

# Update on immunopathogenesis and immunotherapy in multiple sclerosis

Rebecca C Selter<sup>1</sup>  
Bernhard Hemmer<sup>1-3</sup>

<sup>1</sup>Department of Neurology, Klinikum Rechts der Isar, Technische Universität München, Munich, Germany; <sup>2</sup>Munich Cluster for Systems Neurology (SyNergy), Munich, Germany;

<sup>3</sup>Competence Network on Multiple Sclerosis, Munich, Germany

**Abstract:** Multiple sclerosis is a chronic inflammatory demyelinating disease of the central nervous system. Both genetic and environmental factors are believed to contribute to the pathogenesis of the disease. Histopathological findings suggest that multiple sclerosis is an immune-mediated disease, involving both the cellular and humoral immune systems. Within the last 20 years, several disease-modifying therapies for the treatment of multiple sclerosis were established. Moreover, promising new substances are currently being tested in clinical trials and will likely broaden the therapeutic opportunities available within the upcoming years.

**Keywords:** multiple sclerosis, immunopathogenesis, disease-modifying therapy

## Immunopathogenesis of multiple sclerosis

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS), affecting approximately 1.3 million worldwide.<sup>1</sup> The majority of MS patients will develop significant disability over time. Although the pathogenesis has been the focus of MS research for several decades, the mechanisms leading to evolution and progression of the disease are still uncertain. Several lines of evidence point to an autoimmune pathogenesis, with both genetic and environmental factors contributing to disease susceptibility.<sup>2-4</sup> Large-scale genetic studies in MS have revealed more than 50 gene loci associated with MS, with the HLA-DRB1\*1501 allele being the most important.<sup>5</sup> Interestingly, there is a great overlap with loci observed in other autoimmune diseases, such as diabetes and rheumatoid arthritis. Among the possible environmental factors, infection with Epstein Barr virus and low vitamin D levels seem to be the most important contributors to susceptibility.<sup>3,4,6</sup> Other factors, such as the gut microbiome, have been discussed as possible susceptibility factors based on findings in experimental animal models.<sup>7,8</sup>

A large body of evidence suggests that MS is an autoimmune disease.<sup>9</sup> CNS antigens seem to be the likely targets of the autoimmune response. It is conceivable that in genetically susceptible individuals, an infection or release of CNS proteins into the periphery may trigger loss of self-tolerance towards CNS proteins, probably by activation of myelin-reactive T cells.<sup>10</sup> Viral infections can probably cause bystander activation of T cells in an immunostimulatory context.<sup>11</sup> Moreover, release of autoantigens due to cellular damage by a viral agent can lead to activation of autoreactive T cells due to cross-reactivity between viral antigens and CNS antigens, a mechanism known as molecular mimicry.<sup>10,12,13</sup> After migration into the CNS, autoreactive T cells may become reactivated by antigen-presenting cells presenting CNS autoantigens on major

Correspondence: Bernhard Hemmer  
Department of Neurology, Klinikum  
Rechts der Isar, Technische Universität  
München, Ismaninger Strasse 22,  
Munich 81675, Germany  
Tel +49 89 4140 4600  
Fax +49 89 4140 7681  
Email hemmer@lrz.tum.de

histocompatibility complex molecules to the invading T cells (Figure 1).

Histopathologically, MS lesions are characterized by inflammatory infiltrates consisting of activated T cells, B cells, plasma cells, and macrophages. Whereas CD4+ T cells are mainly found in the perivascular spaces and meninges, CD8+ T cells are located in the parenchyma of MS lesions.<sup>14</sup> In MS lesions, profound demyelination, axonal damage, astrogliosis, and remyelination is observed.<sup>15–19</sup> Besides, deposits of complement proteins and immunoglobulins are seen. Several proinflammatory cytokines and matrix metalloproteinases are active in MS lesions.<sup>13,14,16,20</sup>

In the pathogenesis of MS, CD4+ T cells are believed to release cytokines and immune mediators, which lead to attraction of macrophages and further release of proinflammatory cytokines. CD4+ T cells require for their activation an interaction with major histocompatibility complex class II expressing cells, such as dendritic cells, macrophages, or B cells. Animal experiments suggest that T-helper (Th) 1 cells, which release interferon-gamma and Th17 cells, which secrete Th17, play a key role in inflammation within the CNS. In contrast, Th2 cells, characterized by secretion of interleukins 4, 5, and 10, and regulatory T cells expressing Foxp3, counter-regulate encephalitogenic Th1 and Th17 responses.<sup>21</sup> Moreover, some

