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Requirement for safety monitoring for approved multiple sclerosis therapies: an overview

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Summary

During the last two decades, treatment options for patients with multiple sclerosis (MS) have broadened tremendously. All agents that are currently approved for clinical use have potential side effects, and a careful risk–benefit evaluation is part of a decision algorithm to identify the optimal treatment choice for an individual patient. Whereas glatiramer acetate and interferon beta preparations have been used in MS for decades and have a proven safety record, more recently approved drugs appear to be more effective, but potential risks might be more severe. The potential complications of some novel therapies might not even have been identified to their full extent. This review is aimed at the clinical neurologist in that it offers insights into potential adverse events of each of the approved MS therapeutics: interferon beta, glatiramer acetate, mitoxantrone, natalizumab, fingolimod and teriflunomide, as well as recently approved therapeutics such as dimethyl fumarate and alemtuzumab. It also provides recommendations for monitoring the different drugs during therapy in order to avoid common side effects.

Keywords: activation, acute respiratory distress syndrome, multiple sclerosis (MS)

Introduction

Multiple sclerosis (MS) is an inflammatory disease affecting young adults and is a major cause of disability [1]. MS phenotypes have been differentiated into relapsing–remitting MS (RRMS), primary progressive MS (PPMS) and secondary progressive MS (SPMS). In the majority of patients, RRMS will proceed eventually to SPMS [2]. While relapsing forms of MS appear to be driven primarily by central nervous system (CNS) inflammation, progressive forms of MS are also characterized by extensive neurodegeneration [3]. Two decades ago, the first therapeutic agents were approved for treatment of relapsing forms of this disorder [4]. Since then, the therapeutic options have broadened tremendously. While it is now possible to lower the rate of clinical attacks and the lesion burden on magnetic

resonance images (MRI), questions remain regarding the long-term benefits derived from any of the approved agents. In addition, all the drugs that are currently available for use in patients with MS have potential side effects [5], and a careful risk–benefit evaluation often helps the neurologist to identify the best agent for an individual patient.

Currently, glatiramer acetate (GA) (Copaxone®), interferon beta (IFN-β) preparations (Betaseron®, Extavia®, Rebif®, Avonex®), mitoxantrone (Novantrone®), natalizumab (Tysabri®), fingolimod (Gilenya®) and teriflunomide (Aubagio®) are approved for therapy of relapsing forms of MS in the United States and other countries. Laboratory screening tests for specific complications of these agents are becoming increasingly complex and a daily routine for MS neurologists. The requirement for such tests will be discussed in this review.

GA (Copaxone®)

GA is indicated for therapy in RRMS and in first clinical relapses in patients with MRI compatible with MS. It was approved for RRMS in 1996 by the Food and Drug Administration (FDA) [4]. GA reduces the risk of relapses in RRMS [6] and may decrease disease progression compared to patients who terminated treatment with it [7]. Twenty mg GA are administered subcutaneously (s.c.) daily [8].

GA is a polymer of amino acids (glutamic acid, lysine, alanine and tyrosine). This co-polymer was originally generated to mimic myelin basic protein, and to allow the induction of the MS animal model experimental autoimmune encephalomyelitis (EAE). Unexpectedly, disease resistance was observed [9], which led to clinical trials in MS patients. The complex mode of action of GA is still not understood fully. However, cellular immune responses are shifted from inflammatory to anti-inflammatory cytokines. This T helper type 1 (Th1) to Th2 shift seems to be responsible for some of the effects. Other mechanisms are inhibition of activation and proliferation of encephalitogenic T cells and a modulation of antigen-presenting cells [10–12]. Brain-derived neurotrophic factor (BDNF) production is increased in response to GA treatment. BDNF may possess neuroprotective capacity [13], as it may play an important role in the protection of axons [14].

