J Neurol (2008) 255 [Suppl 6]:93–96
DOI 10.1007/s00415-008-6017-7

Sven G. Meuth
Christoph Kleinschnitz
Heinz Wiendl

Recent clinical trials and future therapies

Abstract Immunotherapy for multiple sclerosis (MS) has developed extremely successfully during the past decade and a number of new strategies were developed for the treatment of the disease. Examples include therapeutic strategies targeting leukocyte differentiation molecules, costimulatory molecules, anti-adhesion molecules, chemotaxis, novel immunomodulators, autologous stem cell transplantation, anti-infectious therapies and strategies for neuroprotection, neurorepair and remyelination. Here we describe examples of monoclonal antibodies, a novel immunosuppressant and interesting neuroprotective strategies.

Key words multiple sclerosis · monoclonal antibodies · neuroprotection

S. G. Meuth (✉) · Ch. Kleinschnitz · H. Wiendl
Universität Würzburg
Klinik und Poliklinik für Neurologie
Josef-Schneider Str. 11
97080 Würzburg, Germany
E-Mail: meuth_s@klinik.uni-wuerzburg.de

Introduction

The possibilities to treat multiple sclerosis (MS) have clearly improved over the past decade: the availability of immunosuppressants (azathioprine, mitoxantrone, cyclophosphamide), the advent of disease modifying drugs (beta-interferons (IFNβ), glatiramer acetate (GA)) in the 1990s and the recent approval of the monoclonal antibody natalizumab have broadened the therapeutic repertoire. However, all substances are only partially effective, some of them are associated with considerable long-term toxicity or the risk-benefit ratio is not entirely clear. There is tremendous activity in the search for new drugs and strategies for MS therapy [15, 17]; the sense of excitement in the field of MS therapeutics is reflected by the soaring number of publications.

Some interesting substances include further monoclonal antibodies (e.g., daclizumab, alemtuzumab, rituximab), oral agents (e.g., fingolimod, FTY720) or novel immunosuppressants (e.g., cladribine) are currently being investigated in clinical trials. Concerning neuroprotective strategies, preclinical research created good scientific rationale and partially prepared strategies or agents, but none of these efforts has yet been realized in clinical practice.

Daclizumab

The interaction of IL-2 and its receptor CD25 mediates a pivotal signal for T cell activation and proliferation. In general, anti-CD25 treatment aims to limit T cell proliferation by blocking IL-2 signaling via its high affinity receptor. The IL-2 receptor(R) antagonist daclizumab is a humanized mAb that interferes with the alpha chain of the IL-2R. Three open-label studies in MS showed that daclizumab is well tolerated and leads to a significant reduction in MRI activity and improvement in several clinical outcome measures [5, 21, 22]. The positive results of the CHOICE study (phase II) have recently been presented. On first glance, these results seem surprising or even paradoxical because CD25 is expressed not only on activated (pathogenic) T cells, but also on suppressor T cells [23]. However, the network of putative regulatory cells is complex and probably includes other subtypes of inhibitory cells [4]. A phase IIb study is currently recruiting patients to test the safety and efficacy of daclizumab in a placebo-controlled, double-blind manner [4].

Alemtuzumab

Alemtuzumab (Campath-1) represents a very good example of an agent with putatively high therapeutic efficacy but a considerable risk of adverse effects. In particular, the phase II trial in the active RRMS population demonstrated an impressively high therapeutic efficacy with a clear reduction of immune activity (tested against a high-dose interferon). Therefore the substance can be viewed as a mild but long lasting form of selective immune ablation. Campath-1 treatment triggers increased antibody-mediated CNS damage by augmenting B cell activity. For unknown reasons, about one third of Campath-1 treated patients develop antibodies against the thyrotropin receptor and subsequent carbimazole-responsive autoimmune hyperthyroidism (Grave's disease) [9, 10]. A phase II clinical trial designed to compare the safety and efficacy of alemtuzumab with IFNβ-1a in RRMS showed highly impressive effects on relapse rates and disease progression [8]. The trial was suspended but relaunched because there was evidence of severe toxicity (idiopathic thrombocytopenic purpura, ITP) including one case of death. Currently, two phase III trials (CARE-MS1, CARE-MS2) have been launched to evaluate clinical efficacy and long-term safety for potential approval.

