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Perspective

The future of multiple sclerosis therapy☆

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ABSTRACT

Multiple sclerosis (MS) represents the prototypic inflammatory autoimmune disorder of the central nervous system and the most common cause of neurological disability in young adults, exhibiting considerable clinical, radiological and pathological heterogeneity. A better understanding of the immunopathological processes underlying this disease have recently led to the design of numerous novel therapeutical approaches. Perhaps most importantly, therapy has changed dramatically over the past decade in that all relapsing forms of MS, including early forms of MS are now being treated relatively aggressively. However, there are still unmet needs in the management of this disease, especially since all of the currently available disease-modifying drugs are only partially effective. Most of the clinically relevant therapeutic agents are not yet available as oral formulations. A substantial number of pivotal and preliminary reports provide encouraging new evidence on advances being made in the development of oral therapies for MS. A different strategy is the development of very potent monoclonal antibodies, given intravenously or subcutaneously, many of which are being examined for clinical efficacy. These agents are potentially more effective, but may carry more serious side effects. Finally, drugs with a known good safety profile are being developed further. These advances are critically reviewed and put into perspective.

1. Unmet needs in MS therapy

Based on the growing immunopathogenetic understanding of Multiple Sclerosis (MS) and with the assistance of modern biotechnology an enlarging arsenal of potential therapeutic drugs has been developed [1]. Several agents have been approved and are now being widely used, and a whole battery of new immunomodulatory treatments is currently being studied or is under development [2,3]. Due to increasing knowledge about the cellular and molecular mechanisms of immune cell migration and activation, the emphasis of drug development has shifted away from indiscriminate immunosuppresion or global immunomodulation towards more selective, target-specific therapies [4,5]. However, recent years taught us that selectivity does not necessarily imply more efficacy [6]. This observation is supported by the recognition of considerable MS disease heterogeneity at the clinical, immunological and pathomorphological level. Thus, in parallel to the sophisticated and elegant immune-selective strategies, concepts of a more general immunosuppression and broader immunomodulation in MS therapy receive increasing attention. Furthermore, emerging treatment strategies take into account the different pathological mechanisms, in particular strategies to protect neurons against axonal damage and loss. Neurodegeneration and lack of significant regenerative mechanisms clearly seem to predominate over inflammatory damages in later stages of the disease course. There is currently no approved medication for patients with progressive MS in the United States, and there is a paucity in clinical trial initiatives. This situation illustrates the need for novel therapeutic interventions for patients with this disease phenotype.

There are other unmet needs in MS therapy: most of the immunomodulatory and immunosuppressive drugs available for treatment in MS are not orally available. Any oral formulation would be highly appreciated by all patients, improving quality of life and increasing adherence to therapy [7]. On the other hand, an increase in clinical efficacy is clearly warranted. With the advent of highly potent novel therapies, rare, but potentially serious adverse effects have been noted, namely infections and malignancies. Thus, there still is an urgent need to develop better therapeutic strategies.

2. Oral agents

Clearly, oral agents if at least as effective or even more effective than the currently available injectable therapies would be a

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welcome advance. Many oral drug candidates are being tested in Phase II and III programs. The currently most promising agents are listed below.

2.1. Cladribine

Cladribine is an adenosine deaminase-resistant nucleoside analogue with selective lymphotoxic specificity. After phosphorylation into the active triphosphate deoxynucleotide the substance accumulates in lymphocytes and monocytes causing DNA damage and subsequent cell death [8]. Its long-lasting lymphocytotoxic activity suggests that it could be useful in modulating conditions involving lymphocyte abnormalities. Thus, cladribine has been extensively tested for the treatment of lymphoid neoplasms and autoimmune disorders, especially MS. The substance is approved for the treatment of hairy cell leukemia since 1993.

Evidence on the efficacy of cladribine in delaying disease progression mainly results from smaller placebo-controlled trials in patients with chronic progressive MS [9,10] and patients with RRMS [11,12]. The clinical observations were underlined by remarkable MRI effects, e.g. nearly complete elimination of enhanced T1 lesions and stabilization of T2 lesion volume. However, although phase I and II studies raised high expectations, a multicenter, double-blind, placebo-controlled study of cladribine patients with SPMS and primary progressive MS (PPMS) failed to show significant clinical benefits after 1 year. No significant effect on whole brain volume changes and T1 "black holes" could be observed [13–16].

Cladribine has recently become available as an oral formulation leading to the initiation of a randomized, double-blind, placebo-controlled phase III study including 1290 patients with active inflammatory RRMS. This trial was launched in April 2005 to further test the safety and effectiveness of this oral immunosuppressant. According to the study protocol, 10 mg cladribine or placebo is given orally over 5 days per month, administered in 2–4 cycles per year. The outcome parameters include relapse rate, EDDS progression and MRI activity. In a recently published press release from Merck Serono signifcant superiority of cladribine compared to placebo has been reported (www.merckserono.net). The annual relapse rate of patients receiving placebo was reported with 0.33, whereas patients on active drug showed rates of 0.14 in the low dose and 0.15 in the high-dose group, pointing to a significant relapse rate reduction of cladribine. The publication of these results is expected soon and should offer a more comprehensive view on these results.

