Early intervention in multiple sclerosis: how can we maximise patient prospects?

Thomas Berger

To cite this article: Thomas Berger (2017) Early intervention in multiple sclerosis: how can we maximise patient prospects?, Expert Review of Clinical Immunology, 13:7, 649-651, DOI: 10.1080/1744666X.2017.1319763

To link to this article: https://doi.org/10.1080/1744666X.2017.1319763
1. Introduction

Multiple sclerosis (MS) is a potentially devastating inflammatory demyelinating disease of the central nervous system (CNS) affecting approximately 1:1000 mainly young adults. Clinical history/examination, presence of cerebrospinal fluid oligoclonal bands, and increasingly MRI findings constitute for MS diagnostic criteria [1], which are applicable already at the first event suggestive for MS and after exclusion of any other relevant differential diagnosis. Relapsing-remitting MS (RRMS), characterized by an unpredictable individual frequency of relapses, bears the risk of incomplete remissions and progressive disability, then termed as secondary progressive MS (SPMS). The etiology of MS remains unknown, but it is assumed that based on genetic susceptibility, yet unidentified environmental factors trigger CNS inflammation [2].

2. Disease modifying therapies for multiple sclerosis

A disease-modifying therapy (DMT) describes a drug, which should modulate MS disease course. Between 1995 and 2016, 12 originator DMTs were approved to reduce relapses and, to some extent, delay disease progression. However, formal proof of true disease course modification, e.g. prevention of conversion from relapsing to SPMS, is lacking.

2.1. DMTs for mild/moderate relapsing (remitting) MS

These treatments include interferon-ß (IFNß) preparations, glatiramer acetate (GLAT), teriflunomide (TERI), dimethylfumarate (DMF), and daclizumab (DAC) [3–11]. Natalizumab (NTZ), fingolimod (FTY), and alemtuzumab (AZM) are available for (highly) active RRMS [12–14] as defined by either at least one relapse in the past 12 months, despite a platform DMT, or at least two severe relapses in the past 12 months in treatment-naive patients, both along with substantial inflammatory MRI activity.

In general, DMTs for mild/moderate RRMS are well tolerated, although transient adverse events (AEs) may frequently occur within the first 1–3 months of treatment, such as: flu-like symptoms (IFNß), injection-site reactions (IFNß, GLAT, DAC), gastrointestinal AEs (DMF, TERI), flush (DMF), and hair thinning (TERI). These AEs are not life-threatening, but may negatively impact quality of life. According to product labels, all these drugs (except for GLAT) mandate routine laboratory monitoring for WBC and liver enzymes at various intervals. Importantly, INFß and GLAT can be used safely in female patients until pregnancy, whereas pregnancy is contraindicated for DAC, TERI and DMF. In case of perceived or occurred pregnancy TERI has to be actively washed out to ascertain non-teratogenic drug plasma levels.

2.2. DMTs for (highly) active relapsing (remitting) MS

For (highly) active RRMS, the European Medicines Agency has approved DMTs with high efficacy but potentially harmful AEs and treatment-related risks. The most potentially life-threatening, albeit rare, condition is JC virus (JCV)-induced progressive multifocal leukoencephalopathy (PML). For NTZ, the combination of treatment duration >2 years and a positive anti-JCV antibody status with an anti-JCV antibody index >1.5 constitutes the highest risk (3–10/1000 NTZ treated patients) [15]. Hence, the serum anti-JCV antibody test offers NTZ-associated PML risk assessment and, more specifically, stratification in the treatment decision-making process. With DMF treatment 5 PML cases have been reported until January 2017, four of these patients had persistent, long-lasting severe lymphopenia (CTC grade 3), a risk factor per se for opportunistic infections. Also for FTY 10 cases of PML have occurred so far with an older age as a common denominator. FTY also requires continuous ECG monitoring before treatment start and during the first 6 h [16] because of potential cardiovascular AEs (bradycardia), testing for antibodies against varicella zoster virus (VZV), and an ophthalmological evaluation 3–4 months after treatment start for rarely occurring macula edema [17]. Prior AZM treatment some laboratory tests are mandatory, too: screening for tuberculosis, VZV antibodies, HIV, and hepatitis. According to the mode of action of AZM, AEs may occur at different time points: infusion-related reactions (including allergic reactions) during infusions, infections within the first 3–4 months after a treatment cycle, and so-called ‘reconstitution autoimmunity’ (including thyroid autoimmunity up to 40% of patients, rare idiopathic thrombocytic purpura [2.6%), and immune nephropathy [<1%]) up to 48 months after the last AZM infusion [18]. Again, important
for daily practice, NTZ may be administered until pregnancy, whereas effective contraception is required for women during and subsequently 2 months after stopping FTY, and for at least 4 months after the last AZM infusion.