Rituximab

Rituximab (mabthera) is a genetically engineered chimeric murine/human mAb against CD20, a differentiation antigen that is found on normal and malignant pre-B and mature B lymphocytes but which is absent on hematopoietic stem cells, activated B cells (plasma cells) and in normal tissues. CD20 is vital for the regulation of cell cycle initiation and differentiation. Two trials investigated the potential use of rituximab in MS: the rituximab in primary progressive (PP)MS trial (OLYMPUS), which is a phase II/III trial, and a phase II study involving RRMS patients, the results of which were recently published [14]: As compared with placebo, patients who received rituximab had significantly reduced activity on MRI (primary endpoint; newly occurring gadolinium-enhancing lesions) as well as reduced relapses for about a year. This is in line with a phase I open study using rituximab, which also showed beneficial effects in reducing MRI and clinical activity [1]. It is interesting to note that the onset of clinical benefit was faster than it could be expected just by depletion or reduction of putatively pathogenic antibodies. This clearly points towards effects of anti-CD20 therapy other than reduction of antibody production, e.g., the antigen-presenting function of B cells [18].

FTY720

The compound FTY720 is derived from the fungus *Isaria sinclairii* and exhibits profound and unique immunoregulatory effects [6, 7]. The therapeutic potency of this agent has already been demonstrated in various EAE models [13, 27]. In an international, double-blind, placebo-controlled phase II study of oral FTY720 involving subjects with active RRMS [16], the total number of enhancing MS lesions on monthly MRI scans (primary outcome) was significantly reduced and volumes of enhancing lesions and new T2-weighted lesions were significantly diminished. In addition, a significantly higher proportion of patients under FTY720 remained relapse-free. The relapse rate under FTY720 treatment was reduced between 53 % and 55 %. Two large phase III studies of FTY720 in MS are currently launched. One study is testing the safety and efficacy of two doses against placebo, the other is assessing the efficacy of FTY720 in a head-to-head design against IFNβ-1a as an active comparator.

Phase III studies will demonstrate whether FTY720 is able to document long-term efficacy and – even more important – safety in larger numbers of patients. It is unpredictable at the moment how chronic interference with lymphocyte homing and migration might affect immune surveillance of parenchymal organs including the CNS during long-term application.

Cladribine

Cladribine is an adenosine deaminase-resistant nucleoside analogue with selective lymphotoxic specificity [2, 24]. Its long-lasting lymphocytotoxic activity suggests that it could be useful in modulating conditions involving lymphocyte abnormalities. Thus, cladribine has been tested for the treatment of lymphoid neoplasms and autoimmune disorders, especially MS. Evidence on the efficacy of cladribine in delaying disease progression mainly results from smaller placebo-controlled trials in chronic progressive MS [3, 26] and RRMS patients [20, 25]. The clinical observations were underlined by remarkable MRI effects, e.g. nearly complete elimination of gadolinium-enhanced T1 lesions and stabilization of T2 lesion volume [25]. Albeit phase I and II studies raised high expectations, a multicenter, double-blind, placebo-controlled study of cladribine in patients with SPMS and PPMS failed to show significant clinical benefit after one year [19]. In addition, no effects on whole brain volume and T1 "black holes" were observed [11, 12]. Since cladribine reduced the number and volume of gadolinium-enhanced T1-weighted brain lesions and overall T2 lesion load, there is a discrepancy between those MRI endpoints and the observed clinical effects [19]. Evaluation of the MRI data led to the conclusion

that cladribine triggers strong and prolonged antiinflammatory effects by MRI criteria but may not influence the mechanisms of continuous tissue destruction and neurodegeneration [11, 12]. The substance is meanwhile available as an oral formulation and a randomized, double-blind, placebo-controlled phase III study in active inflammatory RR-MS has been conducted (CLARITY). Results are expected in 2009.

