REVIEW ARTICLE

Interdisciplinary Risk Management in the Treatment of Multiple Sclerosis

Joachim Havla, Clemens Warnke, Tobias Derfuss, Ludwig Kappos, Hans-Peter Hartung, Reinhard Hohlfeld

SUMMARY

Background: Multiple sclerosis (MS) is the most common autoimmune disease of the central nervous system. There are at least 150 000 persons with MS in Germany. Recent years have seen the approval of new drugs against MS with various mechanisms of action and differing adverse effect profiles.

Methods: This article is based on pertinent literature retrieved by a selective search in PubMed as well as on documentation of relevant risks and adverse effects in “red hand letters” (information bulletins from pharmaceutical companies to physicians about adverse drug effects) and elsewhere, along with data provided by the German Multiple Sclerosis Competence Network.

Results: In recent years, there have been major advances enabling better, more individualized treatment of patients with MS. Physicians must, however, give due consideration to potentially severe or even life-threatening adverse drug effects. These can include, for example, transaminase elevation (hepatotoxicity), cardio- and nephrotoxicity, or lympho- and leukopenia with a variable risk of infection. Among patients taking natalizumab, the cumulative risk of developing progressive multifocal leukoencephalopathy (PML) may be 1:100 or higher, depending on the individual risk profile. Rare cases of PML have also been seen under treatment with fingolimod and dimethyl fumarate. Moreover, any type of immunosuppressive treatment can, at least theoretically, increase the risk of malignant disease. Secondary autoimmune diseases can arise as well: approximately 35% of patients treated with alemtuzumab develop autoimmune thyroid disease within two years, and 2% of patients who take daclizumab have severe autoimmune dermatological side effects. Teriflunomide, fingolimod, natalizumab, mitoxantrone, interferon β 1-a/b, and daclizumab can all damage the liver. There are also psychiatric, reproductive, and vaccine-associated risks and side effects that must be considered.

Conclusion: Newer drugs for MS have enabled more effective treatment, but are also associated with a higher risk of side effects. Interdisciplinary risk management is needed.

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Starting with the introduction of the first interferon (IFN) β preparations over 20 years ago, the treatment of multiple sclerosis (MS) has been developing at an ever-increasing pace (*eFigure*). Because the improved efficacy of some of the new preparations is associated with greater hazards, risk management plans have been implemented and preparation-specific strategies for treatment monitoring established. Effective monitoring requires close interdisciplinary cooperation.

Immunotherapy

The arsenal of medications for the treatment of MS includes a variety of substances with differing mechanisms of action (*Table 1, eBox 1*). These include B- and T-cell-oriented and cytokine-based immunotherapy as well as treatments that influence the adhesion, chemotaxis, migration, and/or activation and proliferation of immune cells. Apart from advances in efficacy and selectivity, there are now a number of modes of administration. Patients can choose among oral, subcutaneous, intramuscular, and intravenous treatments with various dose intervals, and this has a positive effect on treatment adherence (1).

The primary treatment goals are to reduce flare frequency, delay the onset of disability progression, and slow or halt disability progression. Exhaustive licensing studies (phases I to III) have shown that all MS therapeutics achieve meaningful reductions in flare rate, disability progression, and the computed tomography criteria of MS, e.g., lesion burden, lesion activity (contrast medium uptake), and cerebral atrophy (2). No evidence of disease activity (NEDA), i.e., a period of 1 or 2 years with no flares or progression and no activity on magnetic resonance imaging (MRI), i.e., no new gadolinium-enhancing T1 lesions and no new or enlarging T2 lesions, has been proposed as an overall criterion for treatment success. To lend more weight to tissue damage, or in other words the tissue-protective effect of the treatment, lack of acceleration of physiological cerebral volume reduction has been suggested as an additional criterion (NEDA-4). However, the NEDA criteria have not yet been evaluated in clinical studies and do not take account of all disease-relevant clinical factors (e1–e3). Correspondingly, it remains unclear whether treatment decisions should be based on NEDA criteria. Moreover, no studies (head-to-head studies,

Institute for Clinical Neuroimmunology, Biomedical Center and Hospital, Ludwig-Maximilians-Universität München, Munich: Dr. Havla, Prof. Hohlfeld

Department of Neurology, Faculty of Medicine, Heinrich Heine University Düsseldorf: PD Dr. Warnke, Prof. Hartung FRCP

Department of Neurology, University Hospital Basel: Prof. Derfuss, Prof. Kappos

Munich Cluster for Systems Neurology (SyNergy): Prof. Hohlfeld

NEDA comparisons) have been carried out to compare modern immunotherapeutics with one another or with older preparations. Therefore, despite similarities in study design, the effect sizes of various investigations cannot be compared. Furthermore, the improved efficacy of modern immunotherapeutics may go hand in hand with a higher number of severe risks. With the exception of neutralizing antibodies, there are no laboratory parameters to predict the efficacy of individual treatments. Neutralizing antibodies against natalizumab and, though somewhat controversial, antibodies against interferons are consistently associated with diminished response to treatment. For comprehensive accounts of efficacy and effect strengths, we refer the reader to recently published review articles (3). The focus of our review is on the known adverse drug reactions (ADR) of modern treatments for MS.

