Recent Advances in the Treatment for Multiple Sclerosis; Current New Drugs Specific for Multiple Sclerosis

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ABSTRACT

Since the first approved parenteral drug for the treatment of multiple sclerosis (MS) in 1993 (interferon [IFN] beta, and later glatiramer acetate [GA]), today there are both parenteral and oral treatment options for MS. After IFN beta preparations, glatiramer acetate was developed; and, until the approval of natalizumab in 2006, those dominated the treatment of MS. Later on, among oral drug options, cladribine made a promising entry; however, due to safety concerns, it was withdrawn soon. Afterwards, with the understanding of the role of sphingosine-1 phosphate (S1P) receptors in the pathogenesis of MS, fingolimod was approved in 2010, which was followed by other oral agents such as teriflunomide and dimethyl fumarate. Recently newer IV treatment options such as alemtuzumab, rituximab and ocrelizumab have widened the treatment arena. Recently, after submitting new efficacy and safety data, cladribine was approved for MS by EMA, in 2017. Moreover, seven years after its rejection due to safety reasons, in August 2018 FDA

accepted to re-evaluate the data of cladribine as a treatment option for relapsing remitting MS (RRMS). Another oral treatment option, Laquinimod, was not approved because it could not be shown to slow disability progression despite favourable effect in relapsing MS. Newer generation S1P receptor modulators are being investigated currently, and they are expected to come into the treatment arena soon.

In this article, mechanisms of actions, clinical trial results, and side effects of the newer drugs used for MS, are reviewed. IFN beta and glatiramer acetate were not included since they have clinical experience nearing 30 years.

Keywords: Multiple sclerosis; treatment; interferon beta; glatiramer acetate; natalizumab; cladribine; fingolimod; teriflunomide; rituximab; alemtuzumab; dimethyl fumarate; ocrelizumab; sphingosine 1 receptor modulation; laquinimod; daclizumab

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INTRODUCTION

Until late 20th century, multiple sclerosis treatment consisted of mainly corticosteroids and some wide-spectrum immunosuppressants, such as azathioprine, cyclophosphamide and methotrexate. The first disease modifying drug which was approved by American Food and Drug Administration (FDA), was subcutaneous interferon (IFN) beta 1b. After this drug, which started a new era in the treatment of MS, intramuscular IFN beta 1a, subcutaneous IFN beta 1b, and another compound, subcutaneous glatiramer acetate (GA) followed (1). These drugs have been used in MS for nearly 30 years, and are still being used in the first line due to their almost perfect long term safety, other than tolerance issues due to injections (1).

In the last 25 years, due to the developments on the insights of MS pathogenesis, the number of disease modifying treatments in MS added up to 18. Four of these are oral agents (fingolimod, dimethyl fumarate, teriflunomide, and cladribine), approved by some health authorities over the world. A fifth oral agent, laquinimod, did not complete the approval procedures yet. Other drugs, which are parenteral, include IFN beta,

glatiramer acetate, natalizumab, rituximab, daclizumab, alemtuzumab, and ocrelizumab. Although IFN beta and glatiramer acetate are still being used widely in the first line MS treatment, with their clinical experience nearing 30 years, they will not be included in this article dealing with “new” treatment options in MS.

After IFN beta and glatiramer acetate, the first FDA-approved drug was a humanized monoclonal antibody, natalizumab in 2004. It selectively blocks the alpha-4 integrins on lymphocyte surface, therefore interfering with their adherence to the vascular adhesion molecule 1, which is present in the endothelial surface of the vasculature on brain and spinal cord, finally blocking the inflammatory response in the CNS (2). Despite its strong effects on limiting disease activity in MS, after the reporting of 3 cases with progressive multifocal leucoencephalopathy (PML) in clinical trials, natalizumab approval was temporarily suspended in 2005. After the implementation of TOUCH safety recording system, for the early detection of PML, natalizumab was re-approved in 2006. Three major risk factors were defined for developing PML under natalizumab

