

Management of disease-modifying treatments in neurological autoimmune diseases of the central nervous system

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Summary

The therapeutic armamentarium for autoimmune diseases of the central nervous system, specifically multiple sclerosis and neuromyelitis optica, is steadily increasing, with a large spectrum of immunomodulatory and immunosuppressive agents targeting different mechanisms of the immune system. However, increasingly efficacious treatment options also entail higher potential for severe adverse drug reactions. Especially in cases failing first-line treatment, thorough evaluation of the risk–benefit profile of treatment alternatives is necessary. This argues for the need of algorithms to identify patients more likely to benefit from a specific treatment. Moreover, paradigms to stratify the risk for severe adverse drug reactions need to be established. In addition to clinical/paraclinical measures, biomarkers may aid in individualized risk–benefit assessment. A recent example is the routine testing for anti-John Cunningham virus antibodies in natalizumab-treated multiple sclerosis patients to assess the risk for the development of progressive multi-focal leucoencephalopathy. Refined algorithms for individualized risk assessment may also facilitate early initiation of induction treatment schemes in patient groups with high disease activity rather than classical escalation concepts. In this review, we will discuss approaches for individualized risk–benefit assessment both for newly introduced agents as well as medications with established side-effect profiles. In addition to clinical parameters, we will also focus on biomarkers that may assist in patient selection.

Keywords: monoclonal antibodies, multiple sclerosis, neuromyelitis optica, progressive multi-focal leucoencephalopathy

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Introduction

Multiple sclerosis (MS) and neuromyelitis optica (NMO) are two distinct chronic progressive inflammatory diseases

of the central nervous system (CNS) with different pathophysiology and epidemiology. Both are commonly associated with disability, impairment in quality of life, decreased work capacity and high socioeconomic burden [1–4].

Table 1. Drugs and reported (severe) adverse reactions.

Drug	Reported adverse reactions
Alemtuzumab	Leucopenia [71], infusion reactions, infections (herpes viruses, tuberculosis), immune-thrombopenia, thyroiditis, nephritis (Goodpasture syndrome), cancer (thyroid, colon, vulvar) [10–12]
Daclizumab	Elevated liver enzymes, cutaneous symptoms including severe dermatitis, infections [14,22]
Dimethylfumarate	Gastrointestinal symptoms, flushing, lymphopenia, proteinuria, pruritus [123,124]
Eculizumab	Meningococcal infection and sepsis [27], other infections, infusion reactions, pain (headache, arthralgia, myalgia, back, neck), leucopenia, thrombopenia, anaphylactic and cutaneous reactions, dizziness and vertigo, hypertension, oedema, gastrointestinal symptoms, paraesthesia [161]
Fingolimod	Elevated liver enzymes, gastrointestinal symptoms, viral infections (herpes viruses, influenza), other infections (upper respiratory tract), cardiac arrhythmia, macula oedema, dermal malignancy, lymphopenia, pain (head, back) [9,18], respiratory effects [105], haemophagocytic syndrome
Mitoxantrone	Elevated liver enzymes [162], gastrointestinal symptoms, transient alopecia [130,163], infections [145], neutro-/eosinophilia [164,165], systemic/cutaneous symptoms [164,165], teratogenicity, transient/permanent infertility [162], amenorrhoea [130,166], anaemia/leucopenia/thrombopenia [37,162], cardiotoxicity [36,143,150,153,155,167], TRAL [36,37,137,138,142,147–149,159,168]
Natalizumab	Elevated liver enzymes, gastrointestinal and cutaneous symptoms, pain (muscular, headache, arthralgia), dysmenorrhoea, infections, infusion reactions, hypersensitivity [169], neutralizing antibodies [170], PML [35,45,169], melanoma [171]
Rituximab/CD20-antibodies	Infusion reactions, hypotension, anaphylactic and cutaneous reactions, cytokine release, acute respiratory distress syndrome, cardiac events, infections (bacterial, viral) [102], PML [100]
Teriflunomide	Elevated liver enzymes, gastrointestinal symptoms, alopecia, neutro-/lymphopenia, infections (urinary tract, pyelonephritis, nasopharynx), pain (back, arthralgia), paraesthesia [116,117]
Tocilizumab	Elevated liver enzymes, increased cholesterol levels, gastrointestinal and cutaneous symptoms, headache, hypertension, infusion/injection site reactions, hypersensitivity, infections (respiratory tract, pneumonia), neutropenia, thrombopenia, neutralizing antibodies [172–174]

PML = progressive multifocal leucoencephalopathy; TRAL = therapy-related acute leukaemia.

The pathophysiology of MS is complex and highly heterogeneous with both inflammatory and neurodegenerative features [5], resulting in various phenotypes and disease courses.

In contrast, the discovery of aquaporin-4 immunoglobulin (Ig)G as an autoantibody with pathogenetic relevance for NMO [6,7] had a direct impact on therapeutic approaches.