Interdisciplinary risk management

The danger of potentially serious and in some cases even fatal side effects necessitates effective risk management and proper monitoring of the MS treatment (4). However, even well-established risk management programs do not offer complete protection. Despite use of a risk management plan, the incidence of progressive multifocal leukoencephalopathy (PML) in patients treated with natalizumab has not yet decreased (e4). We will now discuss the principal categories of important side effects, basing our remarks in part on the treatment recommendations of the Competence Network Multiple Sclerosis (5) and a selective literature review.

Infection risk in immunocompromised patients with multiple sclerosis during immunosuppressive therapy

The extent of global changes in (differential) blood count and changes in lymphocyte subpopulations varies greatly and is dependent on the active substance used. Inferences with regard to the patient's immune competence often cannot be drawn, because the peripheral blood contains only a small proportion (ca. 2%) of the whole reservoir of immune cells. Not picked up, for example, are the immune cells located in the lymph nodes and other lymphatic organs (6). Therefore, the lymphocytes in the peripheral circulation also permit no direct conclusions regarding the risk of rare infectious complications such as PML. Further information on current risk management plans can be found in an article (in German, with an English abstract) by Klotz et al. (4). Treatment with teriflunomide involves only a slight increase in general infection risk, but the levels of leukocytes (–15%) and thrombocytes (–10%) may go down (e5). No instance of PML during teriflunomide treatment has yet been recorded (as of September 2016), but isolated cases of opportunistic infection have been reported:

- *Klebsiella* sepsis
- Intestinal tuberculosis
- Gram-negative sepsis (7, e6).

Dimethylfumarate leads to a mean lymphocyte reduction of ca. 30% (e7) and in 6% of cases to lymphopenia

with absolute lymphocyte counts of $<500/\mu\text{L}$. In individual patients this leukopenia may persist, sometimes leading to infectious complications (e8, e9). Four cases of PML during treatment of MS with dimethylfumarate have been reported so far (Table 2). Treatment with fingolimod can also be associated with susceptibility to infection (8). A direct connection between the extent of lymphopenia—and, in occasional cases, granulocytopenia—and an increased risk of infection under fingolimod treatment has not been demonstrated (8). To date, nine cases of PML have been reported in patients being given fingolimod alone who had not been treated with natalizumab immediately beforehand (Table 2) (9). Furthermore, cases of generalized fatal varicella zoster virus (VZV) infection/reactivation, cases of herpes encephalitis (herpes simplex virus 1, HSV-1), and one case of cerebral cryptococcosis have been reported (10, 11, e10, e11). Very rarely, hemophagocytic syndrome occurs (6, e12–e14). During treatment with natalizumab, in contrast to other drugs used to treat MS, peripheral leukocyte and/or lymphocyte counts do not fall, but rather rise slightly. The composition of the cell populations also changes (12, e15, e16). A significant degree of lymphopenia is not usual, but if it is found the reason must be sought. Plainly the immune functions suppressed by natalizumab are connected with a measurable change in immune surveillance in the central nervous system (CNS), and they may also be important for defense against opportunistic pathogens in the periphery, such as the PML-triggering John Cunningham polyomavirus (JCV) (13, e17). While other infectious complications during treatment with natalizumab are rare, to date (as of June 2016, Biogen) more than 667 cases of PML have been documented in ca. 490 000 patient-years of natalizumab treatment (Table 2). Thus in a specific risk constellation the cumulative risk of the occurrence of PML over time may be $\geq 1/100$, particularly given that the calculation of PML incidence and especially the estimation of individual PML risk can vary (e18). By definition, such a risk constellation represents a frequently occurring ADR (14). Owing to the regular performance of MRI in patients with MS and awareness of this ADR among MS neurologists, cases of PML in this indication are detected with relative reliability. Nevertheless, the diagnosis is not always easy; it may, for example, be difficult to rule out an MS flare associated with a change in treatment. The JCV deoxyribonucleic acid (DNA) polymerase chain reaction (PCR), on which the diagnosis of PML is often crucially based, may yield both false-negative and (more rarely) false-positive results. This, coupled with the rarity of confirmation by biopsy, means there is uncertainty as to the true number of cases (e19). Clinically, the course of PML is characterized by high morbidity and mortality. Recent investigations suggest that early diagnosis of PML, ideally prior to its clinical manifestation by cranial MRI (cMRI) screening, may be associated with an improved prognosis (Dear Healthcare Provider Letter [Rote Hand Brief], Biogen, 11 March 2016). Apart from PML, cases of herpes encephalitis have been described during treatment with natalizumab (15).