treatment: presence of anti-JCV antibodies, use of natalizumab over 2 years, and prior immunosuppressive treatment, in which case risk of PML development was around 11 in 1000. Therefore, a risk stratification strategy was proposed for patients considering tysabri use, and antibodies for JCV were started to be screened. If the patient is negative for JCV antibody, and if there is no prior immunosuppressant use, then the PML risk becomes much less (<1 in 1000). Globally databases and recording systems were developed by the company producing natalizumab in order to follow up infections, neoplasias and other adverse events occurring under natalizumab treatment (Tysabri Global Observational Program in Safety [TYGRIS], Tysabri Observational Protocol [TOP]). These enabled to follow not only the PML cases associated with natalizumab, but also melanoma cases. It is suggested that patients with cutaneous nevus should be photographed before treatment with natalizumab, and be vigilant about the changes in the appearance of the nevus (3).

Rituximab, an anti-CD20 monoclonal antibody, has been used in blood neoplasias and autoimmune disorders since 1997. After the understanding of the role of the humoral immune system in the pathogenesis of MS, use of Rituximab was considered in MS regarding apoptosis of B cells in circulation, leading to decreasing complement and antibody mediated cellular cytotoxicity, which might lead to decreased antigen presentation, T cell and macrophage activation in the long run. Rituximab was evaluated in three heterogeneous studies for RRMS, and one study for primary progressive MS (PPMS), and was found to be very effective for the relapses in RRMS, and slowed disability progression in a subgroup of primary progressive MS patients (those younger than 51 years, with at least one contrast enhancing lesion) (4). Due to these reasons, it has been used off label for MS in many countries. As side effects, infusion related events and infections were common, with a rate of serious infections around 1–2% of the patients. In patients with disorders other than MS, cases with PML have been reported. Moreover, a decrease in anti-JCV antibody index could be shown in patients receiving rituximab, and this was thought to be due to diminished antibody production due to rituximab, rather than having anything to do with the risk of developing PML (5). There has also been concerns about increased susceptibility to thrombotic events (6). Therefore, the company producing rituximab has developed another similar molecule, ocrelizumab, with the aim of lesser side effects; and it was recently approved by FDA (7).

Ocrelizumab is a humanized anti-CD 20 monoclonal antibody, for intravenous infusion. It has been approved for both RRMS and PPMS. Its mechanism of action is thought to be through depletion of CD20 expressing B lymphocytes leading to an immunomodulation. When 600 mg ocrelizumab is applied every 24 weeks, CD20 and concomitantly CD19 expressing B lymphocytes are depleted. In OPERA I and OPERA II trials, ocrelizumab significantly decreased annual attack rates when compared to subcutaneous interferon beta; similar effects continued on the open label extension study. In the ORATORIO study, ocrelizumab was shown to slow 12-week disability accumulation in PPMS patients. Ocrelizumab is a generally well tolerated drug with side effects associated to infusion reactions, and infections. In the clinical trials active drug arm had a higher rate of neoplasia, which requires caution (8).

Another humanized monoclonal antibody is alemtuzumab, which binds to CD52, expressed by T and B lymphocytes, monocytes, macrophages, and eosinophils. After the infusion alemtuzumab depletes all CD52 expressing cells mainly in the peripheral blood, and to a lesser extent, in the lymphoid tissue. Alemtuzumab has the longest lasting effect on immune system among drugs used for MS. Alemtuzumab is given 12 mg/day by IV infusion for 5 consecutive days following IV methylprednisolone, and after 12 months a repeat dose is given 12 mg/day for 3 consecutive days. Efficacy and safety of alemtuzumab was shown in CARE MS I and CARE MS II studies with an active comparator (subcutaneous interferon beta

1a). In the CARE MS extension study, it was shown that efficacy persisted, with 56% of the patients requiring no more treatment for MS including a third dose of alemtuzumab. Mostly the side effects were mild to moderate infusion related events, mild infections, and induction of secondary autoimmunity. Serious opportunistic infections such as listeria meningitis or CMV activation have also been reported. Among the secondary autoimmunity, the most common was thyroid related disorders in 42% of the patients, resulting in either hypo or hyper thyroidism. Other rarer autoimmune disorders include immune mediated thrombocytopenia (ITP), and rare cases of autoimmune nephropathies. It has been suggested to screen the patients for serum anti-GBM antibodies (9). After one death related to ITP in the phase 2 CAMMS II trial, a safety vigilance program has been developed. Both the physician and the patient are educated about the probable signs and symptoms of any autoimmune disorders, and renal, and hematological functions are screened monthly, and thyroid functions are screened every 4 months, for the first 48 months after treatment (10).