T cells may not only cause harm to CNS tissue, but also prime regeneration of MS lesions.<sup>22</sup>

CD8+ T cells also seem to be involved in the pathogenesis. In contrast with CD4+ T cells, CD8+ T cells can directly interact with and damage major histocompatibility complex I/antigen-expressing cells, such as neurons and oligodendrocytes.<sup>23</sup>

As a consequence of the release of proinflammatory cytokines and cellular damage, microglia are activated and monocytes and macrophages are recruited into the lesion. Further CNS antigens are released and presented to potentially autoreactive T cells. Epitope spreading may lead to a broadened autoimmune response involving further autoantigens.<sup>24</sup>

Alongside T cells, B cells are believed to play an important role in the pathogenesis of MS. B cells are important antigen-presenting cells in the peripheral immune system and possibly also in the CNS. They can capture soluble proteins by their specific B cell receptor, process and present peptide antigens bound to major histocompatibility complex class II molecules to autoreactive T cells. Plasmablasts and plasma cells can release immunoglobulins which probably bind to autoantigens on glial cells.<sup>25–27</sup> Possible mechanisms of antibody-mediated pathogenicity include complement activation or antibody-dependent cellular cytotoxicity.<sup>26,28</sup> Indeed, the complement protein C9neo, which is part of the terminal lytic membrane attack complex, and immunoglobulin G deposits have been detected at the border of MS plaques.<sup>20,26</sup> Moreover, the

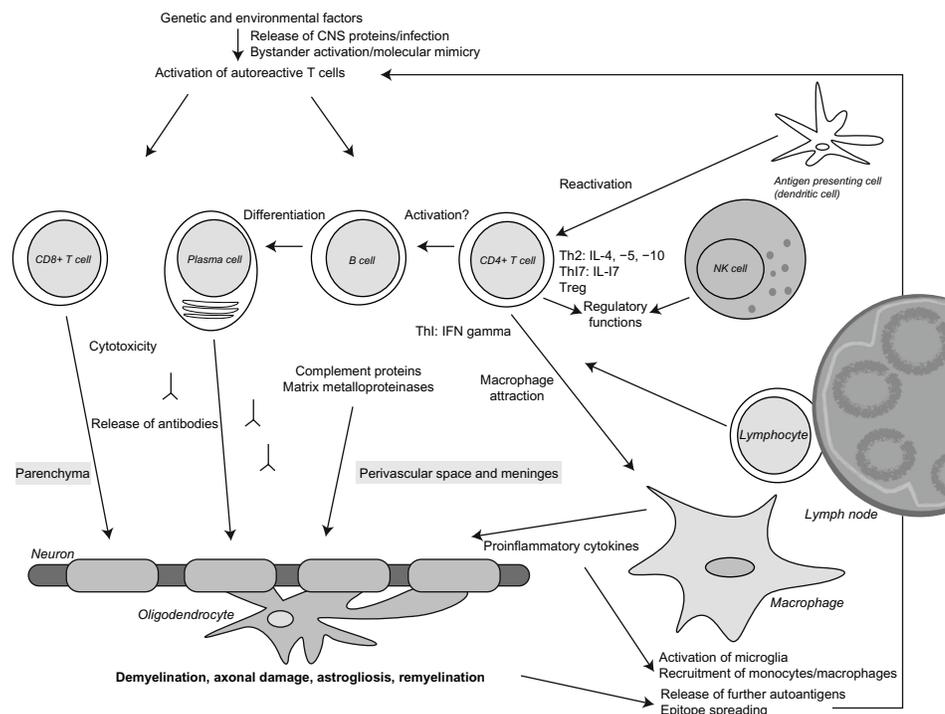


Figure 1 Immunopathogenesis of multiple sclerosis.

Abbreviations: Treg, regulatory T cell; NK cell, natural killer cell; IL, interleukin.

