelin basic protein proliferation within two months of infusion and reduced IFN- $\gamma$  production by myelin basic protein-specific lines. During the study no significant changes in clinical or MRI parameters were observed [14].

## 3. Immune Sequestration

### 3.1. Fingolimod (FTY720)

It, an oral sphingosine-1-phosphate (S1P) analog, acts as a partial agonist on S1P receptors, inducing internalization of the S1P receptor, thereby inhibiting the mechanism necessary for lymphocytes to migrate out of secondary lymphoid structures. It is associated with significant reductions in circulating B- and T-cells, particularly in central and naïve memory T-cells, with lesser reductions on effector memory T-cells [15]. As a result of its lipophilic nature, it crosses the blood-brain barrier (BBB) and possibly also down modulates S1P1 in astrocytes and neural cells, thereby decreasing astrogliosis, a phenomenon associated with neurodegeneration in MS [16].

A recent multicenter, randomized, double-blind, placebo-controlled Phase III study with extension in RRMS Pt demonstrated that compared with placebo, it orally at doses of 1.25 and 5 mg, decreased the relapse rates by 50% and number of new focal inflammatory lesions by 80% [9]. About two years, the average annualized relapse rate in Pt receiving it was 0.21, 80% remained free of new enhancing MRI lesions and 75% - 77% of Pt remained free of relapses. In addition, Pt initially receiving placebo showed a significant improvement in clinical parameters of MS after switching to it in the extension study, which was sustained at month 24 [44]. Side effects included nausea, headaches, nasopharyngitis, bradycardia, diarrhea, and dyspnea. In the 5 mg dose group bradycardia was seen more frequently. One case of melanoma, three of basal cell carcinoma and three of squamous cell carcinoma were reported. Two fatalities occurred during the trial, and were associated with herpes and chicken pox virus infection. In addition, a single case of hemorrhagic encephalitis was reported but with an unclear causal relationship [17].

### 3.2. SB-683699

It is an oral medication that is thought to inhibit leukocyte trafficking across the BBB by antagonism of  $\alpha$ -4 integrins. A Phase II trial in Pt with RRMS evaluating the efficacy and safety of it (150 - 1200 mg twice daily) in the development of MRI-confirmed new brain lesions at six months [18].

## 4. Non-Specific Immune Modulation

### 4.1. Laquinimod (Quinoline-3-Carboxamid)

It is a once-daily, orally administered immunomodulatory compound that is being developed as a disease-modifying therapy for RRMS. The anti-inflammatory properties of it are thought to be secondary to down regulation of major histocompatibility complex Class II gene transcription factors, stimulation of neurotrophin-4, neurotrophin-3 and, suppression of the metabolic activity of CD14+ and NK cells, promotion of apoptosis in CD8+ and B-cells, activation of the anti-inflammatory IL-4 pathway in CD4+ cells, and brain-derived neurotrophic factor. As a result, there is a cytokine balance in favor of anti-inflammatory T-helper (Th)-2/Th-3 cytokines, with inhibition of proinflammatory and cytokine-related genes. A Phase IIb study in 306 Pt demonstrated that an oral daily 0.6 mg dose of it significantly decreased MRI disease activity by a median of 60% versus placebo in

RRMS Pt [19]. A Phase III trial was evaluating the efficacy of it 0.6 mg daily in Pt with RRMS [20].

It appears to be well tolerated, with only transient and dose-dependent raises in liver enzymes. A case of Budd-Chiari syndrome occurred after one month of exposure in a patient with underlying hypercoagulability. Unlike its precursor substance, linomide, no cases of serositis or myocardial infarction have been reported so far in Pt receiving it [44].

#### 4.2. BG00012

It is an oral formulation of dimethyl fumarate (DF) that may exert a combination of anti-inflammatory and neuroprotective biological effects. Although its exact mechanism of action is not known, it is thought to inhibit immune cells by stimulating the expression of anti-inflammatory cytokines, such as IL-10, IL-4, and IL-5. Hence, it is thought that DF can cause a shift from a Th-1 (pro-inflammatory) to a Th-2 (anti-inflammatory) T-cell response [21]. By producing Phase II detoxification genes and upregulation of the Phase II detoxification enzyme, NAD(P)H:quinone oxidoreductase-1, it may have a neuroprotective therapeutic effect [22].

A previous multicenter, controlled clinical trial of it orally involving 257 people with RRMS receiving various doses of BG00012 capsules or placebo showed a dose-dependent reduction in active inflammation on MRI scans [23]. Tolerability was good overall, with side effects, including flushing and abdominal pain, commonly occurring in the active treatment group [44].

#### 4.3. Teriflunomide

It is an inhibitor of mitochondrial dihydroorotate dehydrogenase, an enzyme critically involved in pyrimidine synthesis (PS). Because activated lymphocytes largely depend on *de novo* PS, decrease of pyrimidine might result in inhibition of immune-cell proliferation [24]. There is some evidence from *in vitro* studies suggesting that it causes Th-2-mediated anti-inflammatory cytokine activation.