As most immunotherapies in neuroimmunology have been studied in MS [8–22] and – to a lesser extent – in NMO [23–27], this review focuses on disease-modifying drugs (DMDs) for these autoimmune CNS entities. Treatment options for other neuroimmunological diseases of the central or peripheral nervous system and neuromuscular disorders such as neuro-sarcoidosis [28,29], myasthenia gravis [30] or chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [31] have been reviewed in [32,33].

Whereas first-line agents used in MS such as interferons and glatirameracetate exhibit moderate efficacy, we have witnessed several decades of use with highly favourable safety profiles [34]. In contrast, newer agents have surprised us with unexpected and sometimes even severe adverse drug reactions (SADR) or unanticipated high frequency of SADRs (Table 1) [35–37].

Due to the hypothesized selective mechanisms of action, fewer side effects were anticipated for different therapeutic monoclonal antibodies (mAb) coined initially as ‘magic bullets’ [38]. Rare but occasionally fatal adverse drug reac-

tions have evolved; however, their pathophysiology is still not well explained. Based on potential SADRs, approval for substances such as natalizumab (NAT), mitoxantrone (MX) and – at least in some countries – fingolimod (FTY) was restricted to patients refractory to first-line MS treatment options or with highly aggressive disease course; but labelling is different from the formal inclusion criteria of respective clinical trials. In addition, restriction to escalation therapy may carry the risk of omission bias, i.e. the decision not to treat patients with potential high benefit in order not to put them actively at risk for SADRs. In the face of newly introduced highly efficacious treatment options, strategies are thus needed that allow patient selection and counselling based on individualized safety and efficacy considerations. Selected patient groups at risk of rapidly developing high disability may particularly benefit from a ‘hit hard and (relatively) early’ treatment strategy.

Optimization of the benefit-to-risk ratio for individual substances can be achieved on multiple levels, including (a) patient selection according to clinical/paraclinical criteria, (b) optimization of treatment and monitoring protocols, (c) identification of patients at higher risk for SADRs and (d) the development of biomarkers for treatment response and/or risk profile (Fig. 1).

In the following we will discuss these aspects, focusing on treatment of MS and NMO with mAbs (NAT, alemtuzumab, daclizumab and others), FTY, teriflunomide, dimethylfumarate (DMF) and MX.

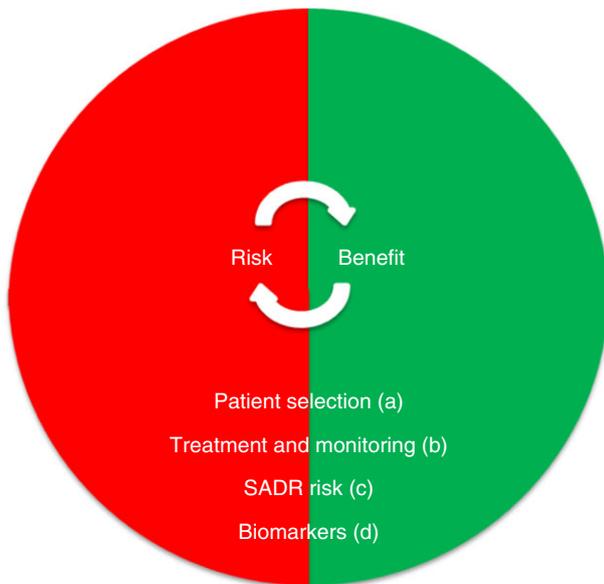


Fig. 1. Factors of risk–benefit assessment.

Monoclonal antibodies

Natalizumab

Patient selection. The alpha-4-integrin-inhibitor natalizumab (Tysabri®) [39] was approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2005/06 for the treatment of highly active forms of the relapsing–remitting disease course (RRMS), but not chronic progressive forms [primary or secondary progressive MS (PPMS, SPMS)]. Efficacy in SPMS is under investigation in a Phase IIIb study, ASCEND in SPMS (A Clinical Study of the Efficacy of Natalizumab on Reducing Disability Progression in Subjects With SPMS; ClinicalTrials.gov NCT01416181). Therapeutic efficacy has also been reported in paediatric cohorts with high disease activity [40,41].

In NMO, the use of NAT should be avoided, as current data suggest negative effects on relapse rate and disease progression as well as severe astrocyte damage in spite of natalizumab treatment [42,43].

Treatment and monitoring. Monthly NAT administration is standard treatment. So far, there are only few data on the prolongation of infusion intervals [44]. The REFINE trial (Exploratory Study of the Safety, Tolerability and Efficacy of Multiple Regimens of Natalizumab in Adult Subjects With Relapsing Multiple Sclerosis (MS); ClinicalTrials.gov NCT01405820) is investigating both different dosing schemes and application routes [intravenous (i.v.), subcutaneous (s.c.)]; thus far, this approach cannot be recommended outside clinical trials.