Potential side effects of GA include immediate post-injection reactions such as flushing, chest pain, palpitations, anxiety, dyspnoea, urticaria and constriction of the throat. These side effects are usually self-limited and occur unpredictably several months after initiation. Chest pain may be associated with post-injection status, but it also may occur without a temporal relation to injections. Lipoatrophy has been reported [15,16]. To avoid skin necrosis the patients should follow injection techniques as stated in the prescribing information. Antibodies targeting GA have been reported, but it is not plausible that they antagonize its actions *in vivo*. Usually, many of these side effects are self-limited or can be avoided by proper injection [8]. Whereas flu-like symptoms are less frequent in patients on GA therapy compared to patients on IFN-β treatment, injection side reactions are more common in patients under GA treatment [17]. Recent reports have shown hepatic toxicity under treatment with GA [18,19]. These reports need to be validated.

No laboratory monitoring is required during GA therapy (see Table 1).

GA is a pregnancy category B (see Table 2), meaning that no adverse effects on embryonal development were observed in animal reproduction studies. Well-controlled clinical trials in pregnant women are lacking. Consequently, GA should be used during pregnancy only if clearly needed [8].

IFN-β

IFN-β was first approved for MS in the in 1993. There are three different products available – IFN-β-1b preparations (Betaseron®, Extavia®) that are administered s.c. every other day, and IFN-β-1a preparations that are either administered s.c. (Rebif®) three times weekly or intramuscularly (i.m.) (Avonex®) once a week [4].

IFN-β is a purified, lyophilized protein product generated by recombinant DNA techniques. In response to viruses, IFN-β is produced by the innate immune systems. A reduction of T cell activation, a cytokine shift in favour of anti-inflammatory effects, induction of regulatory T cells and prevention of leucocytes from crossing the blood–brain barrier have been shown. In addition, IFN-β leads to higher neutrotrophic factor expression, promotes anti-viral effects and apoptosis of autoreactive T cells. The exact mechanisms by which IFN-β benefits patients with MS are currently not known [20].

The most common side effects are flu-like symptoms. Symptoms may be minimized by the intake of analgesics or anti-pyretics prior to injection. As with GA, injection site necrosis and reactions have been reported. Again, proper injection technique and the change of injection site are of importance in reducing the occurrence of these side effects. Injection side effects are more common in patients receiving IFN-β-1a three times weekly s.c. when compared with patients under IFN-β-1a weekly i.m. [21]. Allergic reactions and anaphylaxis are rare complications that have to be considered severe. In the case of anaphylaxis, treatment with interferon has to be discontinued. Severe hepatic injury has been reported under treatment with IFN-β preparations, mainly when therapy occurs in combination with other hepatotoxic agents. Depression has been reported in patients treated with IFN-β. Therefore, symptoms of depression have to be monitored, and treatment discontinued as indicated. In addition, haematological abnormalities including lymphopenia, neutropenia,

Table 1. Therapy monitoring in approved therapeutics. Possible side effects.

	Potential side effects	Recommended monitoring
Glatiramer acetate	Flushing, chest pain, dyspnoea Palpitations, urticaria, skin necrosis	None
Interferon beta	Flu-like symptoms, injection-site necrosis Depression, allergic reactions Hepatic injury, neutropenia Lipoatrophy	Liver enzymes Blood count Thryroid testing Neutralizing antibodies
Mitoxantrone	Congestion heart failure Urine colour blue-green Birth deficiency, sterility Hair loss, nausea	Left ventricular ejection fraction ECG, differential blood count, Liver enzymes, pregnancy testing
Natalizumab	PML, fever, joint pain Liver disease, melanoma Allergic reactions	JC-virus Neutralizing antibodies
Fingolimod	Bradycardia, heart failure Fever, diarrhoea, liver disease Macular oedema, skin cancers Enzephalities	ECG, cardiological evaluation Ophtalmological evaluation VZV-antibodies, liver enzymes
Teriflunomide	Hepatic injury, elevated liver enzymes, infections, polyneuropathy	Liver enzymes, pregnancy testing, white blood count
Alemtuzumab	Autoimmune disorders (thyroid disorders, immune thrombocytic purpura), infusion-related side effects	Complete monthly blood counts, testing for autoimmunity
Dimethyl fumarate	Lymphopenia, gastrointestinal side effects	White blood cell count

PML: progressive multi-focal leucoencephalopathy; ECG: electrocardiography; VZV: varicella zoster virus.

anaemia and leukopenia have been reported [22–27]. Two other relatively common side effects of IFN-β therapy in patients with MS are thyroid autoimmunity and hypothyroidism [28], although other reports could not show a significant increase in thyroid dysfunction or anti-thyroid autoantibody positivity [29,30].