TABLE 1

Overview of the drugs used to treat multiple sclerosis

Drug	Route and frequency of administration	Side effects
Interferon β -1b	Subcutaneous, every 2 nd day	Influenza-like symptoms, transaminase elevation, injection site reactions, neutralizing antibodies, occurrence or worsening of depressive symptoms
Interferon β -1a	Intramuscular, 1 $\times$ weekly	Influenza-like symptoms, transaminase elevation, injection site reactions, neutralizing antibodies, occurrence or worsening of depressive symptoms
Interferon β -1a	Subcutaneous, 3 $\times$ weekly	Influenza-like symptoms, transaminase elevation, injection site reactions, neutralizing antibodies, occurrence or worsening of depressive symptoms
Pegylated interferon β -1a	Subcutaneous, every 14 days	Influenza-like symptoms, transaminase elevation, injection site reactions, neutralizing antibodies, occurrence or worsening of depressive symptoms
Glatiramer acetate	Subcutaneous, daily or 3 $\times$ weekly	Injection site reactions, post-injection systemic reaction
Dimethylfumarate	Oral, 2 $\times$ daily	Flushing, diarrhea, upper abdominal pain, lympho-/leukopenia, very rarely PML
Fingolimod	Oral, daily	Transaminase elevation, bradyarrhythmia, macular edema, PRES, rarely opportunistic infections (cryptococcosis, PML)
Teriflunomide	Oral, daily	Transaminase elevation, teratogenicity, TEN
Natalizumab	Intravenous, monthly	PML, HSV encephalitis, hepatotoxicity
Alemtuzumab	Intravenous, yearly	Secondary autoimmune diseases (thyroid gland, ITP, glomerulonephritis), herpes reactivation, <i>Listeria</i> meningitis
Daclizumab	Subcutaneous, monthly	Transaminase elevation, skin reactions, infections, gastrointestinal problems, occurrence or worsening of depressive symptoms
Mitoxantrone	Intravenous, every 3 months	Transaminase elevation, cumulative cardiotoxicity, (promyelocytic) leukemia

For many adverse drug reactions (ADR), it is not possible to formulate concrete rates based on clinical practice. The side effects listed represent only a selection of the possible side effects and should be paid particular attention.

ITP, immunothrombocytopenic purpura; HSV, herpes simplex virus; PML, progressive multifocal leukoencephalopathy; PRES, posterior reversible encephalopathic syndrome; TEN, toxic epidermal necrolysis

Current incidence figures and recommendations for minimizing the risk of PML can be found in the *eTable and eBox 2*. Administration of alemtuzumab is followed first of all by depletion of B and T cells in peripheral blood. Because of the lasting treatment-associated depletion of immune cells, which is not amenable to influence after drug administration, a hematologist must be consulted in the event of persisting abnormal findings such as a thrombocyte concentration of more than 100 000/ μ L or cytopenias that do not follow the usual kinetics of repopulation. In line with the mechanism of action, a higher rate of infections is to be expected predominantly in the first 6 months after infusion. Prophylactic administration of aciclovir for 4 weeks is recommended after an infusion cycle. Occasional cases of severe VZV infection or reactivation of a latent virus infection (16, 17, e20), tuberculosis, spirochete gingivitis, *Pasteurella* infection, esophageal candidiasis, *Listeria* meningitis, and nocardiosis have been described (6, 18, 19, e21, e22). One case of so-called carry-over PML after prior natalizumab treatment with a fatal outcome has been reported to date (as of June 2016, Genzyme). In the licensing studies for daclizumab, leukopenia <3000/ μ L was documented in 6% and lymphopenia <500/ μ L in 2% of patients. However, opportunistic infections have not yet been described. Severe infections such as sepsis, pneumonia, appendicitis, cellulitis, urinary tract infection, and viral infections

occurred in <5% of those concerned. During treatment with mitoxantrone all blood cells are greatly reduced. Heightened clinical vigilance with regard to opportunistic infections is thus essential; for example, cMRI and CSF testing in the event of atypical infections or unexplained neurological deterioration.