Safety considerations and monitoring were profoundly influenced by the occurrence of progressive multi-focal leu-

coencephalopathy (PML). This is a relatively rare but potentially fatal (22%) opportunistic viral infection of the CNS which can result in severe disability in 40% of the patients [45]. Epidemiological data on the frequency of NAT-associated PML has shown an increase of PML incidence after a treatment duration of 2 years (i.e. 24 infusions) [45]. Thus, therapy continuation for more than 24 infusions requires updated documented informed consent [46] and re-evaluation of the individual risk–benefit ratio. In addition, adequate counselling of patients and relatives is crucial for the early recognition of symptoms and signs of possible PML, as neuropsychological symptoms may prevail initially.

Regular clinical monitoring and magnetic resonance imaging (MRI) are required to detect symptoms suggestive of PML or suspicious lesions [47]. More frequent MRI scanning should be performed in high-risk patient groups (e.g. 3-monthly after a treatment duration of > 24 months).

SADR risk. Pathogenesis of PML – the most feared potential SADR of NAT – is multi-factorial, comprising cellular immunity of the host [48], reactivation of latent John Cunningham virus (JCV) infection or new infection combined with genetic variation of the virus. Both viral and host factors predisposing for PML development are under investigation. The differentiation between virulent and non-virulent JCV variants may be helpful, but relies on viraemia [49] and so far is not sufficiently validated.

Epidemiological risk factors for PML development are previous use of immunosuppressants, a positive anti-JCV antibody status and treatment duration [45,50–52]. Hence, the estimated PML incidence ranges from $\leq 0.09/1000$ to $11.1/1000$ [45]. A total of 418 NAT-PML cases have been reported (as of November 2013 [53]).

PML must be suspected when new neurological symptoms occur in individuals on NAT therapy. In particular, neuropsychological symptoms and seizures are highly suspicious, whereas spinal or optic nerve symptoms are uncommon. Its diagnosis is based on clinical findings, MRI [47] and the detection of JCV DNA in cerebrospinal fluid (CSF) [35,54], although there are JCV DNA-negative NAT–PML reports [55,56]. In uncertain cases, biopsy of suspicious lesions has to be discussed.

In the course of PML, immune reconstitution inflammatory syndrome (IRIS) can occur with a mean of about 1 month after NAT removal via plasma exchange [57]. This inflammatory reaction directed against JCV can cause additional tissue damage with neurological deterioration after initial improvement after PML diagnosis. NAT and JCV elimination as well as control of IRIS evolution must be covered by PML treatment strategies which comprise plasma exchange, mefloquine, mirtazapine and corticosteroid pulses [35,58]. However, due to relatively low patient numbers, none of these treatment options are evidence-based.

Although the outcome of NAT–PML seems to be better than HIV-associated PML [57], it is associated with disability [45,57]. Seizures occur in more than 50% of patients [59] and are often linked to the appearance of IRIS, explaining the higher rate than in other PML cases; preventive anti-convulsive therapy may thus be beneficial [59].

Biomarkers. Routine anti-JCV antibody testing is established in clinical practice. However, false negative rates have to be considered for both first- and second-generation anti-JCV antibody testing. There is also a considerable proportion of seroconverters and – possibly linked to fluctuating antibody titres at the detection threshold – patients reverting from seropositive to seronegative [45,52,60,61].

The prevalence of anti-JCV antibodies differs in patient groups according to age and gender [52]. Two studies reported antibody titres rather than mere serostatus. In one study, sera from patients who were diagnosed later with PML exhibited higher anti-JCV antibody reactivity than other seropositive patients [52]. In five patients from whom sera prior to PML diagnosis were available, antibody titres increased 5–10 months before PML diagnosis [61]. Methodological issues such as fluctuating serostatus around assay cut-points [52,61] and false negative rates [60] argue for a refinement of assay procedures with better reproducibility in low-antibody reactivity ranges. Thus, a second-generation enzyme-linked immunosorbent assay (ELISA) with a reported sensitivity of 98% [62] was introduced; however, so far an independent validation is lacking. Using this refined assay, the possible value of antibody reactivity for PML risk stratification was reported recently as abstract. Whereas increased immunoreactivity to JCV prior to PML would be biologically plausible, more data are needed to corroborate these initial findings.

Higher NAT plasma levels have been associated with lower body mass index and a supposedly higher risk for the development of PML, which needs to be further confirmed as a possible biomarker feasible for clinical routine [44].

Host factors promoting PML development include the determination of immunocompetence. It has been shown conclusively that both CD4⁺ and CD8⁺ T cells are important in the immune response to JCV and containment of PML [48,63]. Investigation of the role of CD4⁺ T cells has demonstrated a lacking or even anti-inflammatory interleukin (IL)-10 response to JCV in a small number of PML patients [64]. Intracellular adenosine triphosphate (ATP) levels as a functional parameter of T cell function were decreased in CD4⁺ T cells both after long-term NAT treatment and PML of different aetiology [65]. However, this assay was confronted with pre-analytical difficulties, so far impeding application in larger validating studies or clinical routine, as shown by analysis of STRATA samples (Natalizumab Re-Initiation of Dosing; ClinicalTrials.gov NCT00297232) that could not confirm ATP decrease in five pre-PML samples [66]. However, heterogeneous intervals of testing

before PML onset may have influenced these results. It may be hypothesized that individual courses of ATP levels are more critical than absolute ATP level, and that a critical time-point of ATP decrease before PML onset has to be determined.

