The curtain is drawn for both natalizumab and fingolimod (FTY720): a new era of multiple sclerosis therapy has arrived

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'...these drugs (natalizumab and fingolimod) are true examples of successful translational medicine and raise the hope that additional new approaches from basic research can be transferred to the clinic for the treatment of multiple sclerosis patients.'

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A new era of treatment in multiple sclerosis (MS) has arrived. Novel drugs target the migration of T lymphocytes to the CNS in MS. With the introduction of natalizumab (Tysabri™, Biogen Idec), a new therapeutic option is available for the treatment of relapsing–remitting MS [1]. The drug is a humanized monoclonal antibody (mAb) against α4 integrin. α4β1, or very late antigen-4, is required for transmigration of T cells through the blood–brain–barrier. The drug was already on the market in the beginning of 2005, but was withdrawn by the manufacturer Biogen Idec (MA, USA) owing to two cases of progressive multifocal leukencephalopathy (PML), which had emerged during the Phase III study Safety and Efficacy of Natalizumab in Combination With Avonex in the Treatment of Multiple Sclerosis (SENTINEL), in which a combination of natalizumab and interferon (IFN)-β-1a (Avonex™, Biogen Idec) had been given to patients with relapsing–remitting MS [2–4]. Another case appeared in a study in which natalizumab had been administered to patients with inflammatory bowel disease [5]. This Crohn's disease patient had been receiving a number of immunosuppressive drugs before initiation of therapy with natalizumab. He was first misdiagnosed with astrocytoma. In the Phase III study in relapsing–remitting MS, in which natalizumab had been given as a monotherapy for 24 months (Safety and Efficacy of Natalizumab in the Treatment of Multiple Sclerosis [AFFIRM]), no case of PML has been observed [1]. After the emergence of the PML cases, a large safety study was performed by analyzing cerebrospinal fluid (CSF) and nuclear magnetic imaging (NMR) from natalizumab-treated patients [6]. The risk of developing PML with natalizumab given as monotherapy was calculated as 1 in 1000. No additional PML cases have been diagnosed so far. After these painstaking safety investigations, natalizumab was reintroduced into MS therapy in the USA and Europe in summer 2006. Owing to the safety concerns in the USA, the drug is given through a restricted distribution program called Tysabri Outreach: Unified Commitment to Health (TOUCH™). Only prescribers, infusion centers and pharmacies associated with infusion centers registered with the program are able to prescribe, distribute or infuse natalizumab, and patients must be enrolled in, and meet all the conditions of, the program. In Europe, natalizumab is available for relapsing–remitting MS patients who have failed conventional MS treatment with the available IFN-β preparations or patients

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with fast, progressive relapsing–remitting MS. Even though the wording of the licensing in Europe does not contain failure in treatment for MS with glatiramer acetate as an indication for treatment with natalizumab, such patients should be equally treated as patients who have failed treatment with IFN-β preparations. This is also underlined by the licensing in the USA where natalizumab is recommended for patients who have had an inadequate response to, or are unable to tolerate, alternate MS therapies. Therefore, the drug will probably be used in the escalation therapy of MS before further escalation is carried out with chemotherapeutic compounds such as mitoxantrone or cyclophosphamide, or in MS patients who had severe side effects with IFN-β preparations. It must be stressed that the Phase II and III studies with natalizumab were carried out mostly in MS patients who were, in a high number of cases, patients who had not been pretreated with other MS therapeutics beside corticosteroids and presented mainly unproblematic cases [1,7]. The drug now has to prove its efficiency in therapy failures and severe fast-progressive MS cases since, in these patients, the conventional treatments often fail.

The results of the AFFIRM study (double-blind, placebo-controlled; 575 patients completed 2 years follow-up with natalizumab and 281 patients with placebo), in which natalizumab was used as a monotherapy, are impressive [1]. There was a relative reduction of the annual rate of relapses by 68% and a reduction of sustained progression for 12 weeks by 43% compared with controls after 24 months of treatment with natalizumab. The number of gadolinium (Gd)-enhancing lesions as an indicator of acute inflammation was reduced by 92%, new or enlarging T2 lesions by 83% and new T1 lesions by 73% over the 2-year observation period compared with placebo. These impressive results outstrip the IFNs and glatiramer acetate which are currently used for treatment of relapsing–remitting MS. These reduce relapse rate by approximately 30%.

Conversely, one has to be cautious regarding further potential side effects of the drug, which is given intravenously every 4 weeks at a dose of 300 mg. In 4% of the cases, hypersensitivity reactions were found and 1.3% of patients had severe anaphylactic reactions. These are probably due to the fact that the humanized antibody contains mouse sequences and the immune system can react against these. The immunogenic potential of natalizumab is demonstrated by the fact that 6% of all natalizumab-treated patients develop persisting neutralizing antibodies, which lead to a reduction of the efficiency of the drug. In addition, patients who developed neutralizing antibodies had more side effects. Importantly, such antibodies can be used as biomarkers for the drug and MS patients with such antibodies should be withdrawn from therapy. The emergence of PML demonstrates that the interference with immune surveillance of the CNS could be dangerous. In addition, it has been speculated that natalizumab mobilizes JC virus-infected bone marrow cells [8]. Therefore, much caution and monitoring has to be performed to identify additional potential side effects of the drug early, such as opportunistic infections, severe viral infections or tumors. In addition, more has to be learned regarding JC virus biology in context with MS. For this reason, the TOUCH program, under which the drug is distributed in the USA, is of eminent importance and will lead to important long-term data regarding the efficacy and safety of this innovative therapy.

