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Immunological treatment of multiple sclerosis

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ABSTRACT

Treatment of multiple sclerosis (MS) has been a challenge since its first description by Charcot. The advent of immunomodulatory drugs in the mid 1990s brought the first big change in the treatment of MS patients. During the last 10 years there has been an ongoing tremendous evolution of novel treatment options for relapsing-remitting MS. These options include monoclonal antibodies, which inhibit migration of lymphocytes (natalizumab), deplete lymphocytes (alemtuzumab), or block the cytokine receptor interleukin (IL)-2 (daclizumab), teriflunomide that inhibits proliferation of activated lymphocytes, fingolimod that modulates the sphingosine-receptor system, and dimethylfumarate that combines features of immunomodulatory and immunosuppressive drugs. The topic of this review is to discuss currently available treatments and provide an outlook into the near future.

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system that leads to the destruction of myelin and neurons [1]. The disease is clinically characterized by a phase of relapses and remissions that often transitions into a phase of chronic and slow progression of disability [2]. This progressive stage of the disease is thought to be the consequence of ongoing inflammatory damage to neurons and axons [3]. In the beginning, the neurodegenerative damage can be partly repaired or compensated. As inflammation and neurodegeneration continue, there is an exhaustion of the compensatory mechanisms and irreversible neuronal damage accumulates.

The current concept of the treatment of MS is to prevent damage of the CNS from early on. Patients are therefore treated already after the first attack, a disease stage called the clinically isolated syndrome (CIS) [4,5]. Currently available treatments only target the inflammatory component of MS. So far, no treatments are available to directly prevent neurodegeneration or to enhance the repair of myelin or neurons. The main challenge of MS treatment today is to decide which treatment is chosen for which patient. MS is a very heterogeneous disease and the individual prognosis is hard to predict. Biomarkers for the prediction of prognosis as well as biomarkers for treatment response are available on a population level but still need to be validated on the individual patient level [6]. Patients are often started on a baseline therapy that has a moderate efficacy but shows a favorable safety profile. Clinical disease activity exemplified by relapses and disability progression are taken as an indication of an unsatisfactory treatment response [7]. In addition to these clinical parameters, magnetic resonance imaging (MRI) of the brain and spinal cord can be used to detect disease activity that is not clinically apparent [8]. The combination of clinical assessments and MRI of the CNS increases the predictive value and MRI has therefore become a valuable tool for treatment monitoring in clinical practice. With more effective treatments becoming available the treatment goal is to achieve a state of “no evidence of disease activity” (NEDA) [9]. NEDA is defined as (1) no relapses, (2) no disability progression, and (3) no new T2 hyperintense and/or T1 gadolinium (GD)-enhancing lesions in brain MRI (NEDA-3) [10].

During the last 25 years there has been a tremendous progress in the therapeutic arena of MS. During the mid 1990s the first immunomodulatory drugs have shown a benefit in trials with relapsing-remitting MS (RR-MS) patients. Various interferon beta formulations have therefore been registered for RR-MS (Betaferon, [Bayer, Leverkusen] Rebif [Merck, Darmstadt, Germany], Avonex [Biogen, Cambridge, USA]). Subsequently, the novel immunomodulator glatirameracetate (Copaxone Teva, Petach Tikwa, Israel) was introduced as another treatment for RR-MS. In clinical trials these drugs reached a relapse rate reduction of around 30% [11–14]. In addition they had an impact on the inflammatory activity in MRI: a reduction in new T2 and in Gd-enhancing T1 lesions. During the last 20 years these immunmodulatory drugs have accumulated a solid and extensive safety record. This is especially important since young patients are often treated for many years with these drugs. A disadvantage of these treatments is that they have to be injected in frequencies of up to daily. The side effects of

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local injection site reactions and flu-like symptoms in the case of the interferons have contributed to a suboptimal tolerability profile, which often leads to a reduced adherence. To improve this tolerability issue, a long-acting interferon formulation has been developed. This pegylated form of interferon (Plegridy [Biogen, Cambridge, USA]) needs only one subcutaneous injection in 2 weeks. In a 1-year, placebo-controlled trial it showed a similar efficacy as the previous registered immunmodulators (ADVANCE study) [15].

With the establishment of immunomodulatory treatments different questions arose: (1) Which patients should be treated? (2) From what stage of the disease on should treatment be started? (3) Does the efficacy seen during a 2-year clinical trial translate into a reduction of disability progression in the long-term?

So far, only one of these questions has been answered conclusively by different clinical trials. Immunomodulation with interferons or copaxone has a benefit already in patients with CIS [16–19]. This means that treatment should be initiated upon first clinical signs of disease. Unfortunately, we do not have an answer to the question which patients will benefit most from an immunomodulatory treatment. By now, no genetic polymorphism or gene expression profile has been identified that would help selecting patients for a certain treatment [6]. Also a definite answer to the question of the long-term effect of these treatments on disability progression is lacking. Different patient cohorts have been studied to find out if interferon treatment is associated with reduced secondary progression. However, these studies yielded conflicting results [20,21]. The lack of a proper untreated control group that is comparable to the treated group is probably the reason for this continuing uncertainty.