Recently, a lower proportion of L-selectin-expressing CD4⁺ T cells was associated with higher PML risk in NAT-treated MS patients ($n = 8$). Further validation as a potential biomarker for PML risk stratification is warranted [67]. The determination of its biological plausibility remains unclear thus far, as it might express the general activation status of the peripheral immune system or a defective T cell response to JCV infection on different levels [67].

Lesions suggestive of PML may be detected on MRI before clinical PML manifestation [68], which argues for frequent MRI scanning in patients at high risk for PML evolution such as patients on long-term NAT treatment (> 24 infusions) or with previous immunosuppressive treatment. Characteristic PML lesions have been described as large, subcortical, grey-matter-sparing lesions appearing hyperintense on T2 and fluid-attenuated inversion recovery and hypointense on T1 scans; contrast enhancement may occur [47].

Alemtuzumab

Patient selection. The anti-CD52 mAb alemtuzumab (Lemtrada®) has been shown to be highly effective and is approved for active relapsing MS in Europe [10–12,69]. Disease activity is defined as clinical or radiological deterioration [70]. Mechanisms of action include depletion of CD52-expressing T/B lymphocytes, natural killer (NK) cells, dendritic cells and monocytes/macrophages with skewed repopulation leading to a reprogramming of the immune repertoire [71,72]. Already in earlier studies, patients especially with an early relapsing disease course appeared to benefit most from alemtuzumab treatment, leading to the concept of a therapeutic window relatively early during the disease, when highly active immunotherapy may exert most profound effects [72]. This was reflected in the inclusion criteria for the pivotal Phase III trials CARE-MS I and II (Comparison of Alemtuzumab and Rebif® Efficacy in Multiple Sclerosis, Studies One and Two). CARE-MS I included active relapsing, therapy-naive MS patients, whereas CARE-MS II focused on relapsing MS refractory to first-line therapy [10,12]. Especially in terms of disease progression, the latter patient group appeared to benefit most. Whereas current EMA approval is relatively broad [70], careful patient selection is mandatory, as SADR have been reported and thorough adherence to safety assessments is necessary. This is stressed by long-term data from the Phase II trial CAMMS223, with one additional SADR (Goodpasture syndrome), but also sustained reduction of disability accumulation and relapse rates compared

to active comparator [73], revealing the dilemma of long-lasting efficacy *versus* potential SADRs.

Treatment and monitoring. Alemtuzumab is applied intravenously with a first treatment cycle of 12 mg over 5 days, followed by a second therapy cycle over 3 days after 12 months [10,12,69]. Further cycles are not intended, but the question of when and how to continue DMD treatment after two cycles is unanswered. There is no class I evidence for different treatment protocols in this indication.

During and for 1 month after treatment, acyclovir (200 mg twice daily) has to be administered prophylactically.

Therapy surveillance with large treatment intervals, but necessarily close safety monitoring, will be a challenge in clinical practice [74] and emphasizes even more the importance of patient education, counselling and informed consent to assure adherence to safety measures. These include differential blood count, serum creatinine and urine analysis before first administration and monthly afterwards; regular testing of thyroid stimulating hormone (TSH) levels has to be performed before treatment initiation and every 3 months up to 4 years after the last administration [70].

SADR risk. Secondary antibody-mediated autoimmunity, even with fatal outcome, has been observed. This includes cases of autoimmune thrombocytopenia (1–3%), thyroiditis (16–30%) and nephritis due to glomerular basal membrane disease (single cases) (Table 1) [10–12,69]. These SADRs may occur with late onset up to 4 years after treatment cessation [73], which highlights the need for adequate monitoring long after the actual infusion cycles (see above).

SADRs from oncological indications, e.g. myelodysplastic changes and tuberculous hepatitis [75,76], have thus far not been experienced in MS based on available long-term data from applications of CAMPATH-1H in the 1990s [77] or the Phase II trial CAMMS223 [73].

Biomarkers. Pathogenesis of secondary autoimmune phenomena remains incompletely understood, but the skewed repopulation with an imbalance of B cells and regulatory T cells may partly account for these SADRs [78]. The prognostic value of serum IL-21 as a risk marker for the development of secondary autoimmunity [79] was not confirmed. Hence, routine blood parameters and urinalysis remain critical regarding patient safety and early detection of SADRs.

Daclizumab

Patient selection. Daclizumab, used initially in transplant medicine, targets CD25, the alpha chain of the IL-2 receptor (IL-2R α) [80,81]. It is currently investigated on a Phase III level in RRMS after promising Phase II data. Daclizumab was investigated initially in combination with interferon

(IFN)-beta [22]. Meanwhile a modified formulation for s.c. monotherapy [daclizumab high-yield process (dac-HYP)] demonstrated clinical and preclinical efficacy in a Phase II study in RRMS [14]. Inclusion criteria required confirmed clinical or MRI disease activity [14]. A paediatric study on seven patients showed some efficacy of daclizumab as second-line treatment; however, four children experienced further disease activity [82].