Secondary autoimmune diseases

Around 35% of patients treated with alemtuzumab develop an autoimmune disease of the thyroid gland within the first 48 months. Both hyper- and hypothyroidism are possible. In most patients with mild or moderate disease the prognosis is favorable. This complication reaches its peak in the third year of treatment. For this reason, patients must be monitored clinically and by means of laboratory tests for at least 48 months following the last infusion of alemtuzumab, independent of their anti-thyroid peroxidase (TPO) antibody status before the inception of treatment. A further autoimmunological risk is nephropathy, including anti-glomerular basal membrane disease (a-GBM). In studies, nephropathy occurred in ca. 0.3% of patients, a rate classed as "occasional" by the German Federal Institute for Drugs and Medical Devices (BfArM). Signs of nephropathy, such as an elevated blood creatinine level, hematuria, and/or proteinuria should prompt immediate consultation of a nephrologist. In addition, immunothrombocytic purpura (ITP, acute Werlhof disease) has been observed in around 1% of

TABLE 2

Drugs licensed for multiple sclerosis with which progressive multifocal leukoencephalopathy has been observed

Drug	Number of cases observed on monotherapy	Current number of cases of PML per 1000 patients treated ^{*1}	Source
Natalizumab	667 cases of PML (664 MS, 3 Crohn's disease)	667/152 500 = 4.22/1000 patients (as of June 2016)	hcp.biogen-international.com/tysabri_update.aspx?ID=22076 (as of June 2016)
Fingolimod	9 cases of PML ^{*2}	9/160 000 = 0.056/1000 patients (as of October 2016)	Novartis, data on file (as of October 2016)
Dimethylfumarate	4 cases of PML ^{*3}	4/170 000 = 0.0235/1000 patients	Biogen, homepage Tecfidera (as of May 2016)

All numbers are based on data from the manufacturer. There may be slight inconsistencies arising from differences in calculation methods.

MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy

^{*1} The number of cases per 1000 patients should be understood as only a rough indication of the therapeutic risk, as it does not adequately portray the cumulative risk during long-term treatment or the change in risk when treatment is discontinued. Furthermore, factors known to influence the individual risk, e.g., during treatment with natalizumab, are not considered. Please refer to the *eTable and eBox 2* for details of risk stratification and risk management during treatment with natalizumab.

^{*2} In addition to these nine cases of PML on fingolimod, at least nine cases of so-called carry-over PML have been reported in which PML was reported shortly after switching from natalizumab to fingolimod (as of June 2016). These cases of PML are thus attributed to natalizumab.

^{*3} Several cases of PML have been reported in association with fumarate derivatives prescribed for other indications, e.g., psoriasis. In most of these cases, however, comorbidity and comedication meant that there was no unambiguous causal connection between fumarate and the development of PML

patients treated with alemtuzumab. Occasional cases of autoimmune hepatitis and colitis have been described during treatment with daclizumab, possibly indicating that this drug does not always boost immunoregulatory mechanisms but may sometimes weaken them. A BfArM communication in August 2014 reported an accumulation, in patients treated with IFN β 1-a/b, of cases of thrombotic microangiopathy (TMA), some with fatal outcome, and of nephrotic syndrome with various underlying nephropathies.

Dermatological risks

Of patients treated with daclizumab, 30 to 70% experience cutaneous side effects and 2% suffer severe autoimmune dermatological side effects (20). The most frequently observed adverse effects, such as exanthema and eczema, have no local relationship to the injection sites. They may be persistent, and there may be a long latency period between treatment and adverse effect (20). At the beginning of treatment with IFN β 1-a/b or glatiramer acetate, the skin may exhibit irritation at the injection site. Lipoatrophy may occur on long-term administration of glatiramer acetate.

Hepatotoxicity

Acute or chronic liver damage with elevation of transaminases may be diagnosed in patients being treated with teriflunomide, fingolimod, natalizumab, mitoxantrone, IFN β 1-a/b, or daclizumab. Isolated cases of fulminant liver failure have also been described, e.g., in a patient treated with IFN β 1-a (e23). For this reason, close monitoring of the liver function parameters glutamate-pyruvate transaminase (GPT) and γ -glutamyl transferase (γ -GT) is necessary, particularly in

the early phase of treatment. If the transaminase levels continue to rise and reach 3 to 5 times the upper limit of normal (ULN), treatment should be interrupted or discontinued (4).

