28. Giuliano FA, Rampin O, Benoit G, et al. Neural control of penile erection. In Impotence. (A Melman, ed.). Urol Clin North Am 1995;**22**: pp 747–766.
29. Sipski ML, Alexander CJ, Rosen RC. Physiological parameters associated with psychogenic sexual arousal in women with complete spinal cord injuries. Arch Phys Med Rehabil 1995;**76**:811–818.
30. Brindley GS, Gillan P. Men and women who do not have orgasms. Br J Psychiatry 1982;**140**:351–356.
31. Janus SS, Janus CL. The Janus Report on Sexual Behavior. New York, John Wiley & Sons, 1993.
32. Marson L. Central nervous system control. In Textbook of Erectile Dysfunction (C Carson, R Kirby, I Goldstein, Eds.). Oxford, Isis Medical Media, 1999, p. 73.
33. Zivadinov R, Zorzon M, Locatelli L, et al. Sexual function in multiple sclerosis: a MRI, neurophysiological and urodynamic study. J Neurol Sci 2003;**210**:73–76.
34. Betts CD. Bladder and sexual dysfunction in multiple sclerosis. In Neurology of Bladder, Bowel, and Sexual Dysfunction. (CJ Fowler Ed.). Boston, Butterworth-Heinemann 1999, p 289.
35. Ghezzi A, Zaffaroni M, Baldini S, et al. Sexual dysfunction in male multiple sclerosis patients in relation to clinical findings. Eur J Neurol 1996;**3**:462.
36. Fowler CJ, Miller JR, Sharief MK, et al. A double blind, randomised study of sildenafil citrate for erectile dysfunction in men with multiple sclerosis. J Neurol Neurosurg Psychiatry 2005;**76**:700–705.
37. Valleroy M, Kraft G: Sexual dysfunction in multiple sclerosis. Arch Phys Med Rehabil 1984;**65**:125–128.
38. Minderhoud JM, Leemhuis JG, Kremer J, et al. Sexual disturbances arising from multiple sclerosis. Acta Neurol Scand 1984;70:299–306.
39. Barak Y, Achiron A, Elizur A, et al. Sexual dysfunction in relapsing-remitting multiple sclerosis: magnetic resonance imaging, clinical, and psychological correlates. J Psychiatry Neurosci 1996;**21**:255–258.
40. Shaughnessy L, Schuchman M, Ghumra M, et al. Sexual dysfunction in multiple sclerosis. In Sexual and Reproductive Neurorehabilitation. (M Aisen. Ed.). Totowa, NJ, Humana Press, 1997, p 169.
41. Yang CC, Bowen JR, Kraft GH, et al. Cortical evoked potentials of the dorsal nerve of the clitoris and female sexual dysfunction in multiple sclerosis. J Urol 2000;**164**:2010–2013.
42. Hulter BM, Lundberg PO. Genital vibratory perception threshold (VPT) measurements in women with sexual dysfunction and/or sexual pain disorders. Eur J Sexual Health 2006;**15** (Suppl. S33).
43. Rosen RC, Riley A, Wagner G, et al. An international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997;**49**:822.
44. NIH Consensus Development Panel on Impotence. Impotence. JAMA 1993;**270**:83–90.
45. Wagner TH, Patrick DL, McKenna SP, et al. Cross-cultural development of a quality of life measure for men with erection difficulties. Qual Life Res 1996;**5**:443–449.
46. Rosen R, Brown C, Heiman J, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther 2000;**26**:191–208.
47. Lue TF. Editorial comment. J Urol 1996;**156**:552.
48. Dasgupta R, Wiseman OJ, Kanabar G, et al. Efficacy of sildenafil in the treatment of female sexual dysfunction due to multiple sclerosis. J Urol 2004;**171**:1189–1193.
49. Salonia A, Rigatti P, Montorsi F. Sildenafil in erectile dysfunction: a critical review. Curr Med Res Opin 2003;**19**:241–262.
50. Zusman RM, Morales A, Glasser DB, et al. Overall cardiovascular profile of sildenafil citrate. Am J Cardiol 1999;**83**:35C.
51. Betts CD, Jones SJ, Fowler CG, et al. Erectile dysfunction in multiple sclerosis. Brain 1994;**117**:1303–1310.
52. Lundberg PO. Priapism. Review. Scand J Sexol 2000;**3**:13–24.
53. Rivas D, Chancellor M. Complications associated with the use of vacuum constriction devices for erectile dysfunction in the spinal cord injured population. J Am Paraplegia Soc 1994;**17**:136–139.
54. Singer C. Erectile and ejaculatory disturbances: overview of diagnosis and treatment. In Sexual Dysfunction: A Neuro-Medical Approach. (C Singer, WJ Weiner, Eds.). Armonk, NY, Futura, 1994, p 45.
55. Kandeel FR, Koussa VK, Swerdloff RS. Male sexual function and its disorders: physiology, pathophysiology, clinical investigation, and treatment. Endocr Rev 2001;**22**:342–388.