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presence of intrathecal immunoglobulin G synthesis and detection of clonally expanded B cells in the cerebrospinal fluid and brain lesions of MS patients argue for a substantial role of B cells in MS.<sup>29</sup> The clinical relevance of these findings is supported by a clinical trial demonstrating that patients with lesions characterized by complement and immunoglobulin G deposition respond exceptionally well to therapeutic plasma exchange.<sup>30</sup> More recently, the role of cortical lesions has come more into the focus of MS research. In contrast with white matter lesions, cortical lesions seem to be mainly driven by meningeal inflammatory infiltrates and soluble factors from the cerebrospinal fluid (CSF).<sup>31,32</sup> Therefore, histopathological findings suggest a role of both the cellular and humoral immune systems in the pathogenesis of MS.

### Disease-modifying therapies in multiple sclerosis

During the past 20 years, several disease-modifying substances have been developed for treatment of MS. Figure 2 and Table 1 summarize established therapies and drugs currently evaluated in clinical trials.

### Immunomodulatory and immunosuppressive therapies

This group of drugs aims to suppress or alter immune responses in the periphery. The mechanisms are rather nonselective and affect a broad range of immune cells.

### Interferon beta

The first immunomodulatory drug approved for the treatment of relapsing-remitting forms of MS was interferon-beta 1b in 1993. The pivotal trial showed a significant reduction in relapse rate and the number of active lesions on magnetic resonance imaging.<sup>33</sup> Within the following years, several formulations of interferon-beta 1a and 1b came onto the market. In secondary progressive MS, interferon-beta 1b delayed disease progression in the European trial but failed in the US trial.<sup>34,35</sup> Detailed analysis of the trials suggested that interferon-beta 1b is active in secondary progressive MS, as long as relapse activity is present.<sup>36</sup> Accordingly, the drug was approved for treatment of secondary progressive MS with ongoing relapse activity in Europe. Moreover, in patients with clinically isolated syndrome, conversion to clinically definite MS was significantly delayed by early treatment with interferon-beta.<sup>37,38</sup> The mechanism by which interferon-beta decreases inflammatory disease activity in MS is still unknown. Different mechanisms are likely to be important, such as its effects on cytokines, chemokines, and metalloproteinases, and also the modulation of lymphocyte activation and migration and proliferation of regulatory T cells.<sup>39,40</sup>

### Glatiramer acetate

Glatiramer acetate is an amino acid copolymer consisting of L-alanine, L-lysine, L-glutamic acid, and L-tyrosine,

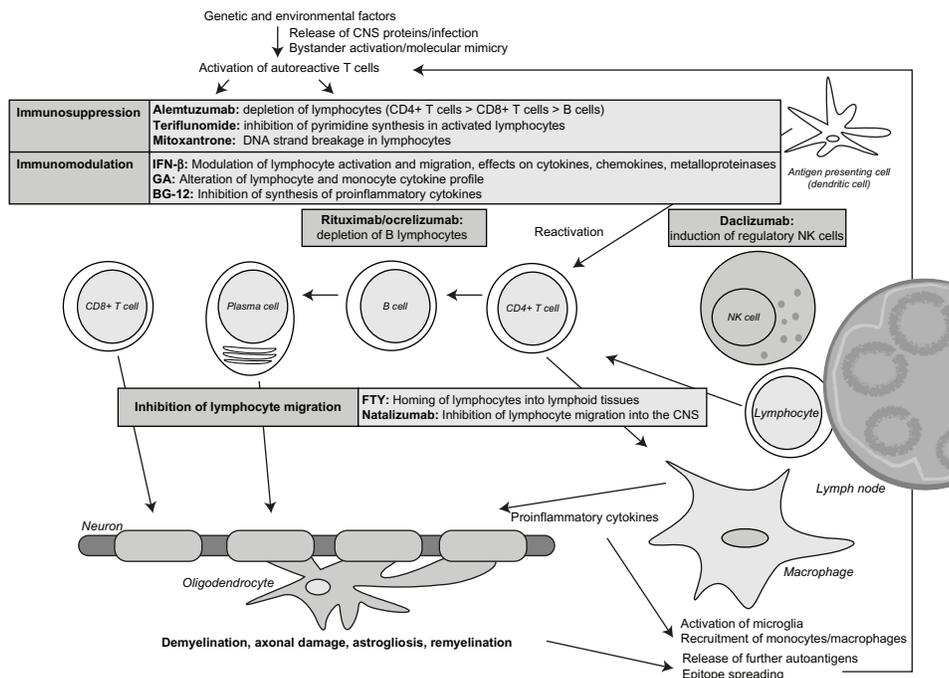


Figure 2 Established and emerging multiple sclerosis therapies.