Oral form of cladribine, a purine nucleoside analogue was tested in the phase 3 CLARITY trial against placebo, and shown to decrease the annualized relapse rate in patients with clinically isolated syndrome (CIS) (1). Cladribine was used over first 5 days of a month, and repeated similarly once more after one month. After one year if the lymphocyte counts were over 800/mm², the same treatment course was repeated once more. At the end of 96 weeks, annualized attack rate was decreased by 57%, 3-month disability progression was slowed by 33%, and contrast enhancing lesions decreased by 86% (1). In the same trial, a subgroup of highly active patients had even more dramatic results, with a reduction of annual attack rate by 66% and disability progression by 82% (11). Lymphopenia was seen in 21.6% in 3.5 mg group, and 31.5% in the 5.25 mg group (12). Cladribine is a synthetic purine analogue exerting a cytotoxic effect mainly on the lymphocytes, and to a lesser extent monocytes and other hematopoietic cells. Cladribine acts as an antineoplastic agent with immunosuppressive effects, which is due to the enzymatic activity of cytosolic 5'nucleotidase which dephosphorylates phosphorylated cladribine (12). T and B lymphopenia occurring in a dose-dependent manner, is thought to be the mechanism of effect in RRMS (1). Lymphopenia should be monitored closely, and dose should be interrupted if lymphopenia is severe. There are no reported cases of PML associated to cladribine in patients with MS; however, it was reported in cases with hairy cell leukemia using cladribine (13, 14). If the patient needs to be immunized, it should be done 4–6 weeks before cladribine. Live attenuated vaccines should not be done during lymphopenia. Active contraception is needed during cladribine use, until 6 months after the last dose, since it may be teratogenic (1, 11, 13).

The results of CLARITY trial lead to a fast approval of cladribine in Russia and Australia. However, European Medicines Agency (EMA) suspended an approval due to serious side effects (herpes virus activation, tuberculosis activation and 3 cases of neoplasia), which lead to withdrawal from the market globally in 2010. However, when long term data was evaluated for safety, it was noted that cladribine's effects on disease activity for 4 years, without further dosing (13). This led to an EMA approval of cladribine in the use of MS in the summer of 2017; and FDA decided to evaluate the files of cladribine as a treatment option in RRMS.

Daclizumab is a humanized IgG1 anti CD25 molecule, which is a subunit of high affinity IL-2 receptor. The phase 3 DECIDE trial showed that subcutaneous daclizumab once every month were superior to weekly intramuscular interferon beta in both reducing attack rate and radiological parameters. It was also shown that daclizumab decreased the disability progression, increased quality of life, and its effects were continuous for 3 years and longer. These results led FDA approval in May 2016 for RRMS patients who were unresponsive to one or two previous disease modifying drugs (15). However, after one death with fulminant hepatic

failure, and four cases of severe hepatic injury, plus 7 cases of encephalitis or meningoencephalitis, it was withdrawn in March 2018.

The first oral agent approved for MS was fingolimod in 2010, a sphingosine 1 phosphate (S1P) analogue. S1P receptor subgroups are expressed on many different cells including lymphocytes and neurons. S1P receptors 1–3 are expressed in immune cells, cardiovascular system and central nervous system; S1P1 is mostly present in T and B lymphocytes and regulates the egress of lymphocytes from the lymphoid tissue. S1P4 is expressed in lymphoid and hematopoietic tissues, and S1P5 is expressed in the central nervous system, influencing neurogenesis, neuronal functions and neuronal migration. S1P1–3 receptors are also present on smooth muscle and endothelial cells, regulating vascular homeostasis and permeability. S1P1 receptors on atrial myocytes regulate heart rate.

