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Review Article

Mechanism and adverse effects of multiple sclerosis drugs: a review article. Part 1

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Abstract: Multiple Sclerosis (MS) is chronic, inflammatory, a neurologic disorder of the central nervous system (CNS). Although the exact mechanisms of MS have not been yet discovered some drugs are found helpful for its treatment. These drugs which are divided into the first line, second line and third-line therapies, have demonstrated to be helpful for MS patients based on immune basic of the disease. Previous studies have been indicated that deterioration of MS condition is associated with a stronger immune system. Most of these therapies impact on the immune system and immune cells including shifting immune cell populations toward a Th2 dominant population or suppression of the immune system so that auto-reactive immune cells cannot attack myelin sheath of neurons. Beside many beneficial effects of these drugs, some adverse effects (AE) have been reported in many experiments and clinical trials among patients suffering from MS. In this review, we conclude some AEs of beta interferon, mitoxantrone, natalizumab and fingolimod, reported in different papers and we continue the rest of the drugs in second part of our review article.

Keywords: Mechanism, adverse effect, multiple sclerosis, drug

Introduction

Multiple Sclerosis (MS) is a chronic, immune-mediated inflammatory disease of the central nervous system (CNS) mostly affecting young adults [1, 2]. Although there is still a great deal of uncertainty about the exact etiology and pathogenesis of MS the impressive role of the immune system and immune cells have been well documented [3, 4]. It should be noted that genetic factors and also environmental factors including exposure to Epstein-Barr virus (EBV), vitamin D insufficiency or even hormones can also contribute to MS condition [5]. Different epidemiologic studies indicate that MS occurs two times most likely in women than in men [6]. Some drugs are found helpful for the treatment of MS. These drugs which are divided into the first line, second line and third-line therapies, have demonstrated to be helpful for MS patients. Disease-modifying therapies DMTs have been utilized to ameliorate MS condition including Intramuscular interferon beta-1a (IM IFNb-1a, Avonex®), subcutaneous IFNb-1a (SC IFNb-1a, Rebif®), subcutaneous IFNb-1b (SC IFN-beta-1b, Betaferon®, Extavia®) and glatiramer acetate (GA, Copaxone®). Most of these drugs act on the immune system and suppress immune cells so that auto-reactive immune cells will be unable to attack myelin sheaths of neurons. The most commonly used drug for MS patients is interferon-beta available in three formulas: Avonex, Rebif, and Betaseron [7]. Besides the clinical efficacy of these drugs, there have been some adverse effects (AE) reported in experimental studies and clinical trials. For the first time, to the best of our knowledge, in this review article, we aimed to briefly describe mechanisms of actions of these drugs and then conclude the AE of them. (Drug's information are summarized in **Tables 1** and **2**). It should also be explained that this systematic review over these drugs was done using PubMed and Goggle Scholar research engine and searching for different clinical trials and review articles all around the world. That would be a very long review article if we wanted to bring all these drug complications in only one

Table 1. Charcteres of clinical usage of multiple sclerosis drugs

Drug name	Mechanism	Line of therapy	Indication	Form, dosage, route and frequency	Disease modifying therapies	Immunomodulatory
Interferon beta 1a	Effects on the endothelial cells of BBB	First line	RRMS and CIS	Injection, 30 mcg I.M. once a week or 44 mcg S.C. three times a week	Yes	No
Interferon beta 1b	Effects on the endothelial cells of BBB	First line	RRMS, SPMS and CIS	Injection, 250 mcg S.C. every other day	Yes	No
Mitoxantrone (antineoplastic drug)	Intercalating with DNA repair and inhibiting the topoisomerase II	Second line	RRMS, SPMS and PRMS	Injection, 12 mg/m^2 I.V. every three months or 8 mg/m^2 I.V. every month	Yes	No
Natalizumab	Targeting the α4-chain of α4β1 integrin	Second line	RRMS	Injection, 300 mg I.V. every month	Yes	No
Fingolimod	Sphingosine 1-phosohate (S1P) receptor modulator	Second line (First line in United states)	RRMS	Cap.0.5 mg PO Qid, every day	Yes	Yes

BBB: blood-brain barrier, RRMS: relapsing-remiting multiple sclerosis, PRMS: Progressive-relapsing multiple sclerosis, SPMS: scondry-progressive multiple sclerosis, CIS: clinicaly 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.