Experimental research on the factors that are responsible for migration of immune cells into the CNS finally led to the registration of natalizumab (Tysabri, Biogen, Cambridge, USA), a monoclonal antibody that blocks a4 integrin [22]. This integrin has been shown in animal models to be critical for migration of lymphocytes across the blood brain barrier. The pivotal trials with this antibody showed a clear reduction of relapses and disability progression [23,24]. Also MRI parameters of brain inflammation responded dramatically to this treatment. Natalizumab was therefore considered as a major breakthrough in the treatment of RR-MS. Unexpectedly, already during the clinical trial phase a severe side effect of natalizumab treatment emerged: progressive multifocal leukencephalopathy (PML) caused by the JC virus. Meanwhile we know that natalizumab is the immunosuppressive drug that is most commonly associated with PML. A number of risk factors have been identified to contribute to an increased risk for PML during natalizumab treatment: duration of natalizumab treatment over 2 years; previous immunosuppressive treatment; a positive JCV-antibody status [25]. The risk of PML led to a more restricted label of the drug. It has been registered only for highly active patients as a first line therapy and for patients that show breakthrough disease despite an ongoing immunomodulatory baseline therapy.

The next step in the development was the approval of fingolimod (Gilenya [Novartis, Basel, Switzerland]), the first oral therapy in MS [26]. Fingolimod is a first in class compound that targets the sphingosin receptor system. It acts as an agonist that binds to the receptor and finally leads to an internalization and degradation of the receptor. Its efficacy is thought to be linked to S1P receptor 1 binding that is expressed on lymphocytes. Lymphocytes need this receptor for an efficient egress from lymphnodes. Treatment with fingolimod leads to a reduction of lymphocytes in the blood that is attributed to a redistribution of lymphocytes to secondary lymphoid organs. Unlike classical immunosuppressive agents fingolimod does not destroy lymphocytes and the redistribution is reversible after stopping of fingolimod. It also does not affect all lymphocytes in the same way but mainly targets naive and central memory T cells and largely spares effector memory T cells that can still be found in the blood [27]. Despite a considerable decrease in blood circulating T cells the overall rate of infections was not significantly increased. However, there seems to be a slight increase of herpesviral infections in fingolimod-treated patients [28,29]. In pivotal trials fingolimod showed an around 50% reduction in relapse rates compared to placebo and also compared to the active comparator Avonex (FREEDOMS and TRANSFORMS trials) [30–32]. Since fingolimod can cross the blood brain barrier and its receptors are also expressed on CNS residents cells (eg, neurons, oligodendrocytes, and astrocytes) it was speculated that it could also have a neuroprotective effect (reduced astrogliosis and enhanced remyelination [33,34]) in addition to its immunomodulatory effect [35] (INFORMS study). However, a well-designed randomized, placebo-controlled phase III trial failed to show an effect of fingolimod on disability progression in primary progressive MS (INFORMS study, https://www.novartis.com/news/media-releases/novartis-provides-update-fingolimod-phase-iii-trial-primary-progressive-ms-ppms). Together with one negative trial of natalizumab-treatment in secondary progressive MS (ASCEND study) this stresses the difficulties we have in treating patients with progressive forms of MS.

Teriflunomide (Aubagio, Sanofi, Paris) was the next oral agent that was introduced as treatment for RR-MS [36]. It is a follow-up compound of leflunomide that is registered for rheumatoid arthritis. Teriflunomide is the active metabolite of leflunomide and inhibits the activity of the dihydroorotate dehydrogenase, a key enzyme in the biosynthesis of pyrimidine in activated lymphocytes. In two large phase III trials the compound showed a significant reduction of relapse rates of more than 30% and a reduction in the proportion of patients who developed a confirmed disability progression (TOWER and TEMSO trials) [37,38]. In a further trial teriflunomide proofed to be effective also in patients with CIS (TOPIC trial) [39].

The up to now last oral compound that has been registered for RR-MS is dimethylfumarate (DMF, Tecfidera [Biogen, Cambridge, USA]) [40]. DMF was originally used to treat patients with psoriasis. The clinical observation that psoriasis patients that had concomitant MS also seemed to benefit from DMF treatment led to the clinical development program of the drug in MS. The mode of action of DMF is still under investigation and mechanisms proposed comprise an activation of the NRF2 anti-oxidative stress response, inhibition of nuclear factor kappa B activation, a shift in the cytokine profile from pro- to anti-inflammatory, and the induction of apoptosis in lymphocytes. Two large controlled trials were performed in patients with RR-MS (DEFINE and CONFIRM trials) [41,42]. Both trials showed a reduction of the annualized relapse rate in DMF treated patients compared to placebo by around 50%. One trial included in addition an open label comparison to Copaxone treatment, which was associated with a relapse rate reduction of around 30% compared to the placebo arm.

The last compound that was registered in the treatment arena of MS is alemtuzumab (Lemtrada [Genzyme, Cambridge, USA]) [43]. Alemtuzumab is a monoclonal antibody against the surface molecule CD52. It leads to a rapid and long-lasting depletion of lymphocytes. It is thought that the treatment of alemtuzumab leads to a reset of the immune response with a change of the T cell receptor repertoire and phenotype of T cells re-occuring after depletion. Two phase III trials have been performed in RR-MS (CARE-MS I and II) [44,45]. Alemtuzumab was tested against Rebif in both trials and could show a significant reduction in relapses rates compared to the active comparator. MS CARE II also showed a significant reduction of disability progression in alemtuzumab-treated patients compared to Rebif-treated patients. Despite these promising efficacy results there is some concern regarding the