Orally it was tested in a randomized, double-blind, placebo-controlled Phase II study. Pt with relapsing forms of MS was randomized to receive placebo, its 7 or 14 mg a day for 36 weeks. It demonstrated a dose-dependent reduction in the number of T<sub>1</sub>-enhancing lesions. It was generally safe and well tolerated. Side effects included arthralgia, diarrhea, alopecia, limb pain, nausea, and nasopharyngitis. Pancytopenia and Hepatic necrosis have been reported in Pt with RA taking it.

A two-year, double-blind, placebo-controlled Phase III study in relapsing MS is in progress [25]. The primary outcome measure is relapse rate. Other ongoing or planned studies of it include a Phase II study of combination with glatiramer acetate, a Phase II study of combination with IFN- $\beta$  and a placebo-controlled Phase III trial in clinically isolated syndrome [26]-[28].

### 5. Failed Trials

#### 5.1. Antigen-Based Immune Therapies

By antigen-based immune therapy, producing of tolerance appears to be a promising strategy in the treatment of autoimmune disorders. Evaluating the induction of a myelin basic protein-derived peptide (MBP8298) in Pt with progressive forms of MS suggested a benefit in disease progression by clinical parameters in a subgroup of Pt with HLA-DR4 and DR2 haplotypes in recent studies [44]. Unfortunately two Phase III/II trials investigating MBP9298 in RRMS and SPMS Pt with HLA-DR2 and four haplotypes were negative [29] [30].

#### 5.2. IL-12 and IL-23 Inhibitors

Both have been strongly implicated in the pathogenesis of MS. IL-23 is induced by activated myeloid cells, and stabilizes and promotes IL-17 production by CD4<sup>+</sup> T-cells, with subsequent tissue inflammation. Circulating mononuclear cells from Pt with MS express high concentrations of IL-23 and IL-12. Ustekinumab is a fully human monoclonal Ab against IL-23/12 p40 that neutralizes IL-23 and IL-12. A Phase II, multicentre, randomised, double-blind, placebo-controlled study was performed evaluating the induction of 27, 90, or 180 mg ustekinumab every four weeks or 90 mg ustekinumab every eight weeks versus placebo. This study did not explain a significant benefit on formation of inflammatory white matter lesions or affect clinical events in Pt with RRMS unfortunately [31].

### 5.3. Atacicept

It is an immunoglobulin (Ig) fusion protein tumor necrosis factor family receptor transmembrane activator, calcium modulator, and cyclophilin ligand interactor which sequesters the B-lymphocyte stimulator of the tumor necrosis factor family (BLys), a proliferation-inducing ligand (APRIL), and B-cell survival factor and thus stops later stages of B-cell development [44]. A recent Phase II clinical trial evaluating safety and efficacy profiles in Pt with MS was stopped because preliminary data suggested an increase in disease activity in Pt receiving it [32].

## 6. Remyelination and Neural Repair

CNS remyelination is mostly taken place by oligodendrocyte (OD) progenitor cells. The remyelination ability is in general incomplete and fails over time. Many environmental factors play a crucial role in promoting or inhibiting myelin repair and OD differentiation. Of these, neurite outgrowth inhibitor Nogo-A and its co-receptors, LINGO-1 and TROY have been studied in both *in vivo* and *in vitro* studies [33]. Injection of anti-Nogo-A Ab resulted in significant axonal growth *in vitro* and in animal models of spinal cord injury [34]. Passive immunization with anti-Nogo-A Ab in animal models of MS resulted in less axonal damage and demyelination compared with controls [35]. Over-expression of LINGO-1 stopped OD myelination and differentiation, whereas attenuation of its function or administration of LINGO-1 antagonist Ab (anti-LINGO-1) increased OD myelination and differentiation [36] [37]. *In vivo* studies explain the presence of LINGO-1 and TROY in a subpopulation of reactive astrocytes, microglia and macrophages in MS brain lesions [38]. Therapy with an Ab antagonist to LINGO-1 function causes the functional recovery and enhanced integrity of axons in rats with experimental autoimmune encephalomyelitis produced by myelin-OD-glycoprotein [39]. Studies of an anti-LINGO-1 monoclonal antibody are under consideration.

Cellular remyelinating strategies, involving both neural stem and embryonic cells, are being proposed as an elective source of brain cells for transplantation and treatment for MS. *In vitro* studies explain that through trans-differentiation neuronal stem cells have the potential to restore neuronal activity and produce new neurons [44]. Adult bone marrow-derived stromal cells were shown to induce similar neuro-regenerative and immunomodulatory effects in the animal model of chronic experimental autoimmune encephalomyelitis [40] [41]. These concepts have led to an interest in the use of stem cells for restoration of neurologic function and neuronal regeneration in MS. Explaining the use of autologous stem cells for the treatment of MS in humans, there are two clinical trials [42] [43].

### Conflict of Interests

Muhammad Nadeem reports no conflicts of interest in this work and reports no financial relationships/grant support from any NGO or Company.

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## Abbreviations

HZV, herpes zoster virus; RR, relapse rate; HA, headaches; SAD, sustained accumulation of disability; IV, intravenous; ITP, immune thrombocytopenic purpura; CEL, contrast enhancing MRI lesions; SQ, subcutaneous; LFT, liver function test; RRMS, relapsing remitting Multiple Sclerosis.



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