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

Drug name	Adverse effects	
	Most common	Less common
Interferon beta 1a	Headache, flu-like symptoms, muscle aches, nausea, fever, asthenia, chills and diarrhea, injection site reactions	Depression, suicide, MS aggravation, gait disturbance and dystonia, Severe lymphopenia, meningioma
Interferon beta 1b	Leukopenia, flu-like symptoms, elevated hepatic transaminases, injection site reactions, headache, fever, malaise and myalgia	Fatigue, depression, arthralgia and paresthesia
Mitoxantrone	Cardiotoxicity, malignancy and hepatotoxicity	Leucopenia, anemia, infection and alopecia
Natalizumab	Headache, fatigue, urinary tract infection, lower respiratory infection, arthralgia, gastroenteritis, vaginitis, diarrhea, and hypersensitivity reactions	Laboratory abnormalities, basal cell carcinoma, breast cancer and cervical cancer
Fingolimod (>0.5 mg qDay increases adverse effects)	Cardiac abnormalities such as dose dependent bradycardia, blood pressure effects, macular edema, some laboratory abnormalities in the liver, enzymes level in blood and possible infection risks	PRES, cryptococcal meningoencephalitis and disseminated cryptococcosis, Kaposi sarcoma, tumefactive demyelination, severe autoimmune hemolytic anemia, asthma deterioration, amenorrhea, peripheral vascular adverse effects, ecchymotic angioedema-like cutaneous lesions, reversible cerebral vasoconstriction syndrome, lymphomatoid papulosis and hemophagocytic syndrome

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

article, so we decided to describe some drugs in this part and the other drugs in the second part of our review article.

Beta interferons

Beta interferons have increasingly moved into the spotlight in treating MS and are considered as first-line therapies. These drugs including interferon-a1a (IFN-a1a) and interferon-β1b (IFN-β1b) are well established, first-line, disease-modifying therapy commonly utilized for treating MS and clinically isolated syndrome (CIS) as approved by food and drug administration (FDA) of the United States. Although the exact mechanism of action of beta interferons are not well understood, it is believed that the anti-inflammatory features besides their effects on the endothelial cells of the blood-brain barrier are the most probable cause of MS amelioration after a therapeutic period with beta interferons. Beta interferons are also highly recommended for MS patients with more mental issues and fewer physical disabilities [8]. As studies show, administration of beta interferons has anti-inflammatory consequences including increased expression of IL-10 which is an important anti-inflammatory cytokine, shifting proinflammatory situation into the anti-inflammatory environment, decreased Th1 and microglia proliferation, decreased antigen presentation, downregulated MHC class II expression on microglia [9, 10]. There are indeed three different forms of beta interferons for treating MS patients including intramuscular IFN-β1a or Avonex (30 micrograms intramuscular once weekly), subcutaneous IFN- β1a which is also known as Rebif (22 and 44 micrograms subcutaneously three times weekly), and IFN-β1b (Betaseron) (8,000,000 units 250 micrograms subcutaneously alternate day injection) [7, 11].

Intramuscular interferon beta 1a (Avonex®)

Avonex is a safe and efficient drug and is one of the DMTs using for MS treatment. AXIOM study [12], which was performed on 235 MS patients, proved that Avonex is safe and well-tolerated with mild to moderate AEs and patients under Avonex therapy experienced less injection site reactions and flu-like symptoms compared to other DMTs. Based on results from a phase III randomized placebo-controlled clinical trial and another study on 284 MS patients, intramuscular Avonex reduced the relapses and disabilities caused by relapses in MS patients [13, 14]. Besides its proven efficacy, data indicated that 89% of treated patients in the study by Jongen experienced one or more AEs. These AEs caused withdrawal from the study in 22 (8.0%) patients and it is believed that interferon beta 1a related complications were the main cause of discontinuation in 6.6% (18 patients) of the study population. In phase III clinical trial, headache, flu-like symptoms, muscle aches, nausea, fever, asthenia, chills, and diarrhea were the most common symptoms which were observed more frequently by treatment group rather than the placebo group. On the other hand, some rare serious adverse events (SAEs) were reported by Jacobs et al. [13] including depression, suicide attempt which, MS aggravation, gait disturbance, and dystonia. It should also be noted that none of these serious side effects were classified as definite interferon beta 1a side effect [13].