Cardiac risks

Cardiac and circulatory risks play a role particularly in treatment with fingolimod, teriflunomide, and mitoxantrone. The heart rate may decrease following the first dose of fingolimod and should therefore be monitored for the first 6 h (21). Moreover, the blood pressure may be slightly elevated by fingolimod and teriflunomide. Mitoxantrone is known to be a cause of considerable cardiotoxicity, particularly in doses over 140 mg/m² body surface area (BSA), but occasional cases of cardiotoxicity have been described in patients with lower total life doses (e24). Cardiac pump function must therefore be closely monitored by means of echocardiography before and during treatment with mitoxantrone. In the event of a 10% reduction, or the occurrence of any absolute value below 50% of the ejection fraction, the treatment should be interrupted or discontinued.

Pulmonary risks

Some drugs used against MS are suspected to be associated with lung pathology. Individual cases of severe interstitial lung disease were reported in patients treated with leflunomide, the precursor of teriflunomide. Vigilance is therefore advisable when using the latter drug. In addition, fingolimod may reduce the forced expiratory volume in 1 s and the diffusion capacity. However, no link has been shown between pulmonary disease and intake of fingolimod (22).

Vaccinations

Various aspects of vaccination in MS patients merit attention:

- Therapeutic immunosuppression may be accompanied by a higher risk of infection with diseases preventable by vaccination.
- The success of vaccination may be reduced by immunosuppression.
- Vaccination may increase disease activity.
- Vaccination may be more hazardous owing to the impairment or suppression of immune defenses, particularly if live vaccines are used.

Nevertheless, the recommendations for vaccination with dead vaccines and toxoids in healthy persons are valid also for MS patients. Attenuated live vaccines, on the other hand, should be avoided if possible, although the individual risk of infection should be taken into account. The success of every vaccination should be verified and the vaccination repeated if the response is found to be inadequate. Information on the response to influenza vaccine can be found in *Table 3* (23–26, e25). A review of vaccination recommendations was recently published by Williamson et al. (27).

Polyneuropathy

In the TEMSO and TOWER studies (teriflunomide), neuropathy was diagnosed in 1.9% (versus 0% in the placebo group) and 2.5% (versus 1.1% in the placebo group) of the patients treated with teriflunomide (e6, 28).

Nephrotoxicity

Nephropathy, both acute and chronic, has been described in individual case reports of treatment with teriflunomide. In the licensing studies, acute renal failure was diagnosed in 1.2% of the patients treated with this drug. However, renal function returned to normal in all patients within 48 days at most and with no specific intervention, despite continuation of teriflunomide treatment. Dimethylfumarate was also shown to affect kidney function in clinical studies. Monitoring of renal function should therefore include urine analysis together with determination of creatinine, glomerular filtration rate, and, if indicated, cystatin C. Nephropathy has also been reported during treatment with IFN β 1-a/b.

Risk of malignancy

An increased risk of cancer is a theoretical possibility in all immunosuppressive treatments. The relatively small absolute case numbers make it difficult, however, to provide a statistical basis for this hypothesis. Accordingly, no elevated risk of malignancy has yet been confirmed for dimethylfumarate, teriflunomide, alemtuzumab, natalizumab, or fingolimod (29). Nevertheless, 13 cases of basal cell carcinoma and six cases of melanoma occurred in the licensing studies for fingolimod. After approval of this drug, further isolated cases of skin tumors (e26, 30) and lymphomatous disease (B- and T-cell lymphomas,

TABLE 3

Response to influenza vaccinations in patients on various treatments for multiple sclerosis

Treatment	Response to influenza vaccination
Interferons	Unchanged vaccination response (23)
Glatiramer acetate	H3N3 2010: 41.7% (GA) versus 79.5% (untreated HC) (23)
Teriflunomide	Slightly reduced response (24)
Dimethylfumarate	No studies in MS
Fingolimod	43% (fingolimod) compared with 75% (placebo) (25)
Mitoxantrone	H1N1 2009: 0% (mitoxantrone) versus 43.5% (untreated HC) (23)
Natalizumab	Inconsistent results: reduction of vaccination response (23.5% [natalizumab] versus 43.5% [untreated HC]) or unchanged response (23)
Alemtuzumab	Debatable no reduction in vaccination response; vaccination against influenza is expressly recommended, possibly with repeat vaccination if the titer is too low: all vaccinations in patients on alemtuzumab should be given at least 6 months after the most recent infusion (26)
Daclizumab	No studies in MS

GA, glatiramer acetate; HC, healthy controls; MS, multiple sclerosis

lymphomatoid papulosis) were publicized (31, e27). Female patients treated with alemtuzumab should be tested annually for human papilloma virus (HPV) to minimize the risk of cervical dysplasia. Leukemia has been reported as an acute or late complication of treatment with mitoxantrone (32, e28, e29).

Ophthalmological risks

Ophthalmological risks have been reported only for fingolimod. During the licensing studies and thereafter, cases of macular edema occurred (incidence 0.5 to 0.7%) (e30, e31). As a rule the macular edema resolved after discontinuation of fingolimod; in individual cases the treatment could be continued under close ophthalmological observation (e32, e33).