2.2. Teriflunomide

Teriflunomide is an analogue of leflunomide (Arava), which is approved for the therapy of rheumatoid arthritis. Teriflunomide belongs to the group of malononitrilamide agents which block the mitochondrial enzyme dihydroorotatedehydrogenase and inhibit T and B cell proliferation [17,18]. Leflunomide has been successfully used to treat rheumatoid arthritis. Teriflunomide has been found to suppress clinical and pathological manifestations of the animal model of MS, experimental autoimmune encephalomyelitis (EAE), probably via the inhibition of the cytokines tumor necrosis factor (TNF) alpha and interleukin (IL)-2 [19-21]. The results from a clinical phase II study evaluating teriflunomide in patients with relapsing RRMS and SPMS have recently been published [22]. Two different teriflunomide dose regimes (7 and 14 mg once-daily) were compared to placebo over an observation period of 36 weeks. The primary endpoint of the study was met since subjects receiving verum (either dose) had significantly less active MS lesions and reduced numbers of new lesions on MRI. EDSS progression was delayed in the high-dose arm and a trend towards reduction in relapses was observed.

Thus, teriflunomide belongs to an interesting category of new oral immunomodulatory agents that are currently tested in phase III trials.

2.3. Laquinimod

Laquinimod (ABR-215062, SAIK-MS) is a new, orally active immunomodulator that was shown to be appoximately 20 times more potent than its "ancestor" roquinimex (linomide) in EAE [23]. The synthetic compound has an excellent oral bioavailability and serves as an immunoregulatory drug without general immunosuppressive properties. Its sustained inhibitory activity has been shown in other autoimmune and inflammatory diseases in several animal models [24–26]. Roquinimex (linomide) efficiently reduced active MRI lesions in phase II and III clinical studies of MS but a phase III trial in MS had to be stopped prematurely due to unexpected severe inflammatory side effects (serositis, myocardial infarction) [27,28].

Two clinical phase I trials with laquinimod demonstrated that the drug is well tolerated by healthy volunteers and patients with MS. The results from a double-blind, randomized, multicenter proof-of-concept study testing two different doses of oral laquinimod (0.1 mg/d and 0.3 mg/d) versus placebo in 180 with RRMS have been published [29]. The duration of the study was 24 weeks. Taken together, a significant difference between 0.3 mg laquinimod/d and placebo was observed for the primary outcome measure, that is the mean cumulative number of active MRI lesions (5.24 versus 9.44, respectively; 44% reduction). This effect was even more pronounced in those patients with at least one active lesion at baseline (52% reduction). Clinical outcome parameters (relapse rate, disability) were not different between the groups. Recently, the effect of 0.3 mg and 0.6 mg laquinimod compared to placebo on MRI-monitored disease activity was assessed in a 36-week phase IIb study. 306 patients with RRMS were included. Compared with placebo 0.6 mg laquinimod per day revealed a 40.4% reduction of the baseline adjusted mean cumulative number of Gd+ lesions per scan, whereas treatment with 0.3 mg per day showed no significant effects [30]. Laquinimod has considerable potential to become a safe and effective oral treatment of MS and is currently tested in a phase III trial.

2.4. Fingolimod

The compound Fingolimod (FTY720) is derived from the fungus *Isaria sinclairii* and exhibits profound and unique immunoregulatory effects [31–33]. After *in vivo* phosphorylation FTY720 forms FTY720P, a high-affinity non-selective mimetic of the sphingosine 1-phosphate receptor (S1P), necessary for lymphocytes to leave lymphoid tissues. Following engagement through the agonist the S1P1 receptor is internalized and can no longer bind to its natural circulating ligand, sphingosine 1-P (S1P). Thus, the agent entraps CD4+ and CD8+ T cells and B cells in secondary lymphatic organs, preventing them from being recruited to possible sites of inflammation [31,34]. This "entrapped" homing of lymphocytes seems to depend in large measure on the expression of different chemokines [34,35]. Furthermore, recent studies imply also a direct impact of FTY720 on dendritic cells [36]. Due to its mechanism of action FTY720 induces a marked lymphopenia in peripheral blood counts, but does not provoke a general immunosuppression, since neither the activation of T cells, nor memory T and B cell responses are impaired.

The potency of this agent has already been demonstrated in human organ transplantation [37]. Furthermore, preclinical studies in various EAE models demonstrated its efficacy [38–40]. The results of an international, double-blind, placebo-controlled phase II study involving 281 subjects with active RRMS have been published [41]. The participants received one of two doses of oral