Neuroprotection

In general, strategies aimed at neuroprotection are challenging because assessment of neuroprotective effects in clinical studies is complicated. Another level of complexity is obtained by the question of patient selection (RRMS, SPMS, PPMS). The ideal time window for therapeutic intervention is undefined so far and different observation periods throughout the clinical trials hamper their comparability. Furthermore, in MS the situation is even more complex due to the dissemination of destructive and reparative processes within the CNS, as compared to other CNS disorders with a clearly defined onset and a single causality (e.g., stroke). Taken together, the transfer from bench to bedside has been disappointing thus far, although a number of agents showed neuroprotective potentials *in vitro* and in animal models of MS. Reasons may lie in the study design and patient selection, but also in the complex nature of MS lesion development (including the lack of knowledge regarding the "window of opportunity" for applying neuroprotective strategies) and difficulties in neuroprotection readout under clinical conditions. It is assumed that the availability of true direct neuroprotective strategies or agents for MS patients cannot be expected within the next 5 years.

Taken together we conclude that some of these agents will fulfill the key requirements in the treatment of a non-fatal disorder, which is convenience of drug administration and long-term efficacy plus safety. It is to be expected that within the next few years, novel oral immunomodulatory as well as further "biologicals" (e.g., monoclonal antibodies) or immunosuppressive agents will be available for the treatment of MS patients which will complement the currently available armamentarium of disease modifying drugs.

Conflict of interest Sven G. Meuth received honoraria for lecturing and travel expenses for attending meetings from Bayer Healthcare/Bayer Vital and Merck Serono and serves as a consultant for Merck Serono. Heinz Wiendl has received honoraria for lecturing, travel expenses for attending meetings and financial support for research from Bayer Health Care, Biogen Idec, Merck Serono, Novartis, Sanofi Aventis, and TEVA. Christoph Kleinschnitz received honoraria for lecturing and travel expenses for attending meetings from Biogen Idec/Elan, Schering, Serono, Bayer and Sanofi Aventis.

References

1. Bar-Or A, Calabresi PA, Arnlod D, Markowitz C, Shafer S, Kasper LH, Waubant E, Gazda S, Fox RJ, Panzara M, Sarkar N, Agarwal S, Smith CH (2008) Rituximab in relapsing-remitting multiple sclerosis: a 72-week, open-label, phase I trial. Ann Neurol 63:395–400
2. Beutler E (1992) Cladribine (2-chlorodeoxyadenosine). Lancet 340:952–956
3. Beutler E, Sipe JC, Romine JS, Koziol JA, McMillan R, Zyroff J (1996) The treatment of chronic progressive multiple sclerosis with cladribine. Proc Natl Acad Sci USA 93:1716–1720
4. Bielekova B, Catalfamo M, Reichert-Scrivner S, Packer A, Cerna M, Waldmann TA, McFarland H, Henkart PA, Martin R (2006) Regulatory CD56(bright) natural killer cells mediate immunomodulatory effects of IL-2Ralpha-targeted therapy (daclizumab) in multiple sclerosis. Proc Natl Acad Sci USA 103:5941–5946
5. Bielekova B, Richert N, Howard T, Blevins G, Markovic-Plese S, McCartin J, Frank JA, Wurfel J, Ohayon J, Waldmann TA, McFarland HF, Martin R (2004) Humanized anti-CD25 (daclizumab) inhibits disease activity in multiple sclerosis patients failing to respond to interferon beta. Proc Natl Acad Sci USA 101:8705–8708
6. Brinkmann V, Davis MD, Heise CE, Albert R, Cottens S, Hof R, Bruns C, Prieschl E, Baumruker T, Hiestand P, Foster CA, Zollinger M, Lynch KR (2002) The immune modulator FTY720 targets sphingosine 1-phosphate receptors. J Biol Chem 277:21453–21457
7. Chiba K (2005) FTY720, a new class of immunomodulator, inhibits lymphocyte egress from secondary lymphoid tissues and thymus by agonistic activity at sphingosine 1-phosphate receptors. Pharmacol Ther 108:308–319
8. Coles A, Group TCS (2007) Efficacy of Alemtuzumab in Treatment-Naive Relapsing-Remitting Multiple Sclerosis: Analysis after Two Years of Study CAMMS223. Neurology 68(Suppl 1):A100
9. Coles AJ, Wing M, Smith S, Coraddu F, Greer S, Taylor C, Weetman A, Hale G, Chatterjee VK, Waldmann H, Compston A (1999) Pulsed monoclonal antibody treatment and autoimmune thyroid disease in multiple sclerosis. Lancet 354:1691–1695
10. Coles AJ, Wing MG, Molyneux P, Paolillo A, Davie CM, Hale G, Miller D, Waldmann H, Compston A (1999) Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. Ann Neurol 46:296–304
11. Filippi M, Rovaris M, Iannucci G, Mennea S, Sormani MP, Comi G (2000) Whole brain volume changes in patients with progressive MS treated with cladribine. Neurology 55:1714–1718
12. Filippi M, Rovaris M, Rice GP, Sormani MP, Iannucci G, Giacomotti L, Comi G (2000) The effect of cladribine on T(1) 'black hole' changes in progressive MS. J Neurol Sci 176:42–44
13. Fujino M, Funeshima N, Kitazawa Y, Kimura H, Amemiya H, Suzuki S, Li XK (2003) Amelioration of experimental autoimmune encephalomyelitis in Lewis rats by FTY720 treatment. J Pharmacol Exp Ther 305:70–77

14. Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ, Bar-Or A, Panzara M, Sarkar N, Agarwal S, Langer-Gould A, Smith CH (2008) B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med 358:676–688
15. Hohlfeld R, Wekerle H (2004) Autoimmune concepts of multiple sclerosis as a basis for selective immunotherapy: from pipe dreams to (therapeutic) pipelines. Proc Natl Acad Sci USA 101: 14599–14606
16. Kappos L, Radu EW, Antel J (2005) Promising results with a novel oral immunomodulator-FTY720-in relapsing multiple sclerosis. Mult Scler 11: S13
17. Kleinschnitz C, Meuth SG, Kieseier BC, Wiendl H (2007) Immunotherapeutic approaches in MS: update on pathophysiology and emerging agents or strategies 2006. Endocr Metab Immune Disord Drug Targets 7:35–63
18. McFarland HF (2008) The B cell – old player, new position on the team. N Engl J Med 358:664–665
19. Rice GP, Filippi M, Comi G (2000) Cladribine and progressive MS: clinical and MRI outcomes of a multicenter controlled trial. Cladribine MRI Study Group. Neurology 54:1145–1155
20. Romine JS, Sipe JC, Koziol JA, Zyroff J, Beutler E (1999) A double-blind, placebo-controlled, randomized trial of cladribine in relapsing-remitting multiple sclerosis. Proc Association of American Physician 111:35–44
21. Rose JW, Burns JB, Bjorklund J, Klein J, Watt HE, Carlson NG (2007) Daclizumab phase II trial in relapsing and remitting multiple sclerosis: MRI and clinical results. Neurology 69:785–789
22. Rose JW, Watt HE, White AT, Carlson NG (2004) Treatment of multiple sclerosis with an anti-interleukin-2 receptor monoclonal antibody. Ann Neurol 56:864–867
23. Sakaguchi S (2005) Naturally arising Foxp3-expressing CD25+CD4+ regulatory T cells in immunological tolerance to self and non-self. Nat Immunol 6:345–352
24. Sipe JC (2005) Cladribine for multiple sclerosis: review and current status. Expert Rev Neurother 5:721–727
25. Sipe JC, Romine JS, Koziol J, Zyroff J, McMillan R, Beutler E (1997) Cladribine improves relapsing-remitting MS: a double blind placebo controlled study. Neurology 48:A340
26. Sipe JC, Romine JS, Koziol JA, McMillan R, Zyroff J, Beutler E (1994) Cladribine in treatment of chronic progressive multiple sclerosis [see comments]. Lancet 344:9–13
27. Webb M, Tham CS, Lin FF, Lariosa-Willingham K, Yu N, Hale J, Mandala S, Chun J, Rao TS (2004) Sphingosine 1-phosphate receptor agonists attenuate relapsing-remitting experimental autoimmune encephalitis in SJL mice. J Neuroimmunol 153:108–121