Pregnancy

All drugs used for treatment of MS are contraindicated, or at least restricted, during pregnancy and breastfeeding. Nevertheless, the increasing number of pregnancy registries supply empirical data that aid decision making in individual situations. *Table 4* provides an overview of the available information on teratogenicity, fertility, passage into breast milk and the placenta, and breastfeeding (33–36).

Pharmacological interactions

Pharmacological interactions are known particularly for teriflunomide. Potent cytochrome-P450 (CYP) inducers reduce the teriflunomide concentration. Teriflunomide inhibits CYP2C8 and organic anion transporter 3 (OAT3) and weakly induces CYP1A2. Correspondingly

TABLE 4

Treatments for multiple sclerosis during pregnancy and breastfeeding (35, 36)

FDA classification	Glatiramer acetate B	IFN β 1-a/b C	Natalizumab C	Fingolimod C	Dimethylfumarate C	Teriflunomide X	Alemtuzumab C	Mitoxantrone D
Fertility	No negative effects in rats No controlled studies in humans	Irregular menstruation in guinea pigs; increased abortion rate in monkeys No properly controlled studies in humans	Reduced fertility in guinea pigs; increased abortion rate in monkeys No properly controlled studies in humans	Reduced gestation rate in rats Not reported in humans	Not reported in animals Not reported in humans	No signs of impaired fertility in male and female rats Not reported in humans	Data from animal studies showed effects on the fertility of humanized mice	No negative effects in rats and rabbits Chemotherapy induced amenorrhea in humans
Teratogenicity	No malformations in rats and rabbits	No malformations in monkeys	No negative effects in monkeys; slight reduction in size of offspring in guinea pigs	Fetal malformations in rats Not reported in humans	Fetal malformations in rats Not reported in humans	Fetal malformations in rats and rabbits Not observed in humans	Embryotoxic in mice	Retarded fetal growth in rats; no teratogenic effects in rabbits Potentially teratogenic in humans owing to the mechanism of action
Transfer through the placenta	Unlikely MW = 5000–9000 Da	Unlikely MW = 18 500–22 500 Da	Yes (in guinea pigs)	Yes	Not reported	Yes (in animals)	Alemtuzumab can pass through the placental barrier	Possible
Passage into breast milk	Unknown/unlikely	Unknown	Yes: IgG4 in second and third trimester	Yes	Not reported	Unknown	Alemtuzumab was transferred to newborn mice via breast milk	Yes
Breastfeeding	Discuss potential risk with patient	Not recommended; discuss potential risk	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended	Not recommended

There are insufficient data on daclizumab. For the latest recommendations on treatment of MS during pregnancy and the breastfeeding period, the reader is referred to the regularly updated expert consensus of the Competence Network Multiple Sclerosis (www.kompetenznetz-multiplesklerose.de).
FDA, Food and Drug Administration; IFN, Interferon; MW, molecular weight; MS, multiple sclerosis

Correspondingly metabolized drugs should be avoided if at all possible. IFN β 1-a/b seems to reduce the activity of CYP-dependent liver enzymes.

Psychiatric risks

Patients treated with IFN β 1-a/b or daclizumab must be monitored for the occurrence or worsening of symptoms of depression. However, depression is only a relative contraindication for these drugs.

Conclusion

The growing number of drugs used to treat MS demands even greater efforts to minimize the potential risks. To this end, interdisciplinary risk management plans are essential. Such plans take account of the type and extent of risks, describe the measures needed for prevention and early detection, and provide practical advice for the necessary monitoring. Individual risk management represents a first step towards individualized treatment. Supplementary information on the risk management plans currently in use can be found in the cited literature (4, 5, e34).

Conflict of interest statement

Dr. Havla has received consultancy fees from Novartis, Genzyme, and Biogen. He has received reimbursements of congress attendance and travel costs from Novartis, Biogen, Merck Serono, and Bayer.

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Prof. Derfuss has shares in Novartis. He has received consultancy fees from Biogen, Merck Serono, Bayer, Novartis, Roche, Mitsubishi Pharma, Genzyme, and Geneuro. Congress attendance and travel costs have been reimbursed by Biogen, Genzyme, Novartis, Bayer, and Merck Serono. He has received lecture fees from Biogen, Genzyme, Novartis, Bayer, Merck Serono, and Roche. He has been the beneficiary of study support (third-party funds) from Biogen, Novartis, Geneuro, and Roche.

