

Review Article

Mechanism and adverse effects of multiple sclerosis drugs: a review article. Part 2

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Abstract: Multiple Sclerosis (MS) is an autoimmune, inflammatory disease of the central nervous system (CNS) mostly affecting young adults. The exact mechanism and pathogenesis of MS remain still undiscovered but there have been useful treatments with different efficacy rates. Most of these therapies are divided into the first line, second line and third line, impact on the immune system and immune cells. These drugs are approved to be useful in MS, but like any other therapies, adverse effects (AE) are associated with these drugs. In this review, we continue the survey over mechanisms of actions and AEs of MS drugs. Physicians must be aware of such AEs and complications to choose the best drug for each patient.

Keywords: Mechanism, adverse effect, multiple sclerosis, drug

Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory of the central nervous system (CNS) with unknown etiology and a higher incidence in women [1, 2]. The roles of the immune system and immune cells can be accounted as an important basis for this disease [3] but some environmental factors and hormones have also been recognized to influence MS [4, 5]. Based on the immune basis of MS, some treatments and drugs have been discovered with different efficacies and indications for MS which mostly suppress the immune system so myelin sheath could be saved or the patient could experience a remission course. Unfortunately, there are some adverse effects (AE) associated with these drugs which can be considered mild or even severe. Previously in the first part of the review article, we had a survey on mechanisms of actions and some AEs of some MS drugs and here we continue our survey over these drugs: Glatiramer acetate, Alemtuzumab, Dimethyl Fumarate, Teriflunomide, Laquinimod, Rituximab, Daclizumab, and Cladribine. This systematic review article is performed by searching PubMed and Goggle Scholar research engine and by reviewing dif-

ferent clinical trials and former review article about different MS drugs. In the end, we summarize these AEs. (Drug's information are summarized in **Tables 1** and **2**).

Glatiramer acetate (GA, Copaxone®)

GA is a first-line disease-modifying agent utilized for the treatment of patients with relapsing-remitting MS (RRMS). Although there is still a question mark on the exact mechanism of action of GA, it is believed that binding to the major histocompatibility complex class II molecules is the most likely mechanism for GA [6, 7]. GA has been proven itself as an efficient and safe drug for treating RRMS but like other drugs utilized for MS treatment; some adverse effects have been reported among GA treated patients. Such AEs include injection site reactions or symptoms of a systemic immediate post-injection reaction including flushing, chest pain, palpitations, anxiety, dyspnea, tachycardia, throat constriction and urticarial [8, 9]. The symptoms begin within at least 30 minutes after injection and resolve spontaneously. As studies demonstrate, the AEs mentioned above have been observed among 10% of patients treated with MS and it should be noticed that Nicolau's syn-

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Table 1. Charcteres of clinical usage of multiple sclerosis drugs

Drug name	Mechanism	Line of therapy	Indication	Form, dosage, route and frequency	Isease modifying therapies	Immunomodulatory
Glatiramer acetate [68]	Binding to the major histocompatibility complex class II molecules	First line	RRMS and CIS	Injection, 20 mg S.C. every day	Yes	No
Alemtuzumab [68]	Humanized monoclonal antibody of the IgG1 subclass against CD52	Second line or third line	RRMS	Injection, 12 mg/d I.V. for five days followed by 12 mg/d I.V. for three days one year after the first course	Yes	No
Dimethyl Fumarate [68]	It's unclear by inducing lymphocytopenia	First line	RRMS	Cap. Starting dose: 120 mg Bid for 7 days. P.O maintenance dose 240 mg Bid. P.O	Yes	Yes
Teriflunomide [68]	An noncompetitively and reversibly inhibition of mitochondrial enzyme dihydro-orotate dehydrogenase (DHODH)	First line	RRMS	Coated tab.14 mg P.O every day	Yes	Yes
Laquinimod [48]	Protection of neurons by decreases IL-17 levels and migration of leucocytes to CNS	First line	RRMS and SPMS	Cap, 0.6-1.2 mg P.O once daily for every day	No	Yes
Rituximab (antineoplastic) [54]	Depleting CD20 ⁺ B lymphocytes via cell mediated and complement-dependent cytotoxic effects	Second line	RRMS	Infusion, 4×375 mg/m ² or 1000 mg at week	No	No
Daclizumab [59]	Inhibiting of activation of lymphocytes (anti-CD25)	Second or third line	RRMS and SPMS	S.C injection, 5 ml once monthly	No	Yes
Cladribine [64]	Depleting both CD4 ⁺ and CD8 ⁺ lymphocytes	First line	RRMS	0.07 mg/kg/day sc. 5 days/month or 0.1 mg/kg/day iv days for 4 months	No	Yes

BBB: blood-brain barrier, RRMS: relapsing-remiting multiple sclerosis, PRMS: Progressive-relapsing multiple sclerosis, SPMS: scondry-progressive multiple sclerosis, CIS: clinically isolated syndrome, SC: sub cutaneous, IV: intra venous, IM: intra muscular, Amp: ampule, Cap: capsule, CNS: central nervous system, P.O: per os, Qid: quater in die.