Immunotherapy of multiple sclerosis

Sven G. Meuth, Stefan Bittner & Heinz Wiendl
Department of Neurology, University of Würzburg, Würzburg, Germany

Abstract: Multiple sclerosis (MS) is regarded as a prototypic inflammatory autoimmune central nervous system disorder causing neurological disability in young adults. Recommended basic immunomodulatory therapies of MS are currently interferon beta and glatiramer acetate. Both have proven to be clinically and paraclinically effective and clinical evidence suggests that treatment should be initiated as early as possible.

However, despite the fact that therapeutic options for MS have significantly been widened over the past decade there is still tremendous activity in the search for new treatment options for MS.

One important development in the field is reflected by the substantial number of promising results for oral therapies. Various phase III clinical trials are currently being initiated or are already underway evaluating the efficacy of a variety of orally administered agents, including cladribine, teriflunomide, laquinimod, fingolimod and fumaric acid. It is hoped that these oral therapies for MS further broaden our armament for MS therapy.

Introduction: Multiple sclerosis (MS) is the most common neurological cause of disability in young adults with a lifetime risk of one in 400. MS is considered as an autoimmune inflammatory disorder of the central nervous system (CNS) which is influenced by environmental factors and susceptibility genes (1,2). Both temporal and spatial dissemination of lesions in the CNS is needed to clinically diagnose MS. The risk for developing clinically definite MS (CDMS) is highest when asymptomatic white-matter lesions in the brain can be found by MRI (3). But also patients with an isolated clinical deficit as for example optic neuritis (clinically isolated syndrome; CIS) are at risk of developing MS in the course of time. In one follow-up study, the 10-year risk of developing CDMS was 39%, the 20-year risk was 49%, the 30-year risk was 54% and the 40-year risk was 60% (4). The diagnostic criteria for MS (McDonald criteria) take these findings into consideration and allow diagnosing MS even before a second clinical event. Instead MRI evidence of dissemination of CNS lesions in time and space is sufficient for the diagnosis of MS (5,6). The presence of oligoclonal bands doubles the risk for having a second attack while not influencing the development of disability (7).

In the course of years, the majority of MS patients develop progressive neurological disabilities. About 50% of MS patients will use a cane to support walking within 10 years and the disease course of most MS patients will develop into a secondary progressive form of the disease displaying substantial residual clinical deficits (8,9). The disease activity in early phases of the

© 2009 The Authors
Journal Compilation © 2009 John Wiley & Sons A/S

https://doi.org/10.1017/S092427080003266X Published online by Cambridge University Press

disease is apparently a strong predictor for the timing of disability as irreversible deficits may accumulate with each disease exacerbation. Therefore CIS and RRMS though not classified as progressive forms of MS strongly contribute to progressive persistent clinical impairment. This concept is the reason to initiate MS treatment at the earliest time point possible. The therapeutic approaches to the various forms of MS (CIS, RRMS, SPMS, PPMS) have been changed profoundly over the last decade and several novel disease-modifying therapies have been established (10–12). The current treatment strategies of the various subforms of MS will be discussed in the following paragraphs. Furthermore we describe a number of new, oral substances including cladribine, teriflunomide, laquinimod, fingolimod and fumaric acid currently tested in clinical trials. These substances are awaited to broaden our armament for MS therapy.