Treatment and monitoring. The ongoing dac-HYP Phase III trial DECIDE (Efficacy and Safety of Daclizumab High Yield Process Versus Interferon β 1a in Patients With Relapsing-Remitting Multiple Sclerosis; ClinicalTrials.gov NCT01064401) has left the 300-mg dosage in favour of a 150-mg subcutaneous dosage every 4 weeks.

SADR risk. The mode of action of daclizumab appears to be pleiotropic despite selective blockade of IL-2R α : thus, expansion of regulatory CD56^{bright} NK cells [80,83], reduction of proinflammatory signals [84] and interaction between T cells and antigen-presenting cells (APC) have been described [81].

To date, data on daclizumab show good tolerability and safety (Table 1) [14,22]. However, the Safety and Efficacy Study of Daclizumab High Yield Process to Treat Relapsing-Remitting Multiple Sclerosis (SELECT) reports a fatal case after a series of events with initial possibly drug-related dermatitis [14]. A single case report on secondary CNS vasculitis has recently been published and was evaluated as linked to daclizumab treatment [85]. Long-term data and data from the Phase III trial are pending.

Biomarkers. Putative surrogate markers, especially CD56^{bright} NK status, have been described for daclizumab-treatment responders [84]. In addition, they have been suggested for risk evaluation [85].

Other mAbs

Several other mAbs are being investigated in clinical programmes or used on an off-label basis for otherwise treatment-refractory neuroimmunological disease.

The chimeric anti-CD20 mAb rituximab (MabThera[®]) is approved for haematological indications. In several countries, rituximab is recommended as first-line treatment for NMO, although not approved for this indication. For the malignant NMO disease course refractory to other treatment options, use of the IL-6-receptor mAb tocilizumab (RoActemra[®], approved for rheumatoid arthritis) or the terminal complement inhibitor eculizumab (Soliris[®], approved for paroxysmal nocturnal haemoglobinuria) has been reported.

Patient selection. Especially for substances used on an off-label basis, patient selection is based on single-case

decisions, sometimes supported by preclinical experimental data.

Beneficial outcomes in smaller studies were reported for the anti-CD20 mAb rituximab in different neurological autoimmune conditions such as RRMS [8,15], NMO [86–88], myasthenia gravis [30,89] and multi-focal motor neuropathy [90,91]. In PPMS, only a subgroup of younger patients with focal inflammatory activity on cranial MRI appeared to have some benefit from rituximab treatment. There are some data on rituximab use in paediatric populations with different neuroimmunological conditions [92–94].

Treatment with the IL-6 receptor mAb tocilizumab was efficacious in single cases of NMO refractory to rituximab [23,95] and other neuroimmunological conditions [96–98].

Inhibition of the complement system via eculizumab has been tested in a small number of NMO patients with positive results. As mostly feared from treatment of paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome, it was associated with one case of meningococcal sepsis from a total of 14 patients [27].

These concepts will have to be confirmed in larger prospective trials to evaluate efficacy and safety in neurological patient cohorts.

Treatment. Although formally off-label in each of the neuroimmunological disorders, rituximab is recommended as the first-line DMD for treatment of NMO in respective guidelines with two suggested regimens (haematological protocol 375 mg/m² body surface area weekly over 4 weeks *versus* 2 × 1 g) [46,99].

SADR risk. Adverse effects reported mainly from other indications are given in Table 1.

Rituximab-associated PML cases are described in rheumatoid arthritis, systemic lupus erythematosus and haematological populations, with combined rituximab and immunosuppressants [100,101]. However, the risk appears to be considerably lower than with NAT–PML in MS [101]. Due to the high frequency of infusion-related adverse events [102], newer anti-CD20 mAb have been studied on a Phase II level, the humanized ocrelizumab [17] and human ofatumumab [21]. Results of further studies are pending. The clinical development of ocrelizumab in rheumatoid arthritis has been abandoned due to adverse effects. Eculizumab treatment has raised the special concern of meningococcal infections [27].

Biomarkers. Data on specific biomarkers for most of the agents described are widely lacking.

Repopulation of B cells via detection of CD19⁺ and CD20⁺ cells is sometimes used to determine reinfusion intervals for rituximab treatment, as it may be correlated with disease activity [103].