In summary, the current DMTs demonstrate groupwise (based on phase III clinical trials) efficacy ranges from roughly 30–50% (treatments for mild/moderate RRMS) to 50–80% (treatments for [highly] active RRMS) relative reduction of annualized relapse rates, which are mirrored by substantial (up to >90%) relative reduction of inflammatory-related MRI parameters. Although clinical trials are usually short-term (on average 2 years), the clinical and MRI results are, together with an overall moderate reduction of disability progression, extrapolated (along with experiences from open-label extension and observational studies registries) to improve long-term disease course modulation, namely to either stop (inflammatory) disease activity or to at least delay disease progression, e.g. conversion to SPMS. However, formal proof of true disease course modification in this sense is still lacking. The side-effects and risks of DMTs are managed by respective risk-minimization programs, pharmacovigilance monitoring and education/support to secure physician and patient alertness.

3. Patient prospects

In essence, this is a physician’s view on the benefits and risks of available DMTs. However, are the therapeutic advantages per se sufficient to maximize patient prospects and does this view anyway match the prospects of patients? Not necessarily, as patients and physicians may have diverging perspectives, or at least a different ranking of MS-related importances. The primary mutual importance between patients and physicians is the diagnosis of MS. MRI-based diagnostic criteria allow continuously earlier diagnosis of MS (up to so-called radiologically isolated syndromes). However, the earlier the diagnosis, the higher the potential risk of misdiagnosis [19]. The worst-case scenario is a misdiagnosed patient with subsequent treatment associated harm (either by exposing a wrong patient to a wrong treatment or to AEs) [20]. Once the diagnosis of MS is established, a communication process starts, which is time-consuming, but of utmost importance for the patient’s future, living with MS. Patients need to be extensively informed about their diagnosis, prognosis, and treatment options. Sooner or later, questions will arise and support may be sought concerning coping strategies, outing, lifestyle (changes), symptoms and their management, quality of life, family-related issues (including pregnancy), working capacities, socioeconomic implications, information sources (close people, brochures, patient organizations, internet), etc. How can we as physicians meet all this demands of our patients, are we even able to do so? Yes, we can – by seeding an individual management approach from the very beginning. Physicians need to learn more about the person diagnosed with MS, about individual attitudes and behaviors, their understanding, personality (including fears and risk perception), expectations, and (life) planning. This process also allows our patients to get the best available information to engage with their MS diagnosis, or simply gives a chance for a second opinion elsewhere. A lifetime diagnosis urges assurance and preparation sooner, especially in the very early disease phase. Different pressure groups increasingly proclaim early if not immediate treatment, thus potentially rushing physicians and patients in anxiety to forfeit opportunities in the future disease course. However, immediate treatment is pragmatically only necessary in a minority of patients with severe (clinical or radiological) manifestation at diagnosis. The majority of patients will benefit – for all the aforementioned reasons – from a controlled clinical and MRI follow-up after diagnosis in 3–6-month intervals. Any clinical or MRI indicator of ongoing/current inflammatory activity in this short, consecutive time frame(s) will be most suitable, and early enough to start a DMT.

Shared decision-making is mandatory for choosing then the individual DMT. This does not mean that the patient should be just offered a basket of treatment options. It means that upon the physician’s treatment recommendation – guided by individual factors, such as clinical and/or MRI based anticipation of prognosis but also patient personality and preferences (e.g. pregnancy plans) – the patient is convinced about the benefits of the specific treatment. The treatment motto must be clearly discussed: (1) the treatment goal is: no disease activity at all; (2) ‘in for a penny, in for a pound’: if a DMT is not effective it should be switched (or even escalated) immediately to another treatment to achieve the treatment goal; (3) treatment expectations should be realistic: all DMTs are prophylactic but not symptomatic treatments, any improvements of existing symptoms (e.g. fatigue, cognitive dysfunction) are at best bystander effects of DMTs, thus, concomitant drug and/or non-medicinal symptomatic treatment may be added; (4) patient and physician need to agree on a prospective plan 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; and (5) patient-reported treatment outcomes should be encouraged to centralize patients’ quality of life and to complement physicians’ outcome assessments.

4. Conclusion

In conclusion, patients’ prospects can be maximized at an early disease stage, but we need to be clearly aware that treatment effects emerging from clinical phase III trials, which are designed and performed to seek future authority approval, are a doubtless important but not exclusive puzzle piece for a successful individual MS management. Neurologists have been taught that apart from diagnostic procedures and prescribing recipes the time spent with a patient is a valuable future investment, specifically in the individual management of a chronic, life-long diagnosis/disease such as MS. Instead of caviling about lack of time and resources excellency in modern MS management requires a neurologist’s commitment and willingness to face the challenges (increasing spectrum of DMTs, monitoring DMTs and disease activity, patient prospects and demands, documentation, reimbursement hurdles, etc.).

Funding

This paper was not funded.
Declaration of interest

T Berger has participated in the last 12 months in meetings sponsored by and received honoraria (lectures, advisory boards, consultations) from pharmaceutical companies marketing treatments for multiple sclerosis: Biogen, Genzyme, Merck, Novartis, Ratiopharm, Roche, Sanofi-Aventis, TEVA. His institution has received financial support in the last 12 months by unrestricted research grants (Biogen, Novartis) and for participation in clinical trials in multiple sclerosis sponsored by Alexion, Biogen, Merck, Novartis, Roche, Sanofi Aventis, TEVA. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

4. Excellent overview about multiple sclerosis.