Subcutaneous interferon beta 1a (Rebif®)

Safety and efficacy of subcutaneous interferon beta 1a administration has been highlighted in RRMS patients during some studies including PRIMS [15, 16]. Injection-site inflammation, headache, flu-like symptoms, elevations of hepatic transaminase levels and asymptomatic white blood cell abnormalities were the most common AEs reported in PRIMS study. These AEs were observed during the first 3-6 months of subcutaneous interferon beta 1a therapy. Another clinical trial called EVIDENCE was conducted to evaluate the safety and efficacy of Rebif and Avonex in RRMS patients [17]. This comparative study showed that injection site reactions and asymptomatic hepatic and white blood cell abnormalities were more frequently observed in subcutaneous interferon beta 1a administered patients rather than in the Avonex group. Injection site reactions were reported in 83% and 28% of patients treated with Rebif and Avonex respectively. This AE caused 4 patients in Rebif treated group and one Avonex treated patients to discontinue therapy. Asymptomatic laboratory abnormalities were also common in both treated groups. Mild hepatic abnormalities were observed in 54% of Rebif treated group and 48% of Avonex treated MS patients. Furthermore, severe hepatic abnormalities were reported in six patients in

both groups. The other frequently reported AE was white blood cell abnormalities, observed in 11% and 5% of patients treated with Rebif and Avonex respectively. Severe lymphopenia occurred in 3 MS patients during Rebif therapy and in 1 patient with Avonex treatment. As suggested by Gama et al. [18], meningioma occurs most likely in MS patients during the course of immunomodulatory drugs such as interferon beta-1a and beta-1b as SAEs but due to the unknown mechanisms, further studies are demanded.

Interferon beta 1b (Betaferon®, Extavia®)

Betaferon Efficacy Yielding Outcomes of a New Dose (BEYOND) study [19] is clinical trial targeting the comparison of efficacy, safety and tolerability of interferon beta 1b 50 μg and 250 μg and glatiramer acetate. During this study, there were some AEs among patients treated with beta interferon. Expected leukopenia besides flu-like symptoms and elevated hepatic transaminases were more frequently reported among interferon treated patients than in glatiramer acetate treated group. On the other hand, injection site reactions were more commonly reported by MS patients treated with glatiramer acetate which may be due, at least in part, to a higher incidence of pain, pruritus, induration, swelling, and irritation at the injection site among these MS patients. Other AEs such as fatigue, depression, arthralgia, and paresthesia were reported almost equally among treated groups. A 16-year long term follow-up study was performed on interferon beta 1b treated RRMS patients to evaluate clinical, MRI, cognitive and patient-reported outcomes [20] Safety data from this study also demonstrate that injection site reactions, flu-like symptoms, headache, fever, malaise, myalgia, and elevated liver transaminase were the most common expected typical AEs among Betaseron treated patients. Feinstein and colleagues also reported that the association of depression and suicide ideation with Betaseron treatment is not yet definitely proven [21].