Treatment of clinically isolated syndromes:

Interferon beta: The effect of interferon beta (IFN) on the progression time from CIS to CDMS has been investigated in three multicenter, double-blind, placebo-controlled trials: The Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) trial in 2000 (13), the Early Treatment Of Multiple Sclerosis (ETOMS) trial in 2001 (14) and the Betaferon/Betaseron in Newly Emerging Multiple Sclerosis For Initial Treatment (BENEFIT) trial in 2006.

383 patients with a first demyelinating event were enrolled in the CHAMPS study. In addition, patients had to exhibit two ore more asymptomatic lesions on MRI to be included into the study (13). The treatment group received intramuscular IFN beta-1a 30 μg once a week. The interim analysis showed a significant lower cumulative probability of the development of CDMS in the IFN beta than in the placebo group after 3 years (OR 0.56; 95% CI 0.38–0.81; $P = 0.002$). Therefore the trial was stopped and assessment of both outcome measures (development of CDMS and changes in findings on MRI of the brain) revealed that treatment benefit was also seen in patient subgroups based on age, gender and baseline brain MRI parameters. The beneficial effect of IFN beta-1a when initiated at the first clinical demyelinating event in patients with MRI evidence of subclinical demyelination in the brain was observed in patients with different manifestations (spinal cord syndromes, brainstem-cerebellar syndromes and optic neuritis) (15). The CHAMPIONS study (Controlled High Risk Avonex Multiple Sclerosis Prevention Study in Ongoing Neurological Surveillance) was initiated as a 5-year open-label extension of the CHAMPS study in order to assess the long-term efficacy of early treatment with IFN beta. 53% of patients enrolled in CHAMPIONS (203/383; $n = 100$, initial treatment group; $n = 103$, delayed treatment group). The median time to start IFN beta-1 treatment in the delayed treatment group was 29 months. The cumulative probability of development of CDMS was significantly reduced in the initial treatment group (5 year incidence 36 ± 9%) in comparison to the delayed treatment group (49 ± 10%; $P = 0.03$) (16).

In the ETOMS study, 309 patients were recruited but four clinically silent white matter lesions (or only three if one of them was enhancing after administration of gadolinium) were required for this study (14). Half of the patients received subcutaneous IFN beta-1a at 22 μg once a week and half placebo. Progression to CDMS was observed in fewer patients in the IFN group than in the placebo group (OR 0.61; 95% CI 0.37 – 0.99; $P = 0.045$), the time point at which 30% of patients had developed CDMS was significantly later in the treatment group and the number of relapse rates per year were significantly lower. MRI readout revealed fewer new lesion formations in the IFN group.

In the BENEFIT study 468 patients were recruited after their first demyelinating event and two clinically silent brain MRI lesions. Half received subcutaneous IFN beta-1b 250 μg e.o.d. and half placebo (17). 45% of the placebo patients progressed to CDMS and 85% fulfilled the McDonald criteria after 2 years. The treatment group showed significantly delayed conversion to CDMS (OR 0.50; 95% CI 0.36 – 0.70; $P < 0.0001$) and to McDonald criteria MS (OR 0.54; 95% CI 0.43 – 0.67; $P < 0.00001$). A post-randomisation follow-up of all patients over an additional 3 years which was completed by 392 patients (84%) showed that the risk of progression of disability was reduced by 40% (18).

Any patient with a high risk for converting into CDMS may therefore be considered as suitable for IFN beta treatment. It is nevertheless still challenging to sort out those CIS patients who will develop CDMS and this question has been addressed by a number of studies. The majority of patients with CIS and additional asymptomatic white-matter lesions as assessed by MRI will convert into CDMS (19–23). The Optic Neuritis Treatment Trial (ONTT) showed that the number of brain lesions in patients with monosymptomatic optic neuritis is a strong marker to identify patients with a high risk of developing CDMS (24). Nearly 90% of patients with CIS and an abnormal MRI in the beginning were found to progress into CDMS in a 14-year prospective study (3) in contrast to only 21% of the patients with normal baseline MRI. The disease course after 20 years of follow-up was relapsing-remitting in 58% while 42% had further progressed into SPMS. A moderate correlation between T2 lesion volume at all time-points and 20-years EDSS was found (r(s) values 0.48 to 0.67; $P < 0.001$ and MSFC z-score (r(s) values (–0.50) to (–0.61); $P < 0.001$) (25). There are several reasons to initiate therapy with IFN beta without unnecessary retardation (26). First, pathological events in the beginning of the disease are a strong predictor for the timing of disability and axonal damage caused by inflammation is an early feature of MS. Moreover, the inflammatory process in RRMS proceeds continuously and is not restricted to phases with clinical symptoms. Finally, the activity of the immune system may be influenced more easily in the beginning of the disease and it may be more difficult to deal with later on. Therefore, an early immunomodulatory therapy is the most effective strategy at the moment to control and limit the progression of disease (27). Surrogate markers like MRI will help to identify those patients with CIS who will profit most from early treatment with IFN beta.

