Editorial

What adverse events occur with disease-modifying therapy in multiple sclerosis?

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Multiple sclerosis (MS) is a potentially devastating inflammatory demyelinating disease of the CNS affecting approximately one in 1000 people, mainly young adults. Relapsing-remitting MS (RRMS), characterized by an individual frequency of relapses, bears the risk of incomplete remissions and further progressive disability, then termed as secondary progressive MS. The etiology of MS remains unknown, but it is generally assumed that, based on a certain individual genetic susceptibility, as yet unidentified environmental factors trigger its autoimmune cascade in the CNS [1].

A disease-modifying therapy (DMT) describes a drug that modulates MS disease course either as an immunosuppressant or immunomodulator. However, this description appears increasingly arbitrary. The lack of an appropriate pharmacological classification based on specific modes of action of respective drugs causes inconsistencies and confusion. The semantic confusion (an immunosuppressant does *per se* also modulate the immune system and vice versa) preserves the opinion that immunosuppressive drugs are more dangerous than immunomodulators in terms of tolerability, adverse events (AEs) and risks; and the recently added term 'selective immunosuppressant' may intuitively be placed right in between. As a consequence, (selective) immunosuppressants for MS therapy are labeled as 'use with caution' in clinical practice, unnecessarily delaying a more effective treatment in patients with active disease and, thus, causing potentially devastating consequences. This confusion is topped by different drug approvals by different health authorities: the benefit–risk evaluation of the same selective immunosuppressive drug (e.g., fingolimod) led to different approved indications by the EMA [101] and the US FDA [102]. Taken together, perception of a drug's benefit–risk is obviously not only based on clinical trial evidence. However, apart from these formal issues, it should be kept in mind that treatment decision making is an exclusively individual process, which needs to balance the individual risks and consequences

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of MS and the potential benefits, safety and risks of a DMT at a given disease stage.

Between 1995–2001 the first DMTs were approved to reduce relapses and, to some extent, delay disease progression. These standard (or baseline) DMTs for RRMS include IFNβ preparations (IFNβ-1a 30 µg once weekly intramuscular, IFNβ-1a 22/44 µg three-times a week subcutaneous [sc.], IFNβ-1b 250 µg every other day sc.) and glatirameracetate (GLAT; 20 mg everyday sc.) [2–6]. In general, IFNβ and GLAT have a favorable safety profile, which has been documented for more than 20 years [7,8]. AEs of IFNβ/GLAT, such as injection-site reactions (including rare skin necrosis) and flu-like symptoms, usually depend on application routes (intramuscular << sc.) and the drug itself (GLAT < IFNβ) and are not life-threatening, but may negatively impact quality of life [9].

In 2006, natalizumab 300 mg once monthly, intravenously was reapproved as the first monoclonal antibody therapy in neurology by the FDA and EMA for active RRMS patients, who either suffered at least one relapse during the last 12 months despite IFNβ/GLAT or are treatment-naive, but had at least two severe relapses within the last 12 months. Natalizumab is highly effective in terms of reduction of inflammatory disease activity and risk of disease progression, both effects even likely to improve (existing) neurological symptoms over time [10–12]. In general, natalizumab is well tolerated: infusion-related reactions (e.g., headache, dizziness and nausea) are uncommon, anaphylactic reactions less than 1% and increase of liver enzymes comparable to experiences in IFNβ-treated patients (1–2.5% of threefold increase of upper normal levels) [10,11]. However, the excellent efficacy and good tolerability of natalizumab must be weighed against the risk of JC virus (JCV)-induced progressive multifocal leukoencephalopathy (PML), which may lead to severe disability or even death. Based on the current global experience with nearly 100,000 natalizumab-treated patients, the overall PML risk is currently at 2.1 in 1000 [13]. The incidence of PML by treatment epoch is relatively low during the first two years, while increasing during the third year (current estimate 1.93 in 1000). A serum anti-JCV antibody test has been developed to improve PML risk assessment. Besides natalizumab treatment duration and a positive JCV antibody status, prior immunosuppressive treatment adds to the risk of PML. Thus, patients, who accumulate all three of these risk factors are at highest risk for PML (current estimate 11.1 in 1000) [13]. On the contrary, patients with negative anti-JCV antibody status and without prior immunosuppressive treatment will have only a hypothetical risk for PML (<0.09 in 1000) [13].