Mitoxantrone

Mitoxantrone is an antineoplastic drug with both immunosuppressive and immunomodulatory effects used for treating MS. This drug is regarded as a second line drug in treating MS. The mechanism of action of mitoxantrone is by intercalating with DNA repair which leads to single- and double-stranded breaks and also by inhibiting the topoisomerase II [22]. Accumulating lines of evidence from clinical trials have highlighted the efficacy and safety of mitoxantrone but like any other drug used for treating MS, some AEs are associated with its use. One of the most important AEs is the late and irreversible cardiotoxicity that is characterized by decreased left ventricular ejection fraction (LVEF) and/or congestive heart failure [23]. In this part of the article, we discuss the most common and important AEs of mitoxantrone: cardiotoxicity, malignancy, and hepatotoxicity. Other AEs of mitoxantrone include leucopenia, anemia, infection, and alopecia in MS treated patients [24]. Cardiac effects are: Repeated Mitoxantrone treatments in some patients cause mild impairment of cardiac functions and morphological changes in the myocardial cells. Mitoxantrone which has an anthracycline structure, alters Ca2+ releasing and uptake mechanisms in the sarcoplasmic reticulum of myocardial cells. Mitoxantrone delays calcium uptake by sarcoplasmic reticulum (SR) but enhances SR calcium release [23]. As Ghalie et al. [25] indicated, two of the 1378 MS patients, monitored for evidence of cardiac dysfunction and (LVEF), experienced congestive heart failure. LIEF was >50% in all 779 patients who had completed baseline and had to follow up LVEF testing. A “significant decline in LVEF from baseline” was observed in five of 28 patients with MS who received a minimum cumulative dose of 37.5 mg/m^2 of mitoxantrone based on what Avasarala et al. proclaimed [26]. Taken together, these data show that cardiotoxicity is an important AE during mitoxantrone therapeutic period and patients should receive LVEF monitoring prior to each dose. Complications about malignancies are: The most common malignancy occurring among mitoxantrone treated patients is acute myelocytic leukemia (AML) which is due to the inhibition of the topoisomerase II which is associated with a higher risk of secondary leukemia [27]. Therapy-related acute leukemia (TRAL) was first reported in 1998 in a MS patient by Vicari et al. [28] and after 36 months follow-up, the TRAL risk was 0.07% in 1378 patients [29]. It also should be noticed that regional differences observed in reports about the association of mitoxantrone and AML are notable. Based on reports by Martinelli and colleagues [30], 30 cases of

AML occurred during a multicenter retrospective cohort study on 3220 MS patients in Italy which gives us a high TRAL incidence (0.93%). On the other hand, studies in Germany showed a lower TRAL rate (0.25%-0.41%) in a large cohort study on 2261 patients [31]. While another cohort study on 802 French patients resulted in a TRAL incidence of 0.25% after 6.7 years of follow-up [32]. All these data demonstrate that MS patients should be informed that AML as another potential AE which might occur during treatment with mitoxantrone and monitoring tests should be operated. Hepatotoxicity complications are listed as: In about 15% of mitoxantrone treated MS patients (12 mg/m^2), transient increases in the serum bilirubin concentration and in the activity of hepatic enzymes were observed [33]. Hartung et al. [34] also reported an increase in gamma-glutamyl transpeptidase and aspartate aminotransferase in mitoxantrone treated patients. These elevations might be due to the detrimental effects of mitoxantrone on hepatocytes. It should also be noted that peroxidase-catalyzed mitoxantrone oxidation causes an increase in oxidative stress which is associated with the production of free radical species [35, 36].

Natalizumab (Nat)