Another novel compound has recently been introduced into the thinking of the MS community: fingolimod (FTY720) is potentially one of the first orally administered compounds against MS [9]. The main action of the drug seems to be reducing T-cell migration: encephalitogenic T cells are trapped in lymph nodes and do not enter the CNS. The drug targets sphingosine-1-phosphate (S1P) receptors. The five isoforms ($S1P_{1–5}$) are widely distributed in the body and are involved in a multitude of physiological cycles, such as leukocyte migration, cardiovascular development and vasoregulation, neurogenesis, and endothelial cell function [10]. Apart from $S1P_2$, the drug targets all of these receptors. Whereas $S1P_1$ is mostly involved in lymphocyte migration, $S1P_3$ is important in heart rate regulation and $S1P_5$ in glia physiology. This wide receptor specificity explains a number of side effects. It also explains potential additional beneficial effects in MS, such as axon protection owing to direct effects on oligodendrocytes that make the myelin sheaths [11]. The structure of the drug has great similarity to the receptor agonist S1P. Upon *in vivo* phosphorylation, fingolimod is converted to its phosphate ester metabolite, which acts as a high-affinity ligand for the G-protein-coupled receptors $S1P_1$ and $S1P_{3–5}$. Initially, fingolimod acts as an agonist, but probably then leads to sustained receptor surface loss.

> 'Novel therapy is urgently needed for patients with primary progressive and secondary chronic–progressive MS. Therefore, drug developments should also try to target aspects of glial and neuronal integrity and circuits since, so far, all available treatments mainly affect the immune system but, to a large extent, do not have effects on protective pathways within glia or neurons.'

A Phase II study (double-blind, placebo-controlled; 88 patients completed 6 months of study with fingolimod 1.25 mg per day, 81 patients with 5 mg per day and 81 patients with placebo) has just been published, in which patients with relapsing–remitting MS were treated with fingolimod, demonstrating impressive results [9]. Within the 6-month observation period, there was a reduction in relapses of 55% in the 1.25 mg per day group and 54% in the 5 mg per day group. The Gd-enhancing lesions were reduced by 43% in the 1.25 mg per day group and by 62% in the 5 mg per day group. T2 lesions were reduced by 54% in the 1.25 mg/day group and by 70% in the 5 mg/day group. In the extension phase of the study, patients from the placebo group were switched to fingolimod either 1.25 or 5 mg/day. In this

extension study, the effects on relapse rate and NMR parameters could be preserved over the observation time of another 6 months and patients formerly receiving placebo profited well by the treatment with fingolimod. There were a number of side effects, which were more common in the group treated with the higher dose of fingolimod 5 mg/day compared with fingolimod 1.25 mg/day by comparable therapeutic efficiency with regard to relapse frequency. The side effects included temporary reduction of heart rate shortly after application of the first dose of the drug. Peripheral and lymphocyte blood counts decreased to approximately 20–30% of baseline in the fingolimod-treated patients. Nasopharyngitis, dyspnea, diarrhea, nausea and an increase in alanine aminotransferase were the most common long-term side effects. In addition, there was one case of posterior reversible encephalopathy syndrome in the group treated with fingolimod 5 mg/day. The ongoing Phase III studies (FTY720 Research Evaluating Effects of Daily Oral therapy in Multiple Sclerosis [FREEDOMS] and TRial Assessing injectable interferoN vS FTY720 Oral in RrMS [TRANSFORMS]) will demonstrate if the drug should be made broadly available for MS therapy.

The basic therapeutic principles of both natalizumab and fingolimod influencing the T-cell trafficking and migration into the CNS have been evaluated initially in experimental autoimmune encephalomyelitis, the animal model of MS [12,13]. Therefore, these drugs are true examples of successful translational medicine and raise the hope that additional new approaches from basic research can be transferred to the clinic for the treatment of MS patients. There is further need for drug development for MS since, so far, there is no cure for this detrimental disease that normally affects young adults and leads to disability being a major gash in life perspective, and is also a great socioeconomic burden. Novel therapy is urgently needed for patients with primary progressive and secondary chronic–progressive MS. Therefore, drug developments should also try to target aspects of glial and neuronal integrity and circuits since, so far, all available treatments mainly affect the immune system but, to a large extent, do not have effects on protective pathways within glia or neurons. Unlike the claim of some researchers that animal models are not useful in MS research [14], in my opinion and the opinion of other experts, animal models are absolutely necessary for finding and profiling such innovative novel drug targets that could lead to an improved quality of life of patients with MS [15]. Therefore, animal models that mimic MS course and pathology to a high degree should be used in basic research [16–18]. Such models are partly available and there should be a common consensus between researchers in academia and industry regarding which model should be used for each question. The curtain has opened, some actors have appeared, more will follow. We are living in exciting times….

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