Fingolimod 0.5 mg once daily was approved as the first oral treatment in RRMS by the FDA as a standard baseline therapy in 2010 [101] and by the EMA as treatment escalation (similar to the approval of natalizumab) in 2011 [102]. Pivotal trials demonstrated that fingolimod effectively reduces annualized relapse rates, but with a less pronounced effect on disease progression, which requires further confirmation [14,15]. Fingolimod is, in general, also well tolerated, however, there are some specific potential AEs and risks to be considered. First, and most important for daily clinical practice, fingolimod is classified as FDA pregnancy risk category C due to its teratogenic potential [101]. Thus, women of childbearing potential have to use effective contraception during and for 2 months after stopping fingolimod treatment. Second, due to the potential of fingolimod to cause cardiovascular AEs (e.g., bradycardia, AV-block and hypotension), especially within 6 h after the first intake of fingolimod, and due to an FDA and EMA re-evaluation of fingolimod owing to 11 cases of unexplained deaths in patients treated with fingolimod, both health agencies advised the performing of continuous electrocardiographic monitoring before the start of treatment and during the first 6 h [103,104]. In addition, there are specific warnings for patients with concomitant cardiac disorders or specific concomitant treatments (e.g., certain antiarrhythmics or β-blockers). Third, before initiating fingolimod, patients without a history of chickenpox or without vaccination against varicella zoster virus should be tested for antibodies against varicella zoster virus [101,102]. Fourth, due to a rare risk of macula edema all patients should be evaluated by an ophthalmologist after 3–4 months of treatment. In the cases of a prior or current uveitis or where there is a history of diabetes this examination should be done before treatment initiation [101,102]. Finally, white blood cell count should be done every 3–6 months during

treatment. As a matter of its mode of action fingolimod 0.5 mg causes a lymphopenia, which was clinically relevant in up to 5% of patients with lymphocyte counts under 0.2×10^9/l [14,15]. Lymphocytes should return to normal levels within 6–8 weeks after stopping fingolimod treatment. However, individual patients may take much longer for lymphocyte reconstitution [16], which needs to be considered in case a patient with prior fingolimod treatment starts with another DMT.

In summary, MS patients and neurologists are faced with substantial facts regarding DMTs: first, not only has the number of approved DMTs escalated, but also their treatment efficacy (as commonly suggested, but deduced from only single clinical trials with active comparators) and, not unexpectedly, their potential side effects and risks.

Second, for all approved DMTs, clear indications and patient management plans are available. They are mandatory to provide the patient with the best practice of treatment monitoring and to assure the patient that the current treatment decision is the most effective choice.

Third, postmarketing surveillance, especially by long-term studies (for IFNβ and GLAT), but also several national or regional patient registries (for natalizumab), demonstrated that these DMTs are well tolerated with favorable safety profiles over the long term and that, especially in the case of natalizumab, no other safety signals apart from the rare risk of PML did emerge. The broad use of fingolimod at present should allow the collection of similar representative long-term data within the coming years.

Fourth, for natalizumab-induced PML, risk factors have been identified, although the pathogenetic mechanisms of PML development in these individual cases is still unknown. A major advantage in the PML risk minimization plan is the availability of a specific and sensitive serum anti-JCV antibody test.

However, aside from these substantial facts, there are (among many others) two substantial remaining cautions: first, the trump card for an effective treatment response is the correct diagnoses: MRI-based diagnostic criteria allow ever earlier diagnosis of MS (up to so-called 'radiologically isolated syndromes'); however, the earlier the diagnosis of MS, the higher the potential risk of misdiagnosis. The worst case scenario is a misdiagnosed patient with subsequent treatment-induced harm (either by exposing the patient to the wrong treatment or to AEs) [17]. Although nearly scientifically ignored, it is a rising issue of utmost importance in the MS community [18,19], and therefore warrants priority attention, at least in daily clinical practice.

Second, another highly challenging issue is regarding the sequential use of natalizumab and fingolimod (as well as potentially emerging treatments, e.g., alemtuzumab, teriflunomide and fumaric acid). On the one hand, the sequential use of either natalizumab or fingolimod after IFNβ or GLAT treatment was documented to be safe in the pivotal clinical trials [10,11,14,15]. On the other hand, the consequences of sequential use of natalizumab and fingolimod or vice versa are completely unknown. In April 2012, the first patient previously treated with natalizumab for 3.5 years and then switched to fingolimod after a 6-week washout period, was reported as having been diagnosed for PML 4 months later [Novartis, 14 April 2012; Pers. Comm.]. Although information on this case is scant and there are controversies as to 'which is the hen and which is the egg', it clearly demonstrates that there is a need for prospective and systematic treatment monitoring. It is unlikely that this need will be satisfied by sponsored clinical trials, however, national and regional patient registries are able to mirror 'real life' practice and, especially, to identify potential adverse signals in the sequential use of DMTs.

Finally, in the treatment decision making process we should recall, that it is the patient who takes the risk – either for her/his potential MS disease consequences or potential DMT side-effects/risks. Therefore, benefit–risk evaluations and perceptions are likely to vary among patients and between patients and their physicians.

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