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KEY MESSAGES

- The increasing variety of treatment options for multiple sclerosis (MS) requires knowledge and management of an expanding range of risks.
- Some of the new-generation drugs for treating MS lead to substance-specific adverse drug reactions (ADR).
- Risk management plans for the monitoring of treatment are an important instrument in minimizing the individual risks of MS treatment.
- Close interdisciplinary cooperation is necessary to achieve this goal.
- Registry studies are required to document rare ADR and identify associated surrogate parameters.

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Corresponding author

Dr. med. Joachim Havla
Institut für Klinische Neuroimmunologie
Biomedizinisches Zentrum und Klinikum der Ludwig-Maximilians Universität
Marchioninistr. 15, 81377 München, Germany
Joachim.Havla@med.lmu.de

Supplementary material
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Interdisciplinary Risk Management in the Treatment of Multiple Sclerosis

by Joachim Havla, Clemens Warnke, Tobias Derfuss, Ludwig Kappos, Hans-Peter Hartung, and Reinhard Hohlfeld

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eTABLE

Risk stratification of progressive multifocal leukoencephalopathy*

Positive anti-JCV antibody status Estimated risk of PML per 1000 patients			
Natalizumab treatment (duration in months)	Antibody index ≤ 0.9	Antibody index $>0.9 \leq 1.5$	Antibody index >1.5
1–12	0.1	0.1	0.2
13–24	0.1	0.3	0.9
25–36	0.2	0.8	3
37–48	0.4	2	7
49–60	0.5	2	8
61–72	0.6	3	10
Negative anti-JCV antibody status Estimated risk of PML per 1000 patients: 0.1			

* Current risk stratification by means of John Cunningham virus (JCV) serology for patients being treated with natalizumab (e44)
PML, Progressive multifocal leukoencephalopathy

eFIGURE

Ever since the licensing of the first interferon β preparation in 1995, the number of preparations available for the treatment of relapsing-remitting multiple sclerosis has grown constantly. In parallel, the treatment goals have become more ambitious. Flare reduction and slowing of disability progression remain the primary aims, but stability of MRI findings is also a goal (NEDA 3 und 4).

DMF, dimethylfumarate; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; IFN, interferon; i.m., intramuscular; i.v., intravenous; MRI, magnetic resonance imaging; MSFC, Multiple Sclerosis Functional Composite; NEDA, no evidence of disease activity; PEG-IFN, pegylated interferon; p.o., per os; s.c., subcutaneous