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Table 2. Summarization of most and less adverse effects of drugs

Drug name	Adverse effects	
	Most common	Less common
Glatiramer acetate	Injection site reactions or symptoms of a systemic immediate post-injection reaction including flushing, chest pain, palpitations, anxiety, dyspnea, tachycardia, throat constriction and urticarial	Anxiety, psychosis, breast cancer, cutaneous lymphoma, necrotizing cutaneous lesions
Alemtuzumab	Infusion related symptoms, cytokine storm, increased risk of autoimmune diseases and increased risk of infections	Immune thrombocytic purpura
Dimethyl Fumarate	Gastrointestinal symptoms and flushing	Lymphopenia, leukopenia, elevation of hepatic aminotransferase, proteinuria, severe articular, musculoskeletal pain and transient hair loss
Teriflunomide	Gastrointestinal symptoms, hair thinning, neutropenia and lymphopenia	Hepatic abnormal alanine aminotransferase concentrations, a slight increase in blood pressure and a decreased hair density
Laquinimod	Elevation of ALT, abdominal pain, back pain, cough, respiratory tract infections, headache, asthenic conditions, insomnia, nausea and vomiting, dizziness, arthralgia, and diarrhea	Serositis, pericarditis, myocardial infarction
Rituximab	fever, chills, headache, urticarial and infections	hypotension, bronchospasm, rigors, leukopenia, and angioedema, MCC, PML
Daclizumab	Transient elevation of liver enzymes, infections and cutaneous AEs	CNS vasculitis
Cladribine	lymphopenia, leucopenia, upper respiratory infection, muscle weakness, hypertonia, purpura, rhinitis, ataxia, Injection site pain, injury, dizziness, and tremor	herpes zoster, developing neoplasms such as malignant melanoma, a pancreatic carcinoma and an ovarian carcinoma

PRES: posterior reversible encephalopathy syndrome, MS: multiple sclerosis, ALT: Alanine transaminase, MCC: Merkel cell carcinoma, PML: Progressive multifocal leukoencephalopathy, AEs: adverse effects, CNS: central nervous system.

drome, a rare complication after intramuscular injection of certain drugs was observed by Gaudez [10]. Moreover, E. Pjrek [11] presented a case of the schizoaffective episode as an adverse effect of GA treatment in which they believe that anxiety, as a result of injection reactions correlates with psychosis. GA is also believed to be associated with breast cancer and cutaneous lymphoma [12, 13]. In a case-report, Bosca and colleagues also have reported two cases of necrotizing cutaneous lesions as a side effect of GA [14]. These reported AEs will count as serious AEs, requiring more basic molecular studies. GA has been used as a disease-modifying drug for RRMS for almost two decades and as the results show, during this period no cumulative toxicities or late-emerging adverse events and no increase of opportunistic infections or malignancies have been reported [15].

Alemtuzumab

Alemtuzumab is a second or third line disease-modifying therapy (DMT) and a humanized monoclonal antibody of the IgG1 subclass against CD52 [16] approved for the treatment of relapsing forms of MS. CD 52 is present on the surface of lymphocytes and with lower expression on the cell surface of monocytes, macrophages, eosinophils, and NK cells. It should also be paid attention that CD52 is highly expressed on the surface of malignant lymphocytes which explains the efficacy of alemtuzumab in treating leukemia. Besides the efficacy of alemtuzumab through clinical trials, also some AEs occur among treated patients. These complications include: infusion-related symptoms, cytokine storm, increased risk of autoimmune diseases and increased risk of infections [17]. Infusion related side effects: These complications occur most commonly during the first week of alemtuzumab therapy. Rash and flu-like symptoms are also associated with "early dose" reactions. First dose AEs might happen due to immediate cytokine release syndrome after intravenous (IV) administration. Significantly increased IL-6, tumor necrosis factor-alpha (TNF- α) and interferon-gamma (IFN- γ) are also observed following alemtuzumab administration which can be called as cytokine storm [18]. Cytokine storm may occur with administration of all monoclonal antibodies such as rituximab and alemtu-