Fingolimod is phosphorylated *in vivo* with sphingosine kinase, and the resulting fingolimod phosphate binds to 4 out of 5 S1P receptors with high affinity. When it binds to the receptor on the surface of the lymphocytes, it induces the degradation of the receptors, and inhibits lymphocyte egress from the lymph node, thus decreasing the auto-aggressive lymphocytes invading the CNS. Fingolimod decreases the Th17 cells in the peripheral blood of the patients with relapsing MS. Memory T-lymphocytes lacking CD62L and CCR7 receptors, are present in intestinal epithelial surface, intestinal lamina propria, lungs, kidneys and peritoneum. Those memory T-lymphocytes lacking CD62L and CCR7 are not affected by fingolimod; therefore, immunological functions remain intact in the peripheral tissues.

Clinical trials showed that fingolimod decreases the attack rate, disability progression, new or enlarging T2 lesions or active lesions on brain MRI, and slowed brain atrophy (16).

The most common side effects associated with fingolimod include headache, liver function test abnormalities, viral infections, diarrhea, back ache and cough. The first 6 hours following the first dose, heart rate may decrease due to slowed atrioventricular transmission. This is a reversible effect due to fast internalization of the receptors, and receptor desensitization on atrial myocytes. Although usually the bradycardia is asymptomatic, it requires the patients to be monitored for the first 6 hours, and overnight if there is symptomatic bradycardia. Although fingolimod traps lymphocytes in the lymph nodes, it does not cause lymphadenopathy, since only 2% of the total lymphocytes are present in the circulation. Moreover, after the treatment cessation, lymphocyte levels return to normal range. Fingolimod may cause an increased susceptibility for viral infections due to decreased memory T-cell functions; however, it does not influence humoral immunity against viruses or bacteria (16). In the TRANSFORMS trial, there were two lethal infections in the 1.25 mg dose group; one disseminated primary varicella zoster, and one herpes encephalitis. Another case switched from natalizumab to fingolimod has developed PML; later a few cases of PML with only fingolimod use were also reported (16).

Secondary macular edema due to retinal S1P receptor modulation leading to increased vascular permeability, has been reported in 0.5% of patients receiving 0.5 mg fingolimod. FDA requires ophthalmological exam before initiation of fingolimod treatment. Macular edema is most prevalent in the first 3–4 months after treatment onset, therefore ophthalmological examination should be repeated at that time. Fingolimod should be stopped in the case of macular edema (16).

Since fingolimod can cross the blood brain barrier, it may have effects on neurons and other CNS cells, it has been suggested that it might decrease neurodegeneration and induce endogenous repair mechanisms (16). Some animal studies showed fingolimod may have neuroprotective effects against glutamatergic excitotoxicity (16, 17).

Teriflunomide is the second approved oral medication for MS. It is the active metabolite of leflunomide which was used for rheumatoid arthritis. Teriflunomide acts through dihydro-orotate dehydrogenase enzyme affecting pyrimidine synthesis which disrupts DNA synthesis leading to a cytostatic effect on proliferating T and B lymphocytes, thus blocking the inflammatory cascade. Teriflunomide was approved by FDA for the treatment of MS in 2012.

In the TEMSO trial 7 mg and 14 mg doses were compared to placebo in RRMS. Both doses decreased the attack rate, prolonged the time to first attack, and increased the attack free patients. There were no difference concerning brain atrophy (18). In the TOWER trial, teriflunomide decreased the attack rate, and confirmed disability progression (19). In TOPIC trial, both doses decreased the development of RRMS in patients with clinical isolated syndrome (20).

In the clinical trials, most common side effects were headache, liver enzyme abnormalities, diarrhea, alopecia and nausea. Liver function test abnormalities could be seen in 15% of the patients, therefore they should be monitored before and during the treatment period. Alopecia, seen in 13%, is usually mild and usually recovers after the first months (18, 19).