There is a large body of evidence regarding the impact of Nat in treating RRMS [37] and some other autoimmune diseases such as ulcerative colitis and Crohn's disease [7, 38]. Nat is indeed a humanized monoclonal antibody against adhesion molecules expressed on lymphocytes. The mechanism of action of Nat is by targeting the α4-chain of α4β1 integrin [39] which results in inhibition of lymphocyte migration into CNS via BBB. Nat is recently suggested by Baroncini and colleagues [40] to be superior to fingolimod in those MS patients who do not respond to first-line therapies. Treatments with Nat are considered as a second-line therapy. Besides satisfying efficacy and safety results from phase III clinical trials including AFFIRM [41] and SENTINEL [42], some AEs had been reported among patients treated with Nat. These side effects were: headache, fatigue, urinary tract infection, lower respiratory infection, arthralgia, gastroenteritis, vaginitis, diarrhea, and hypersensitivity reactions. As studies show, 6% of Nat treated patients and 4% of the placebo group discontinued the therapy due to adverse effects in a two-year phase III AFFIRM study [41]. During AFFIRM study, 9-12% of patients in Nat treated group produced antibodies against the drug despite the fact that Nat is a humanized antibody. Another finding of this study was that developing antibodies against Nat is commonly associated with allergic infusion reactions. Treatment with Nat is also associated with some laboratory abnormalities including higher levels of plasma lymphocytes, monocytes, eosinophils, and basophils [41, 42]. There were also some SAEs reported in Nat treated patient. Data about infections as a complication: In clinical trials, Nat did not appear to increase the overall risk of infection when compared to placebo except for JC virus. However several cases of opportunistic infections occurred in patients with Crohn's disease treated with Nat including a fatal case of Pneumocystis carinii pneumonia, one fatal case of pulmonary aspergillosis, a case of mycobacterium avium intracellulare complex pneumonia, and a case of Burkholderia cepacia pneumonia [43]. PML was also another important complication: Oligodendrocytes infection by JC virus which is known as progressive multifocal leukoencephalopathy (PML) is considered to be another SAE of Nat. PML was first seen in two patients in February 2005 during SENTINEL trial in which patients received both Nat and interferon-β [44, 45]. Another infection with JC virus was reported in a patient with Crohn's disease treated with Nat [46]. Berger [47] indicated that neuropsychological symptoms are common among patients with PML (54%) and based on another study[48] 36% of Nat-PML cases develop seizures, another typical symptom of PML. Further studies demonstrate a direct relationship between the risk of PML and increasing received doses [49]. These data showed the accumulated rate of PML is 0.8 cases for every 1,000 patients treated with 12 or more doses of Nat, and 1.3 cases for every 1,000 patients treated with 24 doses or more [50]. Malignancy: neoplasms occurred in less than 1% of Nat treated patients which were also not significant. Some reported malignancies included basal cell carcinoma, breast cancer, and cervical cancer. It should be noted that during AFFIRM study, one patient with a history of malignant melanoma died as a result of a metastatic melanoma [41, 42].

Fingolimod

FTY720 which is also known as Fingolimod is the first oral treatment approved by FDA in the