zumab [18]. As Moreau suggests, administration of 1 g methylprednisolone can ameliorate this syndrome [19]. Autoimmunity: Autoimmunity had been reported by Hirst [20] in uncontrolled studies as an AE of alemtuzumab. Serious immune thrombocytic purpura was reported in eight patients during two phase III trials [21, 22]. The thyroid gland is also affected in about 20 to 30% of alemtuzumab treated patients. Graves' disease and hypothyroidism are both observed as autoimmune AEs of alemtuzumab. AS Coles and colleagues [23] showed, autoimmune hyperthyroidism occurred in nine patients from a total of 27 patients treated with alemtuzumab. All these data indicate that profound lymphopenia can result in autoimmune side effects which are considered as the main complication of alemtuzumab treatment [24]. Infection: Due to the anti CD52 nature of alemtuzumab and due to the depletion of lymphocytes, increased risk of infections is expected but surprisingly increases in mild-to-moderate infections including upper respiratory infections and urinary tract infections were frequently observed through clinical trials. No increased risk of bloodstream infections was also reported by Silveira [25] in their cohort study of 449 transplant patients receiving alemtuzumab as an immunosuppressant.

Dimethyl fumarate

As the third oral therapeutic agent, dimethyl fumarate (BG00012) is now used for treating relapsing forms of MS and is accounted for a first-line disease-modifying agent. Dimethyl fumarate had been under survey for its effects since 1959 [26]. The exact mode of action of this drug remains a matter of dispute, but it is established that dimethyl fumarate acts on the nuclear factor (erythroid derived)-like-2 (Nrf2) pathway and based on some other studies, it is thought that dimethyl fumarate has immunomodulatory effects [27]. Dimethyl fumarate is a safe and efficient drug with no reported increased risk of infection, including opportunistic infections and no increased risk of malignancy [28, 29]. But besides its efficacy, some AEs occur during the therapeutic period among patients. The main AEs are gastrointestinal symptoms and flushing [30] and as reported by Z [31], some uncommon AEs like Lymphopenia and leukopenia and some long term AEs including PML exist. Gastrointestinal symptoms and

flushing are also reported in all phase II [32] and 2 important phase III clinical trials: DEFINE [33] and CONFIRM [34]. These two phase III trials demonstrate that flushing occurred in 40% of treated patients and caused discontinuation in 3% of patients. On the other hand, gastrointestinal AEs including abdominal pain, diarrhea and nausea happened in 18%, 14% and 12% of patients respectively which caused 4% of patients to discontinue drug administration. It is also important to notice that in both phase III trials, an elevation in the level of hepatic aminotransferase within the first 6 months and slightly increased proteinuria were observed. During DEFINE trial, the level of aminotransferase elevated about three or more times the upper limit of normal in 6% of treated patients but such elevation only occurred in 3% of the placebo group. There are also some recent case reports and case series about rare AEs associated with dimethyl fumarate therapy including severe articular and musculoskeletal pain [35] and transient hair loss [36] which give us new insights for other possible AEs.

Teriflunomide

Teriflunomide is an approved first-line therapy for rheumatoid arthritis which is an active metabolite of leflunomide. The mechanism of action of this drug is by noncompetitively and reversibly inhibition of mitochondrial enzyme dihydro-orotate dehydrogenase (DHODH) which is essential for de novo pyrimidine biosynthesis [37]. Many clinical trials such as phase III clinical trials demonstrate that this drug is well-tolerated and efficient in patients with relapsing forms of MS [38, 39]. But it is also suggested to choose interferon-beta due to AEs reported with teriflunomide therapy [40]. The most common AEs include gastrointestinal symptoms such as diarrhea, dyspepsia, nausea/vomiting, hair thinning, neutropenia and lymphopenia [41]. Besides, hepatic abnormal alanine aminotransferase concentrations, a slight increase in blood pressure and decreased hair density have been reported as the most frequent side effects of teriflunomide by Bayas [42]. In this report, the elevation of alanine aminotransferase was reported in about 54.0% of those patients receiving teriflunomide 7 mg, 57.3% in patients taking teriflunomide 14 mg and 35.9% in the placebo group. It seems that liver toxicity is one of the most important issues among teri-

flunomide administered MS patients especially those who had liver diseases or using other hepatotoxic drugs. One important issue which is noted in different papers is the teratogenic potential of this drug. Due to teriflunomide's teratogenic potential, demonstrated in animals, the FDA categorizes teriflunomide into pregnancy risk category X but no such risk has been indicated in human experiments. As Oh has earlier reported [43], strict contraception is suggested for female patients under teriflunomide therapy. Nasopharyngitis, alopecia, nausea, increases in ALT, paraesthesia, back and limb pain, diarrhea and arthralgia were also the most common AEs among patients with MS during teriflunomide therapeutic period reported in phase II clinical trial [44]. No death, opportunistic infections or impaired immune surveillance were observed during this trial.