Since MS is seen in the reproductive period of young women, teratogenicity is an important issue. During leflunomide use, there were no fetal anomalies; however, teriflunomide may be teratogenic in rodents, therefore its pregnancy category is considered X. Therefore, a firm contraception is required during teriflunomide treatment (18–20). Teriflunomide is slowly eliminated from plasma, which may take months. In the case of hepatic toxicity or pregnancy, elimination can be fastened by cholestiramine or activated carbon use (21).

The third oral drug approved for RRMS is dimethylfumarate (DMF). DMF and combinations of 3-ethylhydrogen fumarate have been used for the treatment of psoriasis in Germany. FDA has approved DMF for RRMS in 2013. DMF is a first-line drug with immunomodulatory and cytoprotective effects. DMF treatment decreases the memory T cells, decreasing the Th1/Th17 proinflammatory cells, increasing antiinflammatory Th2 cells. Latest studies have shown that DMF protects neural stem cells from oxidative damage through Nuclear factor (erythroid derived 2)-like2 (Nrf2) ERK1/2 MAPK pathway, and induces natural anti-inflammatory response of immune cells (22, 23).

In the DEFINE trial, in patients receiving DMF, both relative risk for attacks and EDSS decreased as compared to placebo. New or enlarging T2 lesions and contrast enhancing lesions were also decreased (24). In the CONFIRM trial two doses of DMF were compared with placebo and daily subcutaneous glatiramer acetate (GA). Those receiving twice or three times daily DMF and GA had relative decreases in annualized attack rate by 44%, 51%, and 29%, respectively. Number of patients with an attack and new T2 lesion numbers decreased in all the groups (25).

Most common adverse effects include flushing, abdominal pain, diarrhea, nausea, vomiting, pruritus and papular eruption. Lymphopenia is seen in 6% of the patients, and may be severe; it might be related to PML. In the first year of treatment frequently there is 30% decrease in the lymphocyte count; after the first year lymphocyte numbers are stabilized. However, in some patients there may be severe decreases which may cause infections. Therefore, periodic lymphocyte count monitoring should be done. Two patients with PML have been reported under DMF treatment; one was with prolonged lymphopenia (19–21). Another common side effect is flushing (40%). It usually starts soon after DMF use, and may decrease over time. Taking DMF with the meals may decrease flushing. Using aspirin 30 minutes before taking DMF may also decrease flushing. Other frequent side effects associated with DMF are

gastrointestinal symptoms including dyspepsia, diarrhea, abdominal pain. They also emerge early in the DMF treatment, and decrease over a few months. Only less than 1% of patients have serious gastrointestinal side effects during DMF use (24–26).

All these oral medications are effective as the subcutaneous injection treatments used for RRMS for over decades. Moreover, feasibility of their use and their tolerability increase adherence to the treatment which leads to increased efficacy. Clinical studies have shown that newer oral agents have acceptable side effects when compared to the known side effects of injectables such as IFN and GA. Although there are cases of new side effects reported, they are generally safe (1). However, their long term safety data should be continued to be monitored in the future.

DRUGS THAT WERE NOT APPROVED, AND DRUGS WITH ONGOING TRIALS

Laquinimod is a synthetic agent chemically similar to roquinimex (linomide). Roquinimex was found to be effective in MS in phase 2 trials (27), however, phase 3 trials were terminated due to serious cardiopulmonary toxicity (myocardial infarct, pericarditis, pleurisy). Laquinimod was pharmacologically modified from roquinimex, and was evaluated in RRMS and PPMS patients. In ALLEGRO trial 0.6 mg laquinimod was compared to placebo, and in BRAVO trial it was compared to placebo and intramuscular IFN beta1a; however primary end points were not met. Weak effects on relapse rate, disability progression and MRI parameters were seen (28, 29). Side effects were neck and head ache, and abdominal pain. In a few patients there were ALT elevation, however, during the two years of laquinimod treatment the patients' peripheral mononuclear blood cells did not show any difference by both concentration, and functions and immune responses (27, 28). In the BRAVO trial one patient died to sepsis in the active arm, and 3 patients died in the placebo arm (suicide, accident, pneumonia) (30). Later comparison of 0.6 mg and 1.2 mg of laquinimod in RRMS in CONCERTO trial (31), and the ARPEGIO trial in PPMS patients (32, 33); however later on the company announced that they stopped laquinimod trials.