Abbreviations: IFN-β, interferon beta; GA, glatiramer acetate; BG-12, dimethyl fumarate; FTY, fingolimod; NK cell, natural killer cell.

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**Table 1** Summary of application, assumed mode of action, and current status of drug development

Drug (brand name)	Administration	(Assumed) mode of action	Status of development
Interferon beta-1a (Avonex® [Biogen Idec])	Intramuscularly once a week	Effects on cytokines, chemokines, and metalloproteinases, modulation of lymphocyte activation and migration, proliferation of regulatory T cells	Approved (CIS, RRMS)
Interferon beta-1b (Betaferon®, [Bayer]), Betaseron®, [Bayer], Extavia® [Novartis])	Subcutaneously every other day		Approved (CIS, RRMS; and SPMS with ongoing relapse activity in Europe)
Interferon-beta 1a (Rebif® [Merck Serono])	Subcutaneously three times a week		
Glatiramer acetate (Copaxone® [Teva])	Subcutaneously once daily	Alteration of the cytokine profile of T cells and monocytes, induction of regulatory T cells, induction of neurotrophic factors in immune cells	Approved (CIS, RRMS)
Mitoxantrone (Ralenova® [MEDA Pharma])	Intravenously every three months	DNA strand breakage and inhibition of DNA repair	Approved (highly progressive SPMS, third line in highly active RRMS)
Natalizumab (Tysabri® [Biogen Idec])	Intravenously every 4 weeks	Inhibition of lymphocyte migration across the blood-brain barrier and into the CNS	Approved (highly active or breakthrough RRMS)
Fingolimod (Gilenya® [Novartis])	Orally once daily	Inhibition of lymphocyte egress from secondary lymphoid tissue	Approved (highly active RRMS in Europe, baseline therapy of RRMS in the US)
Alemtuzumab (Campath 1H® [Genzyme])	Intravenously	Depletion of lymphocytes, monocytes, eosinophils, thymocytes	Phase III (RRMS) completed
Rituximab (MabThera® [Hoffmann-La Roche], Rituxan® [Biogen Idec])	Intravenously	Depletion of CD20+ B lymphocytes	Phase II (RRMS, PPMS)
Ocrelizumab	Intravenously		Phase III (RRMS, PPMS)
Ofatumumab (Arzerra®, [GlaxoSmithKline], HuMax-CD20® [GlaxoSmithKline])	Intravenously		Pilot trial (RRMS)
Laquinimod	Orally	Modulation of the Th1/Th2 balance towards a Th2 response	Phase III (RRMS) completed
BG00012 (Tecfidera® [Biogen Idec])	Orally	Inhibition of synthesis of proinflammatory cytokines	Phase III (RRMS) completed/ approved in the US (RRMS)
Teriflunomide (Aubagio® [Sanofi Aventis])	Orally	Inhibition of de novo pyrimidine synthesis in activated lymphocytes	Phase III (RRMS, CIS) completed/approved in the US (RRMS)
Daclizumab (Zenapax® [Hoffmann-La Roche])	Intravenously	Inhibition of proliferation of several immune cells	Phase III (RRMS)

**Abbreviations:** RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PPMS, primary progressive multiple sclerosis; CIS, clinically isolated syndrome; CNS, central nervous system; Th, T-helper.

and was discovered in a model of experimental allergic encephalomyelitis in 1974.<sup>41</sup> It is believed to inhibit the T cell response towards myelin antigens.<sup>42–45</sup> Pivotal studies showed a reduction of relapse rate in patients with relapsing-remitting MS by 29% within two years<sup>46</sup> and a significant decrease in the total number of enhancing lesions.<sup>47</sup> Glatiramer acetate was approved for treatment of clinically isolated syndrome in 2009, having been shown to delay conversion to clinically definite MS in the PreCISe Study.<sup>48</sup> The mechanism by which glatiramer acetate works in MS also remains unclear. It potentially includes alteration of the cytokine profile of T cells and monocytes, induction of regulatory T cells, and induction of neurotrophic factors in immune cells.<sup>49–51</sup>