Glatiramer acetate: The data of a randomized, placebo-controlled phase III study concerning the effect of glatiramer acetate have not been published so far. However, the study was recently completed and communications at a number of meetings suggest that the beneficial influence of GA on disease progression from CIS to CDMS might be comparable to the effect of the interferons. Approval of GA for CIS has been granted recently.

Treatment of relapsing-remitting MS: Various agents are currently approved by the FDA (US Food and Drug Administration) for the treatment of RRMS: Three different IFN beta formulations (subcutaneous IFN beta-1b, Betaferon®/Betaseron®/Extavia®; intramuscular IFN beta-1a, Avonex®; subcutaneous IFN beta-1a, Rebif®), glatiramer acetate (Copaxone®), and mitoxantrone (Novantrone®). However, there is still an intent discussion about which disease-modifying drug should be chosen.

Interferon beta: While clearly effective in MS in a number of clinical trials, the exact mode of action of the interferons is still a matter of debate and various biological activities have been described so far. Among others, interferons inhibit the proliferation of leukocytes, hamper antigen presentation, shift the cytokine production towards an anti-inflammatory Th2 phenotype and reduce the T cell migration capacity across the blood-brain barrier by down-regulation the expression of adhesion molecules and matrix metalloproteinases (28–30).

The first class I trial (multicenter, randomized, double-blind, placebo-controlled) in RRMS demonstrated clinical efficacy of IFN beta-1b (31–33). 372 patients with a maximal EDSS of 5.5 and at least two exacerbations in the previous 2 years were included

© 2009 The Authors

https://doi.org/10.1017/S092427080003266X Published online by Cambridge University Press

into the study. One third received 1.6 million international units (MIU; 50 μg) of subcutaneous IFN beta-1b, one third 8 MIU (250 μg) IFN beta-1b and one third placebo. The annual exacerbation rate was investigated after 2 years and was significantly lowered in both treatment groups compared with the placebo group (annual exacerbation rate placebo: 1.27; 1.6 MIU: 1.17 and 8 MIU: 0.84. Statistical evaluation: 1.6 MIU vs. placebo, $P = 0.0101$; 8 MIU vs. placebo, $P = 0.0001$; 8 MIU vs. 1.6 MIU, $P = 0.0086$). These results might suggest a dose-dependent effect of IFN beta-1b treatment as well, but this was not a primary outcome measure in the design of the study. Evaluation of MRI (T2) revealed that IFN beta-1b patients had significantly lower lesion loads than patients treated with placebo. The 8-MIU treatment also reduced the confirmed 1-point EDSS progression rate but statistical significance was not reached for this parameter (-29%, $P = 0.016$).