When it was understood that the side effects of fingolimod resulted from its effects on many S1P receptors, molecules targeting S1P receptor type 1 attracted attention. There are many drugs in various stages of the pipeline such as ponesimod (ACT128800), siponimod (BAF312), ozanimod (RPC1063), seralifimod (ONO-4641), GSK2018682, and MT-1303.

Siponimod is a functional antagonist of S1P receptor types 1 and 5. It causes a lymphopenia by blocking the egress of the lymphocytes from the lymph node. Its half life is shorter than fingolimod, therefore, lymphocyte levels can return to pre-treatment levels in one week after stopping the treatment (34). Although it was aimed to get rid of the bradycardia effect with siponimod, it has been shown to cause bradycardia, as well (34). A phase 2 trial in RRMS, the BOLD trial, and its extension has been completed (35). In the extension phase of the BOLD trial, MS disease activity remained low, and no new safety concerns were raised (36, 37). On the other hand, the EXPAND trial is the largest one carried out in secondary progressive MS (SPMS) (38, 39). In that trial, siponimod was shown to delay 3 month confirmed EDSS progression by 21%, and 6 month confirmed EDSS progression by 26% (28).

Ozanimod is another S1P1 and S1P5 modulator, which does not require phosphorylation for activation, and its half life is 19 hours. It decreases the circulating lymphocytes in a dose dependent manner, and lymphocyte counts increase to pretreatment levels quickly after stopping the treatment (40). It may cross the blood brain barrier, and wide distribution and slow absorption, its systemic exposure is relatively low. This decreases the first dose bradycardia effect (40). A

combined phase 2/3 trial of ozanimod in RRMS, the RADIANCE trial, two doses of ozanimod decreased cumulative total enhancing lesions when compared to placebo, as well as other parameters (41). There was an acceptable safety profile of ozanimod, with no cardiovascular, pulmonary, ophthalmic, infectious or malignant adverse events (41, 42). In the SUNBEAM trial, RRMS patients received either ozanimod or intramuscular IFN beta1a; in both doses ozanimod decreased annualized relaps rate, as well as favourable effects on MRI parameters. Safety and tolerability was similar to RADIANCE trial (43).

Ponesimod is a selective S1P1 agonist. There is a fast absorption trough time (about 2.5 hours), 30 hours of half life. This leads to the fast elimination within one week after stopping the treatment, which cause the fast reversibility of its pharmacological effects. However, in case of medium or severe hepatic failure, dose adjustment should be made (44, 45). In inflammatory disorders, it reduces the edema, inflammatory infiltration, and proinflammatory cytokine levels (46). In a phase 2b trial, in RRMS, three different doses of ponesimod decreased cumulative numbers of new enhancing lesions. Moreover, it also reduced the attack rate (47). Currently a phase 3 OPTIMUM trial is ongoing comparing ponesimod and teriflunomide in RRMS, expected to end in 2019 (48).

Another S1P modulator is seralifimod, which is a selective S1P1 and S1P5 receptor agonist. This has been shown to decrease enhancing lesions against placebo, in the phase 2 DreaMS trial (49). However, the extension phase of this trial was terminated by the company, because of other developments in the field of MS treatment. Another S1P modulator is GSK2018682, which is an S1P1 and S1P5 modulator. Phase 1 trial of GSK2018682 in RRMS was completed in 2011 (50); however, since it is no longer listed on the company's development plan, it may have been aborted as well. Another molecule is amselimid, a selective S1P1 modulator. Its phase 2 trial in RRMS was favourable, and bradycardia risk was low (51). However, the company does not mention their intentions to go on a phase 3 trial for this molecule. As long as newer generation S1P1 modulators are developed, patients with MS will benefit the special mechanism of action of these molecules.

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