Fingolimod

Patient selection. FTY entails peripheral immunomodulatory effects and direct interactions within the CNS resulting from modulation of sphingosin-phosphate receptors (S1PR) [104]. Approval of Gilenya® for treatment of RRMS differs substantially between FDA and EMA [105,106], reflecting divergent evaluations of its risk–benefit profile. Whereas, in the United States, FTY is approved as first-line therapy, in the European Union it is considered second-line therapy predominantly after a failure of IFN-beta or glatirameracetate. This approach is supported, at least in part, by subgroup analyses of the TRANSFORMS (TRial Assessing injectable interferoN vs FTY720 Oral in RrMS) study, especially for patients with high disease activity on IFN-beta therapy [107]. Ongoing studies investigate the use of FTY in PPMS (ClinicalTrials.gov NCT00731692), in paediatric MS (ClinicalTrials.gov NCT01892722) and in CIDP (ClinicalTrials.gov NCT01625182). Siponimod, a specific modulator of S1PR subtypes 1 and 5, [108] is being evaluated in a trial in SPMS patients (ClinicalTrials.gov NCT01665144).

Specific risk populations comprise patients with predisposing conditions for the development of macula oedema such as diabetes mellitus and (recurrent) uveitis. Patients with pre-existing cardiac arrhythmia, negative dromo- and chronotropic co-medication and pre-existing pulmonary disease should be evaluated closely. In addition, assessment of varicella zoster (VZV) immune status is mandatory [106].

Treatment and monitoring. FTY is administered orally as a 0.5-mg capsule once daily. Before treatment initiation, laboratory investigations including differential blood count, liver enzymes, pregnancy test and VZV status have to be performed. VZV-IgG-negative patients should be vaccinated. Electrocardiography (ECG) and continuous ECG monitoring are recommended during first-dose administration and selectively afterwards. Ophthalmological and dermatological screening are recommended as routine pretreatment investigation, most importantly in risk populations (see Patient selection). Routine laboratory testing, especially for lymphopenia, is required at close intervals; dermatological, ophthalmological and pneumological check-up should be implied in bigger, but regular, intervals or by clinical indication [106]. Because FTY can moderately raise blood pressure, especially in hypertensive patients, blood pressure measurements should be performed regularly.

SADR risk. The described safety measures account for the potential adverse effects of FTY such as pronounced lymphopenia (0.2–1.0%) and cardiac arrhythmia, including symptomatic bradycardia (0.5–2.4%) and atrio-ventricular block (0.2–0.7%), macular oedema (0.5–1%), herpes infec-

tions (2.1–5.5%) and skin malignancies (0–0.7%) [9]. Optical coherence tomography (OCT) may help to detect increased macular volume that seems to occur frequently under FTY treatment; however, macular oedema is a rare condition [109,110].

Two deaths were reported due to herpes virus infections: a primary VZV infection and a herpes-simplex encephalitis [9]. A PML case is being discussed [111], but thus far has not been fully elucidated.

In the post-marketing setting, mainly cardiac events have been reported thus far and have led to extended cardiovascular safety monitoring [112]. Recently, the marketing authorization holder published two fatal cases of haemophagocytic syndrome (HPS) associated with a 9- and 15-month treatment period with FTY. HPS is triggered typically by (viral) infections such as Epstein–Barr virus, as in the cases described. It results in a severe disturbance of the immune system and multi-organ involvement including fever, lymphadenopathy, organomegaly, cytopenia, liver failure and various neurological symptoms. Early diagnosis and treatment of both the triggering condition and the overwhelming immune response via immunosuppressive means are crucial to reduce mortality of HPS.

Biomarkers. The described safety set-up implies several putative biomarkers, although not evaluated formally thus far in terms of prediction of response or determination of SADR development. However, evaluation of lymphocyte counts may serve not only as a necessary safety measurement, but also as a therapy adherence marker.

Subclinical impairment of VZV and Epstein–Barr-virus reactivity have been found recently [113].

Teriflunomide

Patient selection. Teriflunomide (Aubagio®) is the active metabolite of leflunomide, a disease-modifying anti-rheumatic drug (DMARD). It is an inhibitor of the dihydroorotate dehydrogenase and interacts with *de-novo* pyrimidine synthesis [114].

Although the pivotal trial included 8.6% of SPMS patients [115,116], it has been approved by the FDA and EMA for RRMS. Specific contraindications for teriflunomide include severe hepatic or renal disorders and hypoproteinaemia (due to high plasma protein-binding) [117]. As experimental data hint at teratogenic potential, FDA prescription guidelines emphasize the restriction of teriflunomide during pregnancy [118]. It may be hypothesized that teriflunomide treatment may be especially beneficial with co-existing neuroimmunological and rheumatic disorders. Due to the long half-life of the drug and pronounced enterohepatic recirculation, teriflunomide might be an option in patients having difficulties with adherence to treatment schedules, but may be used more cautiously in patients with an impending wish for children.

Treatment and monitoring. Oral teriflunomide is administered once daily, 7 or 14 mg (FDA approval), or 14 mg (EMA approval) [116]. Due to moderate elevation of blood pressure, regular blood pressure controls before and on treatment as well as the exclusion of severe infections before initiation are recommended. Interactions with warfarin [decrease of international normalized ratio (INR)] need to be controlled with frequent INR monitoring. There are no data with regard to marcumar, which is used more commonly in European countries. Adjunctive teriflunomide treatment with IFN- β or glatirameracetate has been evaluated in several trials – Phase II trials showed a favourable safety profile and positive MRI outcomes [119] (and ClinicalTrials.gov NCT00475865), the results of extensions and other studies are pending. Regarding long drug half-life, drug washout after discontinuation can be accelerated via cholestyramine or activated charcoal powder [117], which is relevant in cases of unplanned pregnancy, newly acquired co-morbidities or rapid switch to other immune medications.