In conclusion, treatment with IFN-β is considered safe and well tolerated. However, after the approval of IFN-β cases with autoimmune diseases, including idiopathic thrombocytopenia, hypo- and hyperthyroidism and autoimmune hepatitis, have been reported. Thus, liver enzymes should be monitored in regular intervals in the absence of signs of liver injury (1 month, 3 months and 6 months after initiation and each 6 months afterwards). Known liver disease is a contraindication to therapy with IFN-β. Liver transaminase levels of greater than five times of normal should lead to a dose reduction. If enzyme levels do not convert to normal, treatment has to be discontinued. If enzyme levels normalize after a dose reduction, a return to the full dose can be initiated with ongoing hepatic monitoring. In addition, complete blood counts should be obtained after 1 month, 3 months, 6 months and each 6 months thereafter. Thyroid testing should be performed initially and afterwards only in the case of abnormalities every 6 months and when clinical signs of hypo- or hyperthyroidism are obvious (see Table 1).

Table 2. Potential risk of MS therapeutics in pregnancy.

FDA pregnancy category	Interpretation	Therapeutic agent
A	Well-controlled trials in pregnant women revealed no increased risk for fetus	
B	No well-controlled trials, but animal trials revealed no increased risk or well-controlled trials revealed no risk, whereas animal trials have shown adverse effects	Glatiramer acetate
C	Animal studies have shown increased risk for the fetus or have not been conducted; no well-controlled trials in pregnant women	Interferon beta, natalizumab, fingolimod, alemtuzumab, dimethyl fumarate
D	Studies have shown harm to the fetus; however, the benefit may outweigh risk under certain circumstances	Mitoxantrone
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits	Teriflunomide

Like all therapeutic proteins, IFN-β is immunogenic and can induce the production of binding and neutralizing antibodies [31]. Neutralizing antibodies are up to seven times more prevalent in patients receiving IFN-β-1b every other day or IFN-β-1a s.c. three times weekly, when compared with IFN-β-1a i.m. once a week [21,32]. Routine testing for IFN-β neutralizing antibodies is currently not universally recommended. Testing for neutralizing antibodies might be recommended in the setting of clinical disease progression under IFN-β treatment. If testing is performed, the presence of high titres against IFN-β on recurrent testing or the failure to induce interferon inducible protein (MxA) should perhaps lead to the discontinuation of therapy and a switch to a different class of drug [33].

One lethal case of capillary leak syndrome was reported in a patient with monoclonal gammopathy of unknown significance (MGUS) after one administration of IFN-β-1b. Post-mortem measurements showed a deficiency of C1 inhibitor (C1-INH) that controls the complement system. The release of proinflammatory cytokines appears to have resulted in an uncontrolled activation of complement factor. There are reports of associations of MGUS and C1-INH. An autopsy did not confirm the diagnosis of clinical definite MS [34]. In patients with MGUS and MS who are candidates for IFN-β therapy, the level of C1-INH should be determined.

IFN-β-1b has been assigned pregnancy category C. In animals, significant increases in embryolethal and arbotifacient effects could be shown under doses approximately two to three times higher than the doses used in patients with MS. Well-controlled trials in humans are lacking and not feasible. However, spontaneous abortions have been reported in clinical trials. Women should be informed about this risk and treatment should be discontinued when women intend to become pregnant or during pregnancy [35–37].

A polyethylene glycol (PEGylated) formulation of IFN-β with longer injection intervals is currently under investigation, showing promising preliminary data according to a recent press release [Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) study] [38].