### Mitoxantrone

Mitoxantrone is an anthracenedione which induces DNA strand breakage by intercalation, and also inhibits the DNA repair enzyme, topoisomerase II. In a placebo-controlled Phase III study (MIMS), mitoxantrone reduced disability progression and relapse rates (reduction of relapse rate by 63% during the first year and 68% during the second year of treatment compared with placebo) in highly active relapsing-remitting and secondary progressive MS.<sup>52</sup> Mitoxantrone was approved by the US Food and Drug Administration and several European countries in 2000 for worsening relapsing-remitting MS, progressive relapsing MS, and secondary progressive MS. Suppression of lymphocytes seems to be its

main mode of action. Mitoxantrone may cause cardiotoxicity and acute myeloid leukemia at a rate that was not anticipated when the drug was approved. Accordingly, mitoxantrone is primarily used in highly progressive secondary progressive MS and as a third-line therapy in patients with highly active relapsing-remitting MS.

## Therapies affecting immune cell migration

These drugs primarily impact on migration of immune cells within the peripheral immune system or across the blood–brain-barrier.

### Natalizumab

Natalizumab is a humanized monoclonal antibody against  $\alpha 4\beta 1$ -integrin (very late activating antigen-4), an adhesion molecule expressed on the surface of activated T cells and other mononuclear leukocytes, which is essential for entry of leukocytes into the CNS.<sup>53</sup> Accordingly, migration of lymphocytes is severely impaired in patients treated with natalizumab. In the AFFIRM trial,<sup>54</sup> natalizumab significantly reduced the relapse rate by almost 70% and disease progression by more than 50% in relapsing-remitting MS compared with placebo. Similar effects were observed in the SENTINEL trial,<sup>55</sup> when natalizumab in combination with interferon-beta 1a was compared with interferon-beta 1a alone.<sup>54,55</sup> Natalizumab was approved by the Food and Drug Administration in 2006 for relapsing-remitting MS.

However, during the SENTINEL study, two patients died of progressive multifocal leukoencephalopathy, an opportunistic brain infection caused by the John Cunningham (JC) virus. Until September 2012, more than 250 natalizumab-treated patients developed progressive multifocal leukoencephalopathy. Therefore, natalizumab is only approved as monotherapy for treatment of highly active or breakthrough relapsing-remitting MS. The risk of developing progressive multifocal leukoencephalopathy correlates with both treatment duration and JC virus antibody status. In particular, after 24 months of treatment, the risk of progressive multifocal leukoencephalopathy increases to approximately 4.6 cases per 1000 per year in JC virus antibody-positive patients without prior immunosuppressive therapy. Moreover, a history of immunosuppressive therapy before initiation of treatment with natalizumab increases the risk of developing progressive multifocal leukoencephalopathy.<sup>56</sup> After discontinuation of therapy, disease activity seems to return to the initial level.<sup>57</sup>

### Fingolimod

In 2010, a new oral drug was approved for the treatment of relapsing-remitting MS, ie, fingolimod (FTY720), a sphingosine 1-phosphate receptor agonist. After phosphorylation *in vivo*, FTY720-P binds to the sphingosine 1-phosphate receptor, promoting internalization of the receptor and homing of lymphocytes into lymphoid tissues.<sup>58</sup> This results in a profound decrease of circulating CD4+ T cells and B cells in the blood, and to a lesser extent, in the CSF.<sup>59</sup> Two large Phase III studies have shown significant effects on relapse rate (relative reduction of annualized relapse rate by 54% at a dose of 0.5 mg daily compared with placebo) and CNS inflammation as measured by magnetic resonance imaging compared with interferon-beta 1a (TRANSFORMS study)<sup>60</sup> and with placebo (FREEDOMS study)<sup>61</sup> in relapsing-remitting MS. Relevant side effects include viral infections (herpes viruses), macula edema, skin tumors, elevated liver enzymes, and upper and lower respiratory tract infections. Two patients died in the Phase III trials as a result of viral infections. However, both patients were treated with a high dose of fingolimod, which is no longer used to treat MS. In the US, fingolimod is approved for baseline therapy of relapsing-remitting MS, whereas in Europe it is restricted to patients with highly active disease, comparable with the labeling for natalizumab. More recently, the possible cardiac side effects of the drug have received attention. In December 2011, a patient died suddenly within 24 hours of taking fingolimod for the first time. Therefore, treatment with fingolimod is not recommended without cardiology advice in patients suffering from cardiovascular diseases or taking antiarrhythmic or heart rate-lowering drugs. Cardiac monitoring after the first exposure is mandatory.<sup>62,63</sup>

## Emerging therapies

The drugs described in this section target specific molecules on immune cells and lead to depletion of those cells that express the target molecules.