SADR risk. Long-term safety data on teriflunomide are being followed-up in extensions of Phases II and III trials (ClinicalTrials.gov NCT00228163, NCT00803049) [120]. Experience on SADRs has been widely favourable, but includes the rare occurrence of potentially fatal infections and tuberculosis (Table 1). Whereas severe liver injury was not reported in the clinical development programme of teriflunomide, few cases were reported with leflunomide. Thus, risk assessment for teriflunomide is conservative, with extrapolation from post-marketing experience with leflunomide of more than 2.1 million patient years.

Biomarkers. Plasma levels of teriflunomide can be measured that might be useful in special situations such as pregnancy in order to monitor the rapid elimination procedure [117].

Ongoing or projected studies are investigating the influence of teriflunomide on brain pathology by use of MRI (ClinicalTrials.gov NCT01881191) and the role of lymphocyte subsets as biomarkers for teriflunomide therapy (ClinicalTrials.gov NCT01863888).

Dimethylfumarate

Patient selection. Dimethylfumarate (DMF) is described to have differential modes of action, including anti-inflammatory [e.g. enhanced T helper type 2 (Th2) response, T cell apoptosis] and potentially neuroprotective aspects [modulation of the nuclear (erythroid-derived 2)-related factor (Nrf2) pathway, anti-oxidative effects] [121,122]. Two Phase III trials have shown efficacy of DMF in RRMS [123,124].

Due to possible gastrointestinal side effects, application of DMF in patients with severe gastrointestinal disorders

such as peptic ulcers should be assessed cautiously. Whereas DMF (Tecfidera®) is approved in the United States, as of October 2013 marketing in the European Union has not yet begun.

Treatment and monitoring. DMF is an oral compound administered twice daily at a dose of 240 mg. The administration of 720 mg per day has not shown higher efficacy than the 480 mg daily dose [123,124]. In order to improve the tolerability of DMF, dose titration is recommended. Lymphopenia will presumably be addressed in safety monitoring schedules in European treatment guidelines. This has not been accounted for in US prescription guidelines.

SADR risk. Similar to other agents discussed in this review, for fumaric acid esters there is also experience on the safety profile from other indications than MS. Fumaderm®, a mixture containing DMF as well as other different monoethyl fumarate salts, has been approved for the treatment of psoriasis since the early 1990s, and dermatological experience suggests a favourable safety profile with more than 185 000 patient years. However, PML cases have been reported recently during psoriasis treatment with fumaric esters [125–128], although confounding factors were identified in these cases. Two cases had experienced long-lasting lymphopenia without treatment adaptation, as recommended [126,127]; the other cases had a history of sarcoidosis, cancer, previous mAb (efalizumab) and immunosuppressive (methotrexate) treatment [128]. Tecfidera®, also with differences regarding galenics, is approved for MS. Thus far, no signal for opportunistic infections such as PML have been reported from the clinical programme or the short post-marketing interval (US) with Tecfidera®.

Biomarkers. The regular assessment of leuco- and lymphocyte counts is sensible and may serve treatment surveillance. At 1 year of treatment, leuco- and lymphocyte counts decreased by 10–12% and 28–32% (mean), respectively; 4–5% of patients experienced total lymphocyte counts below 0.5×10^9 per litre [123,124].

As in other DMD treatments, regular MRI under DMF therapy will be reasonable for both therapy monitoring and determining effectiveness.

Mitoxantrone

Patient selection. Mitoxantrone (MX, Ralenova®/Novantrone®) has been approved for the treatment of secondary progressive and progressive relapsing MS following two placebo-controlled trials [19,129] and two studies comparing MX or MX in combination with methylprednisolone (MP) to MP alone [130,131]. Data on MX in primary progressive MS (PPMS) is discouraging [132–134], but has gained relevance in NMO treatment [24,25]. Although not formally approved, MX has been used in children with aggressive forms of MS [135].

Treatment and monitoring. Different treatment protocols may be an influencing factor for SADR development, especially in terms of therapy-related acute leukaemia (TRAL) [136]. Whereas an intravenous infusion every 3 months according to the placebo-controlled, double-blind, randomised, multicentre, phase III trial of mitoxantrone in secondary progressive multiple sclerosis (MIMS) protocol [129], including dose adaptation according to leucocyte nadir, is used widely in Germany, dose regimens differ substantially and may not include regular dose adaptation [137,138].

Additional differences may comprise pre- or co-treatments [37]. Thus, MP co-treatment has been shown to increase intracellular MX dosage *in vitro* [139], and may thus increase cellular toxicity.