Mitoxantrone

Mitoxantrone (Novantrone®) was approved in 2000 by the FDA for rapidly worsening RRMS or secondary progressive MS [39]. It has proved its efficacy in several trials [40,41]. Mitoxantrone is administered at doses of 12 mg/m^2 every 3 months intravenously (i.v.) as short infusions. It is an anti-neoplastic cytotoxic agent that inhibits type II topoisomerase and disrupts DNA synthesis. Furthermore, mitoxantrone showed effects on the proliferation of T and B cells and induces natural killer (NK) cell maturation [42,43]. It was first used in cancer therapy. From cancer patients receiving mitoxantrone it is known that there is a dose-dependent risk of developing cardiomyopathy [44].

Because of reports of congestive heart failure and decreases in the left cardiac ejection fraction, cardiac monitoring has been recommended. Heart failure may occur during or after termination of therapy with mitoxantrone [45,46]. The risk correlates with accumulating doses of mitoxantrone, and a cumulative dose of 140 mg/m^2 should not be exceeded. The incidence of secondary lymphoid cancer is estimated to be between 0·25 and 6%. There seems to be no correlation between the applied dose and the likelihood for lymphoma. These complications have substantially limited the use of mitoxantrone despite its proven efficacy [47].

Prior to initiation of therapy, left ventricular ejection fraction (LVEF) should be obtained by echocardiogram, multi-gated radionucleotide angiography (MUGA) or MRI. Prior to each infusion with mitoxantrone an electrocardiogram (ECG) should be performed. In addition, a quantitative re-evaluation of LVEF should be performed before initiation of mitoxantrone, during therapy with mitoxantrone and yearly after termination of mitoxantrone using the same method utilized at baseline [48]. A significant reduction of LVEF (below 50%) is a contraindication for initiation of therapy with mitoxantrone and a reason for terminating therapy.

Because mitoxantrone leads to a reduction in the number of leucocytes, administration of mitoxantrone is not recommended when neutrophil numbers fall below 1500 mm^3. Complete blood count and differential blood count, as well as thrombocytes and liver enzymes, should be tested prior to each administration. Patients with hepatic insufficiency with threefold elevated liver enzymes should not be administered mitoxantrone, as it is metabolized in the liver (see Table 1) [48,49]. Liver toxicity has been reported in as many as 15% of treated patients [50].

During therapy with mitoxantrone, vaccinations with live virus vaccines should be avoided. The application of other anti-neoplastic agents should be avoided. The patient should be aware that the urine may be blue–green in colour for some days after infusion. Other side effects include transient hair loss or thinning and nausea, and menstrual disorders in females. If there are signs of extravasation, the infusion has to be stopped immediately to avoid tissue necrosis [49].

Patients who have not completed their family planning should be informed that mitoxantrone may cause sterility. As mitoxantrone may cause birth defects, contraception is required during therapy. A pregnancy test should be conducted prior to each administration [49]. Well-controlled trials are currently lacking in pregnant women [51]. Mitoxantrone has been assigned to pregnancy category D by the FDA. Animal data suggest fetotoxicity (low fetal birth weight and retarded development of the fetal kidney) and premature delivery [48] (see Table 2).

Natalizumab

Natalizumab is a humanized recombinant monoclonal antibody against the α4-chain of integrins that was designed to diminish leucocyte migration from the peripheral blood into the CNS. Specifically, very late activating antigen-4 (VLA-4; identical with α4-chain of α4β1-integrin) is decreased in its ability to bind its ligand, vascular cell adhesion molecule (VCAM)-1 [52,53]. Natalizumab received accelerated approval by the FDA in 2004 based on the results after 1 year of treatment in two placebo-controlled trials. The trials were ongoing for another year [54,55]. The agent was withdrawn voluntarily by its manufacturers in 2005, after three cases of progressive multi-focal leucoencephalopathy (PML) in patients with MS and Crohn's disease were reported [5,56,57]. PML is an infection of cells in the CNS with the human polyoma virus JC (JCV). In 2006, natalizumab was reintroduced. It is approved for relapsing forms of MS in the United States [58] and for highly active forms of RRMS (defined as failed response to other therapeutics such as IFN-β or GA, or if disease is evolving rapidly) [58,59].