Laquinimod

Laquinimod is an oral immunomodulatory drug used once-daily for treating MS patients and is a first-line drug for MS treatments. Several studies have been undertaken to ascertain Laquinimod's mode of action but there is still an open question on it. These studies suggest that promoting anti-inflammatory cytokine profile in human peripheral blood mononuclear cells is a result of laquinimod usage in MS patients [45]. The safety and efficacy of laquinimod have been established through clinical trials. Bruck and colleagues [46] indicated that laquinimod is a safe drug and has shown a greater beneficial effect on disability and brain atrophy rather than relapse rate, which suggest the probable efficacy on RRMS and SPMS patients with disability progression. A phase IIa trial operated by Polam [47] showed comparable rates of AEs among laquinimod treated patients and placebo. It should also be noted that during this clinical trial, four emergent SAEs occurred but none of them resulted in discontinuing the therapeutic period: one patient developed iritis and one other patient had "burning sensation". These two patients had been treated with laquinimod 0.3 mg/d. the other emergent serious adverse event was brain contusion in a patient in 0.1 mg/d group and the last one occurred in the placebo group which was urinary tract infection. Also, data from the phase III ALLEGRO trial [48] demonstrate that SAEs occurred in 9.5% (61/550) of

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laquinimod treated patients and 9.5% (53/556) of placebo group. Such side effects include dose-dependent elevation of ALT, abdominal pain, back pain, cough, respiratory tract infections, headache, asthenic conditions, insomnia, nausea and vomiting, dizziness, arthralgia, and diarrhea. It also should be noted that the elevation of ALT level occurred twice as frequently in the laquinimod treated group versus the placebo group. Other rare SAEs of laquinimod is included serositis, pericarditis and myocardial infarction [49].

Rituximab

Rituximab is established as a second-line drug for treating MS is an efficient and chimeric (human/mouse) IgG monoclonal antibody created originally by fusing light and heavy chain variable domains of a murine monoclonal anti-CD20 antibody with human κ light-chain and γ heavy-chain constant regions [50]. The mechanism of action of rituximab is by depleting CD20⁺ B lymphocytes via cell-mediated and complement-dependent cytotoxic effects which result in apoptosis of CD20⁺ B lymphocytes [51]. Despite the significant efficacy of rituximab proven through studies, some mild and transient and some other serious but rare AEs have been reported among rituximab treated patients. Such modest side effects include fever, chills, headache, and urticaria which are considered as infusion-related symptoms. Based on studies, the infusion-related symptoms occur in 77% of lymphoma treated patients and 14% of rheumatoid arthritis (RA) patients [52]. Brennan et al. [53] suggest that a 12-step rapid desensitization protocol can be considered for subsequent infusions in those patients with clinically significant type 1 hypersensitivity reactions and those with positive skin test for rituximab.

The serious complications include hypotension, bronchospasm, rigors, leukopenia, and angioedema. But it should be noted that these serious side effects are rare, as Bar-Or A and colleagues reported no significant SAEs during their 72-week phase I trial [54]. Merkel cell carcinoma (MCC) has been reported in Chronic Lymphocytic Leukemia (CLL) patients who started therapy periods with 2-CdA (Cladribine) and/or rituximab which gives us this idea that developing cancer can be another expected AE

of immunosuppressant drugs like rituximab [55]. Also, PML has been reported as a rare adverse drug reaction of immunosuppressive drugs [56]. Developing infections can be believed as one other AE during rituximab therapy. Data analysis of 356 patients treated with rituximab showed infection events among 30% of them [57]. Bacterial infections occurred in 19% of the study population, 10% developed viral infections and fungal infections were observed in almost 1% of patients.