United States for patients with relapsing-remitting MS and is a second-line drug [7, 51]. Fingolimod is a sphingosine 1- phosphate (S1P) receptor modulator which acts by binding to S1P receptors on lymphocytes and as a result, the lymphocytes in lymph nodes are sequestered and the autoreactive lymphocytes are not able to egress into peripheral circulation and cross the blood-brain barrier (BBB) into CNS [52]. Based on studies carried out on fingolimod, it's been well proven that this drug is effective and safe and it's been recently suggested as a safer drug comparing to dimethyl fumarate [53]. Although some certain AEs exist among patients including cardiac abnormalities such as dose-dependent bradycardia, blood pressure effects, macular edema, some laboratory abnormalities in the liver, enzymes level in blood and possible infection risks [54-58]. As Gajofatto et al. [57] indicates, there have been recently variable rare case reports and case series about SAEs associated with fingolimod therapy including posterior reversible encephalopathy syndrome (PRES), cryptococcal meningoencephalitis and disseminated cryptococcosis, Kaposi sarcoma, tumefactive demyelination, severe autoimmune hemolytic anemia, asthma deterioration, amenorrhea, peripheral vascular adverse effects, ecchymotic angioedema-like cutaneous lesions, reversible cerebral vasoconstriction syndrome, lymphomatoid papulosis and hemophagocytic syndrome. But as Kappos and colleagues demonstrate [56] in FREEDOMS study, there were similar risks of any kind of AE, serious AE, or AE leading in drug discontinuation between the placebo group and fingolimod 0.5 mg. Cardiac complications of fingolimod are: The mechanism of cardiac AEs caused by fingolimod is possibly due to the activation of G-protein-coupled inwardly rectifying potassium (GIRK) channels mediated by S1P on atrial myocytes [59]. Some fingolimod related cardiac AEs have been reported including prolonged symptomatic bradycardia and slowing of atrioventricular conduction [60, 61] which is interestingly reported to be totally reversible using atropine [62]. Lately, Racca et al. [63] proclaim fingolimod to reduce left ventricular systolic function which has no clinical consequences in those MS patients with no previous cardiac disorders. Also, it should be mentioned that these AEs are dose-dependent and ask for advice by cardiologists in patients suffering from heart failure or a history of cardiologic problems. In a pooled analysis of FREEDOMS and TRANSFORMS [55, 64]. A mean decrease of 8bpm was observed in the patient's heart rate 4 to 5 hours after receiving the first dose of fingolimod 0.5 mg and a mean reduction of 11bpm with 1.25 mg fingolimod. In phase III trials, such a decrease in heart rate was asymptomatic. Furthermore, <1% of patients treated with fingolimod reported palpitation, chest discomfort, dizziness and fatigue with no syncope reports. As studies show, the most common abnormality in FREEDOMS and TRANSFORMS [64] was first degree AV block. The mean P-R prolongation was 4.5 milliseconds with the patients treated with fingolimod 0.5 mg and 11.3 milliseconds prolongation among 1.25 mg treated MS patients. Taken together, 4.7% and 0.2% of patients receiving fingolimod showed first degree AV block and second-degree Morbitz 1 block. Vascular: Fingolimod can also effect on the vascular system due to the expression of S1P1, S1P2, and S1P3 on endothelial cells. Vasoconstriction is caused by the direct effect of S1P3 on vascular smooth muscle cells [65]. However, indirect vasodilation is produced by the synthesis of nitric oxide due to the impact of fingolimod [66]. There have been some mild AEs listed for fingolimod on the vascular system. Some studies indicate that the effect of fingolimod on vascular tone can cause headaches [67]. Graler and colleagues [68] showed decreased atherosclerosis development in short therapeutic periods with a low dose of oral fingolimod. Vasospasm in the peripheral vascular system including brachial artery is another example of vasoconstrictions caused by receiving a higher dose of fingolimod [69]. Macular edema: Macular edema was considered as an important AE associated with fingolimod 5.0 mg and 2.5 mg treatment in renal transplant patients [70]. Macular edema occurred in 2.2% of patients taking fingolimod 5.0 mg/daily and 1.3% of whom receiving fingolimod 2.5 mg/daily within almost 4 months of therapy initiation. It should also be noted that macular edema occurred in 0.3% of MS patients treated with fingolimod 0.5 mg and 1.1% of patients on 1.25 mg [55]. Blurred vision and metamorphopsia are symptoms of macular edema which is bilateral in 25 percent of patients [71]. Infections are also other complications: Increased susceptibility to infections is expected as a result of immunomodulatory characteristic of fingolimod. Studies showed

that in treatment groups in FREEDOMS, there was a similar proportion of patients with infection AEs, severe infections, and serious infections but lower respiratory infections and bronchitis occurred slightly more often in fingolimod treated group (5.7-6.8%) than in groups receiving either placebo or IFNβ1a (3.5-4.5%) [55] opportunist infections such as Cryptococcus, toxoplasmosis, and disseminated histoplasmosis were not seen with fingolimod treatment in clinical trials. Laboratory abnormalities are also seen as following: As Willis and colleagues report, Lymphopenia which occurs within hours of the first dose, is considered as the most commonly reported laboratory abnormality [55]. Fingolimod treatment brings lymphopenia via redistribution rather than depletion and effector memory T cells in the periphery are largely spared so as a result, such decrease in lymphocyte count is not so crucial that is seen in HIV infection. Alanine aminotransferase (ALT) increased blood level is also another common consequence of treatment with fingolimod. Besides being dose dependence, these reported abnormalities were asymptomatic and no case of symptomatic liver injury or a pattern/severity indicative of significant hepatocellular damage has been reported [55]. There have been also reports of low platelet counts in the serum of patients under fingolimod treatments [72].

Conclusion

Based on the immune basis of MS, different kinds of drugs are used to suppress the disease. Each of these drugs has its own efficacy and indication of usage but the important issue is that some patients confront different AEs during treatments. In this review article, we had a survey on different AEs associated with some MS drugs which can be a great help for neurologists when choosing a drug. Taken together, along with specific characteristics of drugs, their AEs should also be noticed in order to prevent serious problems for patients.

Disclosure of conflict of interest

None.

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