### Alemtuzumab

Alemtuzumab is a humanized monoclonal antibody against CD52, which is expressed on lymphocytes, monocytes, eosinophils, and thymocytes.<sup>64</sup> Therefore, alemtuzumab leads to depletion of these cells in peripheral blood. In a Phase II study (CAMMS223), alemtuzumab reduced the relapse rate in relapsing-remitting MS by 74% compared with interferon-beta.<sup>65</sup>

Two Phase III studies (CARE-MS I/II) evaluated the safety and efficacy of alemtuzumab compared with interferon-beta in patients with relapsing-remitting MS.<sup>66,67</sup> In both studies, a significant reduction in relapse rate compared with interferon-beta 1a was observed. In one of the trials, a significant reduction in disease progression compared with interferon-beta 1a was also seen. The main side effects of alemtuzumab are autoimmune diseases of the thyroid in up to 19% of patients, idiopathic thrombocytopenic purpura (1%), and, rarely, Goodpasture syndrome.

#### Rituximab/ocrelizumab/ofatumumab

Rituximab is a chimeric antibody directed against CD20, which is expressed on B cells from the pre-B cell to memory B cell stage. The antibody depletes all B cells from the peripheral blood and to a certain extent from lymph nodes, although it has no impact on plasma cells in the bone marrow and inflamed tissue. A Phase II trial in relapsing-remitting MS showed a significant reduction of gadolinium-enhancing brain lesions in patients treated with rituximab compared with placebo.<sup>68</sup> In another Phase II study of patients with primary progressive MS, a reduction in disease progression was observed in a subgroup of young patients with lesion activity on magnetic resonance imaging.<sup>69</sup>

Ocrelizumab is a humanized antibody directed against CD20. In a Phase II study, ocrelizumab significantly reduced the annualized relapse rate (reduction by 80% in the 600 mg group and 73% in the 2000 mg group) and the number of gadolinium-enhancing brain lesions in patients with relapsing-remitting MS.<sup>70</sup> One patient died from systemic inflammatory response syndrome after the first treatment cycle in week 14 of the trial, and a brain autopsy showed signs of hypoxia and brain edema with transcranial herniation. The relationship between treatment and death has remained uncertain. Two Phase III trials are currently recruiting patients with primary progressive MS and relapsing-remitting MS, respectively.<sup>71,72</sup> A small pilot trial with ofatumumab, another CD20-specific antibody, showed significant reduction of magnetic resonance imaging activity in a treatment compared with a placebo group.<sup>73</sup>

### New immunosuppressants and immunomodulators

These drugs impact on immune cells but seem to have fewer side effects than traditional immunosuppressive drugs.

#### Laquinimod

The exact mode of action of laquinimod is not fully understood, although a possible mechanism seems to be modulation of the Th1/Th2 balance towards a Th2 response.<sup>74</sup> In a mouse model of experimental autoimmune encephalomyelitis, laquinimod inhibited the development of disease.<sup>75</sup> In a Phase II study, laquinimod reduced the number of gadolinium-enhancing lesions in relapsing-remitting MS compared with placebo.<sup>76</sup> The Phase III ALLEGRO study showed a reduction in the annualized relapse rate by 23% and of disability progression by 36%.<sup>77</sup> In the Phase III BRAVO trial, the drug was not superior to interferon-beta 1a.<sup>78</sup> Few side effects were observed in the trial and no deaths occurred related to the drug.