Potential side effects are common and can be observed in about 10% of all patients. Side effects include fever, joint pains, headache, dizziness, depression, vaginitis, gastroenteritis, feeling or being sick and sore throat [60]. Herpes infections have also been reported in MS patients under natalizumab therapy, but it is unclear that there is an increased incidence compared to the general population [61].

Severe side effects and complications include PML, allergic reactions and liver disorders. Recently, risk stratification for patients with MS on natalizumab became possible. Specifically, a positive anti-JCV antibody status reflecting infection with JCV [62], previous treatment with immunosuppressants such as mitoxantrone or cyclophosphamide and treatment duration with natalizumab (more than 24 monthly infusions) were determined to be correlated with a higher risk of PML. The risk differs from fewer than one in 10 000 in patients with no risk factors to up to 11 in 1000 in patients with positive JCV status, previous treatment with immunosuppressants and treatment duration longer than 24 months [63]. Recently, a trial investigating the accuracy of JCV seropositivity revealed that there is a false negative rate of JCV in the serum of 37% when compared with the virus load in the urine. Thus, a negative JCV test may underestimate the rate of JCV latency in a given individual [64]. Regular monitoring warrants for clinical signs for PML and JCV testing should be repeated in negative patients every 6 months. Upon suspicion of PML, treatment with natalizumab should be terminated immediately. The clinical and imaging diagnosis of PML should be confirmed by MRI scan, cerebrospinal fluid (CSF) and polymerase chain reaction (PCR) testing for JCV. In cases with suspected PML and absence of JCV copies by PCR in CSF, a brain biopsy could be considered. Plasma exchange is often performed to accelerate the elimination of natalizumab. However, there is no evidence that the use of plasma exchange favourably alters clinical outcomes. In addition, nearly all PML patients develop paradoxical deterioration after termination of natalizumab. Responsible for this deterioration is the immune reconstitution inflammatory syndrome (IRIS), which is known from cases of PML in AIDS patients. In this situation, the use of glucocorticosteroids is recommended [65,66].

Further side effects include liver dysfunction with an increase of liver enzymes and an increase of bilirubin. These effects can be observed typically within days of treatment initiation [60], although delayed reactions have also been described [67]. Even in the absence of relevant clinical signs, liver enzymes should be tested prior to treatment, after 1 month and after 3 months of therapy initiation. Complete blood counts with cell differential, as well as platelet count, should be determined 1, 3 and 6 months after initiation, and every 6 months thereafter [60] (see Table 1). Skin cancers have been reported under treatment with natalizumab [68,69].

Persistent anti-idiotypic antibodies against natalizumab (detected at two time-points) will prevent the drug from being efficient. Thus, therapy has to be terminated. In the case of anaphylaxis or allergic reaction, neutralizing antibodies are typically detectable [54]. The prevalence of neutralizing antibodies appears higher in patients in whom natalizumab therapy was stopped within 6 months of initiation and then restarted later. Because of the risk of allergic reaction, post-infusion observation for 1 h is recommended.

Well-controlled trials in pregnant women are currently lacking. Natalizumab has been assigned a pregnancy category C. In animal studies, a higher rate of abortion was observed at doses seven times the human dose (see Table 2). Natalizumab therapy should be reserved for those patients in whom potential benefits outweigh potential risks [60]. As there is currently no exit strategy for natalizumab that prevents disease reactivation, discontinuation during pregnancy presents its own challenges.

Fingolimod (Gilenya®)

Fingolimod is approved by the FDA for RRMS [70] and in Europe by the European Medicines Agency (EMA) for patients with RRMS and disease activity, despite first-line treatment, or in patients with evolving severe RRMS. It is administered orally as 0·5-mg capsules daily [71]. Fingolimod binds to sphingosine-1-phospate (S1P) receptors on immune cells. Consequently, these immune cells are unable to egress from lymphatic tissue, and subsequently into the CNS [72]. Only lymphocytes that reside within secondary lymphoid organs are affected, which account for approximately 2% of all circulating lymphocytes. In

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