eBOX 1

Brief descriptions (risks, adverse drug reactions)*

- **Interferon β** (IFN β 1-b, s.c., 1995/2008; IFN β 1-a, s.c., 1998; i.m., 1996; PEG-IFN β 1-a, s.c., 2014) has a number of immunomodulatory properties, but bears no increased risk of infection or cancer. Very occasionally, cases of thrombotic microangiopathy have been observed.
- **Glatiramer acetate** (2001; s.c.) exerts a modulatory action on both the antigen-dependent (adaptive) and the antigen-independent (innate) immune system. The side effect profile is benign; there are no signs of increased risk of infection or cancer. The principal side effects are cutaneous and (very rarely) systemic hypersensitivity reactions (37).
- **Dimethylfumarate** (2014, p.o.) is a first-line treatment for relapsing-remitting multiple sclerosis (MS) (e35, e36). Dimethylfumarate was developed from a fumarate established since 1994 in the treatment of psoriasis. The precise mechanism of action has not been conclusively clarified. A suppressive effect on the lymphocyte count is detectable. Anti-inflammatory and neuroprotective effects are debated (e35, e36). Gastrointestinal intolerance, flushing, and an increased risk of infection are the most important side effects recognized so far (e37). To date, four cases of progressive multifocal leukoencephalopathy (PML) have been reported in patients treated with dimethylfumarate. For this reason, interruption or discontinuation of treatment is recommended in the presence of persistent leukopenia $<3000/\mu\text{L}$ or lymphopenia $<500/\mu\text{L}$. At lymphocyte counts between 500 and $700/\mu\text{L}$ (grade 2 lymphopenia), close monitoring of the blood count and increased clinical and magnetic resonance imaging (MRI) vigilance are recommended (4).
- **Teriflunomide** (2014, p.o.) was developed from leflunomide (1999), a substance used in the field of internal medicine and rheumatology. In February 2014, teriflunomide was licensed for the treatment of adults with relapsing-remitting MS. It is a member of the malononitrilamide family and blocks the mitochondrial enzyme dihydroorotatedehydrogenase (DHODH). This results in preferential inhibition of rapidly proliferating, activated T and B cells (28, e6). The side effects include, among others, hepatotoxicity, nephrotoxicity, impairment of bone marrow function, and possibly an increased risk of infection as well as fatal toxic epidermal necrolysis (TEN) (e38). To minimize the risk of opportunistic infections, teriflunomide should be discontinued at an absolute lymphocyte count $<200/\mu\text{L}$. Elimination of teriflunomide, and thus restoration of immunocompetence, can be accelerated by administration of cholestyramine ($3 \times 8 \text{ g}$ per day for 11 days) or activated charcoal ($2 \times 50 \text{ g}$ per day for 11 days).
- **Natalizumab** (2006, i.v.) is licensed in Germany for the treatment of highly active MS. Natalizumab is a humanized monoclonal antibody to the $\alpha 4$ chain of the very late antigen (VLA)-4 integrin. The transmigration of immune cells through the blood–brain barrier is inhibited (e39–41). The principal risk of treatment with natalizumab is PML, a potentially fatal opportunistic infection of the brain.
- **Fingolimod** (2011, p.o.) has been licensed for the treatment of active MS. The substance is a modulator of the sphingosine-1-phosphate (S1P) receptor and brings about retention of certain lymphocyte populations in lymphatic organs (e30, e31). To date, nine cases of PML have been reported in MS patients on fingolimod, together with at least nine cases of so-called carry-over PML in which PML was diagnosed shortly after natalizumab was replaced by fingolimod. These latter cases have been attributed to the previous treatment with natalizumab. If persistent lymphopenia $<200/\mu\text{L}$ occurs in a patient being treated with fingolimod, the policy in Germany is first to confirm the count and then to interrupt or end treatment. The side effect profile comprises increased risk of infection, cardiac conduction disorders, macular edema, and possibly basal cell carcinoma.
- **Alemtuzumab** (2013, i.v.), a humanized monoclonal antibody, is directed against cluster of differentiation (CD)52. CD52 is a protein marker expressed on most leukocytes, particularly on all T and B cells. Alemtuzumab has been licensed for the treatment of relapsing-remitting MS. Antibody-mediated cytotoxicity leads to massive transient depletion of circulating immune cells followed by gradual repopulation, with B cells and monocytes appearing first, then T cells. The principal side effects are infusion reactions, increased risk of infection, and treatment-associated secondary autoimmune diseases (16, e21, e42, e43). Secondary thrombocytopenia may result from treatment-induced idiopathic thrombocytopenic purpura in ca. 1% of cases, and ca. 35% of patients may develop autoimmune disease of the thyroid gland within the first 48 months of treatment.
- **Daclizumab HYP** (2016, s.c.) is a humanized monoclonal antibody to CD25, a subunit of the interleukin-2 receptor. Daclizumab has complex immunomodulating properties; for instance, it inhibits activated T lymphocytes. The side effect profile includes increased risk of infection, skin reactions (exanthema, eczema), hepatotoxicity, and possibly inflammatory intestinal disease (38).
- **Mitoxantrone** (2003, i.v.) is licensed for use in the event that other drugs fail to contain severe, rapidly progressing MS. Mitoxantrone is an anthracenedione and causes single- and double-strand breaks in deoxyribonucleic acid (DNA), particularly in proliferating cells such as the B cell series. Owing to the cardiotoxicity of mitoxantrone, there is currently a lifetime upper dose limit of 140 mg/m^2 body surface area (BSA) in Germany. In addition, cases of secondary leukemia have been reported during and after treatment with mitoxantrone.

* For efficacy data of all preparations (number needed to treat, NNT) (39)
i.m., intramuscular; i.v., intravenous; p.o., per os; s.c., subcutaneous

eBOX 2

Risk management of progressive multifocal leukoencephalopathy during treatment with natalizumab

Summary of current risk stratification during treatment with natalizumab according to the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) (e44):

- Early detection of progressive multifocal leukoencephalopathy (PML) is associated with an improved prognosis for the patient.
- Clinically asymptomatic PML is more often associated with higher survival rates and improved prognosis than symptomatic PML.
- Regular magnetic resonance imaging (MRI) examinations are advisable to diagnose PML as early as possible.
- In patients who have not previously received immunosuppressive treatment and are anti-John-Cunningham-virus (JCV)-antibody positive, the anti-JCV-antibody index is associated with the risk of PML.
- The risk of developing PML is slight with an antibody index ≤ 0.9 .
- With an antibody index >1.5 and in patients treated with natalizumab for more than 2 years, the risk is much higher.
- The patients at highest risk of PML are those in whom anti-JCV antibodies have been demonstrated in combination with natalizumab treatment for more than 2 years and previous immunosuppressive therapy.
- Patients with a high antibody index and more than 2 years' natalizumab treatment but no previous immunosuppressive therapy are also at high risk.