Treatment de-escalation should be considered after 1 year of clinical and paraclinical stability of disease to minimize the risk of at least partially dose-dependent SADRs (e.g. cardiotoxicity). Haematological monitoring should include regular examination of blood counts up to 5 years after cessation of MX [140–142]. Cardiac ultrasound and electrocardiography (ECG) should be performed accordingly, as late-onset cardiotoxicity is described [143].

Thorough monitoring and vigilance is especially relevant for TRAL, as secondary leukaemia is potentially curable if diagnosed early and treated adequately [144], but is associated with potentially fatal complications [145–147] if overlooked.

SADR risk. Discussions about SADR incidence, especially TRAL and cardiotoxicity [36,37,137,138,142,148–152], have led to reassessment of the proper risk–benefit profile of MX.

TRAL incidences vary from 0.07% [149] to 2.82% [138] and are subject to methodological difficulties (e.g. reporting bias especially for meta-analyses [36,149] and largely lacking prospective data). Interestingly, there seem to be regional differences of TRAL incidence with similar German and French estimates [37,142], but higher Italian and Spanish rates [137,138].

Estimates of the incidence of cardiotoxicity are complicated by different definitions of an adverse cardiac event [reporting of clinical events *versus* paraclinical abnormalities in ECG, transthoracic echocardiography (TTE) [153] and radionuclide ventriculography [143,150,154]]. Sub-clinical decrease of left ventricular ejection fraction (LVEF) in TTE may be a dose-dependent effect [153]; however, this has not been confirmed by a study with 14% incidence of LVEF decrease in radionuclide ventriculography without dose-dependency [150]. Data on recovery and prognosis of cardiac events are inconsistent [143,150,151,153,155,156].

Biomarkers. Clinical and paraclinical parameters for the prediction of MX response have been established [157].

SADR development might be associated with pronounced or lasting leucopenia before TRAL onset [37] and

increased brain natriuretic peptide (BNP) in subclinical myocardial injury [158].

In addition to treatment-related factors, genetic factors (genes involved in detoxification: CYP3A4; cellular drug efflux: ABCB1, ABCG2; DNA repair: BRCA2, XRCC5) may influence susceptibility for SADRs [139,155,159]. Pharmacogenetic approaches may help early identification of patients at higher risk for side effects or even individualized treatment schemes.

Discussion and conclusions

The growing spectrum of treatment options for neuroimmunological diseases confronts us with complex risk–benefit considerations and treatment decisions. Whereas established first-line DMDs such as interferon-beta formulations and glatirameracetate are generally safe, newly emerging DMDs with higher efficacy often carry a higher potential of adverse effects with thorough therapy monitoring requirements. Long monitoring intervals, even after cessation of therapy, also pose new challenges for adherence to respective protocols.

If not in the clinical trial setting (FTY, alemtuzumab), post-marketing experience (NAT) has revealed relevant or even completely new safety issues not anticipated previously. We have to keep in mind that, for example, in order to identify an event occurring at a frequency of 0.1% as an adverse drug reaction, a sample size of 50 000 would be necessary to observe a twofold increased adverse event rate in comparison to a control group [160]. This emphasizes the need for thorough post-marketing surveillance, Phase IV trials and drug registries to enhance patient safety. Such studies would also be valuable as validation studies for putative biomarkers.

Principles for optimization of the benefit-to-risk ratio comprise thorough patient selection according to distinct clinical criteria, proper treatment intervals, dosage and duration, the evaluation of (individual) risk profiles for SADRs and the investigation and validation of biomarkers for risk stratification and treatment benefit. The transfer of these principles into clinical practice is difficult, and has thus far been only partially achieved for the substances described.

Treatment decisions may be based not only on ‘classic’ first- and second-line dichotomy and parallel concepts [‘hit hard and (relatively) early’] may be beneficial in distinct patient groups. Current guidelines tend to emphasize individual factors and contraindications to alleviate treatment decisions.

Safety monitoring of patients begins before treatment initiation and outlasts the actual active treatment period as, for many SADRs, late-onset cases have been reported.

For all treatment options discussed, routine laboratory investigations of liver and renal function, thorough assessment of existing severe infections or immunosuppression

for any cause is relevant to allow safe treatment initiation, just as important as the assessment of pregnancy and information of (especially female) patients in terms of reproductive issues.

Regular safety assessments help in the early detection of severe side effects or their prodromal signs and symptoms. Clinical vigilance and education of patients for signs and symptoms of SADRs is key for improving the safety of modern DMD therapy, as early accurate treatment of SADRs is crucial and of prognostic relevance. Early interdisciplinary co-operation is necessary, as SADRs for many agents are described not only in the neurological field (PML, neuropathy, CNS infection), but also in dermatological, ophthalmological and internal medicine. Counselling of patients may also include gynaecological and/or andrological advice.

Biomarkers for SADR prediction and pharmacogenetic approaches for different agents will have to be validated in larger patient cohorts and may alleviate therapeutic decisions in the future.

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