Daclizumab

Daclizumab is another humanized monoclonal antibody used in treating MS. This drug is considered as a second or third-line drug for MS treatments. This antibody directly binds to the α -subunit (CD25 or Tac) of the interleukin (IL)-2 receptor. IL-2 is believed to be a potent activator of lymphocytes. So as a result, daclizumab inhibits activation of lymphocytes [58]. Data from clinical experiments on MS patients during daclizumab therapeutic periods demonstrate a good safety and efficacy profile [59]. It is elucidated that regardless of how good daclizumab acts, some AEs are associated with drug usage among patients. Transient elevation of liver enzymes, infections, and cutaneous adverse events were the most common daclizumab-therapy side effects reported in clinical trials. Rash, atopic dermatitis, allergic dermatitis, exfoliative dermatitis, and erythema nodosum were 5 cutaneous side effects reported by Gold [60] in SELECT study among daclizumab treated group. Results from this study also indicate similar a distribution of herpes virus infections between patients receiving daclizumab and placebo group. Despite the slight increases in the rate of serious infections in daclizumab treated patients in the SELECT and CHOICE [61] studies which had no specific pattern of system involvement, such data claim that the rate of adverse events and serious adverse events were comparable to patients treated with placebo. On the other hand, Ohayon and colleagues recently reported a case of CNS vasculitis in a woman during daclizumab therapy [62]. Based on their study, the etiology of CNS vasculitis was uncertain and due to the lack of evidence for demyelination based on the brain biopsy specimen, the neuro-inflammatory disorder was considered as the possible cause.

Cladribine

Cladribine is a synthetic, chlorinated purine nucleoside analog used for treating MS by targeting both B and T lymphocytes and exploiting the specific enzymatic degradation of deoxynucleotides in lymphocytes and is known as a first-line DMT [63, 64]. Cladribine is activated by deoxycytidine kinase (DCK) through phosphorylation which is highly found inside lymphocytes. The mechanism of action of cladribine is by depleting both CD4⁺ and CD8⁺ lymphocytes through interfering with cell metabolism or DNA repair process which finally stops the cascade of immune events in the pathophysiology of MS. A multicenter, randomized, double-blind, placebo-controlled, parallel-group design phase III study called: CLARITY in a population of chronic MS patients [65] has demonstrated that cladribine is generally safe and well-tolerated. Based on previous studies, some dose-dependent AEs are associated with cladribine administration due to the mechanism of action of this drug, as described above. As Beutler [66] report, thrombocytopenia, leucopenia, and anemia occur due to rare idiosyncratic bone marrow toxicity, possibly as a result of higher doses administration of cladribine. The most common AE among patients treated with cladribine during CLARITY study includes lymphopenia, leucopenia, herpes zoster, upper respiratory infection, muscle weakness, hypertonia, purpura, rhinitis, and ataxia with higher occurrence in treatment groups than in placebo. Furthermore, Injection site pain, injury, dizziness, and tremor were observed more frequently in the placebo group. As Rice reported [65], increased incidence of upper respiratory tract infection, pharyngitis, back pain, and arthralgia are associated with cladribine administration in higher doses of 2.1 mg/kg compared with the lower dose of 0.7 mg/kg. But the clinical significance of these differences remains unknown. Based on Cook and colleagues reports [67], lymphopenia was observed in 21.6% of those patients treated with cladribine 3.5 mg/kg and 31.5% of cladribine 5.25 mg/kg treated patients versus 1.8% of placebo group during CLARITY study. Mild or moderate infections and infestations also occurred slightly more often in cladribine treated group than in placebo with the incidence rate of 48.3% in treated patients and 42.5% of placebo. The important point is that infection with herpes

zoster was observed in 2.3% of patients during the therapeutic period with cladribine versus no herpes zoster infection in the placebo group [67]. On the other hand, developing neoplasms, as SAEs of cladribine which was reported in 1.4% of cladribine 3.5 mg/kg treated patients and 0.9% of cladribine 5.25 mg/kg group with no case reported from the placebo group. It also should be noted that three cases of malignancies were reported in the cladribine 3.5 mg/kg treatment group including malignant melanoma, a pancreatic carcinoma, and an ovarian carcinoma. Also, equivalent results from liver function tests and renal markers among cladribine treated patients and placebo group indicate that cladribine is safe and has no known AEs on liver and kidneys.

Conclusion

MS as a progressive CNS disease has yet no certain cure and most patients face neurological impairments after the onset of the disease. However, there are nowadays different oral and injectable drugs for the disease and more drugs are being discovered. Beside proven efficacy and safety results, gathered from different clinical trials, some AEs and some rare SAEs are associated with each drug reported in different original and case report articles. These AEs make MS treatment to require a careful choose between these drugs by expert neurologists according to each patient's situation and history. Consequently, the understanding of these AEs in treating MS is now evolving at a considerable pace and more and more studies are required to explore them.

Disclosure of conflict of interest

None.

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