#### BG00012 (dimethyl fumarate)

According to *in vitro* data, BG00012 may exert anti-inflammatory effects by inhibiting synthesis of proinflammatory cytokines.<sup>79</sup> In a Phase II study, BG00012 reduced the number of new gadolinium-enhancing and enlarging lesions, as well as the annualized relapse rate in patients with relapsing-remitting MS compared with placebo.<sup>80</sup> Recently, the results of two Phase III trials were published. In both trials, BG00012 significantly reduced relapse rates, compared with placebo, by around 50%. Whereas in the Phase III CONFIRM study,<sup>81</sup> reduction of disability progression by BG00012 was not significant compared with placebo, the DEFINE study<sup>82</sup> showed a significant reduction of disability progression by more than 30%. Further, all secondary endpoints were positive. Treatment with BG00012 was associated with gastrointestinal side effects and flushing. No major side effects or deaths related to treatment were observed.<sup>81,82</sup> Based on the results from the Phase III trials, BG00012 has recently been approved for the treatment of relapsing remitting MS in the US.

#### Teriflunomide

Teriflunomide is the active metabolite of leflunomide and acts as an inhibitor of dihydroorotate dehydrogenase, which is essential for pyrimidine synthesis in activated lymphocytes.<sup>83</sup> In the Phase III TEMSO study, teriflunomide significantly reduced the annualized relapse rate in relapsing-remitting MS by 31% compared with placebo.<sup>84</sup> The TOWER trial in relapsing-remitting MS (teriflunomide versus placebo) showed similar results, with a significant decrease in relapse rates and confirmed progression in patients receiving teriflunomide at 14 mg daily compared with placebo.<sup>85</sup> The ongoing Phase III TENERE trial is comparing the efficacy of

teriflunomide with that of interferon-beta 1a.<sup>86,87</sup> Moreover, the Phase III TOPIC study is currently recruiting patients with clinically isolated syndrome.<sup>88</sup> No major side effects were observed in the clinical trials. Based on two positive Phase III trials, teriflunomide has been approved for the treatment of MS in the US and awaits approval in Europe.

### Daclizumab

Daclizumab is a monoclonal immunoglobulin G antibody directed against the  $\alpha$ -subunit of the interleukin-2 receptor (CD25), which is expressed on several immune cells. In the Phase II CHOICE study, add-on daclizumab together with interferon-beta reduced the number of new or enlarged gadolinium-enhancing lesions compared with interferon-beta alone.<sup>89</sup>

The Phase IIb SELECT study showed a significant reduction in the annualized relapse rate by 50% in the 300 mg dose arm and 54% in the 150 mg dose arm, and of disease activity on magnetic resonance imaging, as measured by number of new gadolinium-enhancing and new or newly enlarging hyperintense T2 lesions in patients with relapsing-remitting MS treated with daclizumab as compared with placebo.<sup>90</sup> The Phase III DECIDE study comparing the efficacy and safety of daclizumab with interferon-beta 1a in patients with relapsing-remitting MS is currently ongoing.<sup>91</sup>

### Stem cell therapy

In the past few years, case reports and results of small, open-label, nonrandomized Phase I and II studies on hematopoietic and mesenchymal stem cell transplantation mainly in relapsing forms of MS were reported.<sup>92–97</sup> Until now, there have not been any Phase III studies on stem cell therapy in MS, although the first randomized, open-label Phase III study on hematopoietic stem cell transplantation is currently recruiting patients.<sup>98</sup> Large randomized controlled trials are needed to evaluate whether stem cell transplantation is more efficacious than the commonly used MS drugs and outweighs the risk of transplantation-related mortality.

### Outlook

During the last two decades, a number of drugs have been approved for the treatment of MS. All drugs significantly reduce relapse rates, and some have profound effects on disease progression, even during the first years of treatment. However, the increasing efficacy of MS therapies has been accompanied by new and sometimes life-threatening side effects. During the next decade, a number of new drugs will

become available for the treatment of relapsing-remitting MS and clinically isolated syndrome. With the increasing number of drugs, safety will become a key issue, especially for baseline therapies. Unfortunately, the safest drugs are also those with the lowest efficacy. We expect that an increase in specificity by selectively targeting particular immune cells that are deeply involved in the disease pathogenesis will eventually pave the way for safe and efficacious drugs for use in clinically isolated syndrome and relapsing-remitting MS. Moreover, treatments that impact on the course of primary and secondary progressive MS are desperately needed. Accordingly, a number of trials have been initiated that will hopefully result in better treatment of these entities. In the long run, a better understanding of the pathogenesis involved is essential to develop highly specific and effective MS therapies that do not have severe side effects.

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