The effect of intramuscularly administered IFN beta-1a treatment was studied in a multicenter, randomized, placebo-controlled study (34–36). 301 patients with an EDSS of 1.0 to 3.5 were included who in addition suffered from at least two clinical events in the last 3 years. Dosage was 6 MIU (30 μg) of intramuscular IFN beta-1a once weekly vs. placebo. The primary outcome measure in this study was time to sustained progression of at least 1.0 point on the EDSS scale. The trial was stopped earlier than anticipated in the beginning and therefore only 57% of the patients enrolled (172 patients) completed 2 years of IFN beta-1a treatment. Study medication resulted in a significantly delayed time to sustained EDSS progression (-37%, $P = 0.02$). The Kaplan-Meier estimate of the percentage of patients with EDSS progression by the end of the 2 years was 34.9% in the placebo group vs. 21.9% in the treatment group. IFN beta-1a treated patients also had a significantly reduced number of disease exacerbations ($P = 0.03$) and a significantly lower number of gadolinium-enhanced lesions in the brain on MRI (-33%, $P = 0.05$) compared with the place group. The annual exacerbation rate over 2 years was reduced from 0.90 in the placebo-arm to 0.61 in the IFN beta-1a-arm. An interesting finding was that the reduction in the attack rate in the therapy group didn't reach statistical significance in the first year (-9.6%) but the reduction in patients after 2 years was significantly lower (-32%, $P = 0.002$). This result suggests that the beneficial effect of IFN beta-1a might be delayed. However, patients who fully completed the 2 years already had a similar reduction in the attack rate in the first year (-29%) which on the other hand suggests that the 2-year completers do not represent the study cohort as a whole. Anyhow, IFN beta-1a clearly showed a significant effect in RRMS in this clinical trial as it reduced the accumulation of permanent physical disability, frequency of exacerbations and disease activity measured by gadloinium-enhanced lesions on brain MRI.

The effect of IFN beta-1a administered subcutaneously was investigated in the Prevention of Relapses and Disability by IFN beta-1a Subcutaneously in Multiple Sclerosis (PRISMS) study. PRISMS was a much larger multicenter, randomized, double-blind, placebo-controlled trial (Class I) in 560 RRMS patients with a maximal EDSS score of 5.0 and additionally at least two relapses in the previous 2 years (37.38). Patients were divided into three groups: Subcutaneous IFN beta-1a at 22 μg (6 MIU) or 44 μg (12 MIU) three times a week or placebo. The relapse rate after 2 years was significantly reduced with both doses of IFN beta-1a than with placebo treatment (mean number per patient: 1.82 for 22 μg, 1.73 for 44 μg and 2.56 with placebo). Risk reduction was calculated as 27% (95% CI 14 – 39) for 22 μg and 33% (95% CI 21 – 44) for 44 μg. MRI assessment revealed significant improvement in the IFN beta-1a treatment group when compared to the placebo arm (median number of T2 active lesions -78%, $P < 0.0001$ and volume of T2 lesions -14.7%, $P < 0.0001$). Moreover, the confirmed 1-point EDSS progression rate was also significantly reduced (-30%, $P < 0.05$) by IFN beta-1a medication. Taken together this study further underlines the therapeutical value of IFN beta in RRMS patients. Additionally, this clinical trial demonstrates that IFN beta can significantly lower both the T2 disease burden as well as the confirmed 1 –point EDSS progression. This study was continued for another 2 years and named therefore PRISMS-4. The former placebo-treated patients were now re-randomized double-blindly to one of the two treatment groups receiving either a low or high dosage of IFN beta-1a (39). This extensions study can be discussed because a bias can not be excluded based on previous drop-outs and the re-randomization. Nevertheless, this extension phase showed both a clinical and a benefit on MRI level for IFN beta-1a. The PRISMS-4 study shows that patients still benefit from treatment in the third and fourth year although the first 2 years of therapy were associated with the greatest reduction in relapse rate and MRI burden. A dose-dependent effect after 4 years was only seen for some clinical and MRI outcomes but not for others.

The OWIMS (Once Weekly Interferon for MS Study) trial IFN beta-1a was administered subcutaneously in a dosage of 22 μg or 44 μg in comparison with placebo. After 48 weeks, a benefit on MRI level was confirmed for IFN beta-1a at 22 μg in RRMS but no significant clinical effect was observed (40).

IFN beta therapy often causes side effects. The most common are flu-like symptoms, elevation of liver enzymes and lymphopenia (32,34,38). These side effects, however, are generally mild and rarely last longer than some months after statement of treatment. Therapy can therefore be continued in most cases. Subcutaneous injection of IFN beta can also cause reactions at the injection site and side effects of IFN beta are observed more often at higher doses. The use of auto-injectors as well as training of patients to correctly inject IFN beta and concomitant anti-inflammatory medication can reduce these problems and therefore increase the compliance of patients.

In summary, IFN beta is effective in RRMS both on a clinical and on MRI level and IFN beta therapy may be considered in any patient with RRMS.

Glatiramer acetate: Glatiramer acetate is a random polypeptide consisting of four different amino acids (glutamic acid, lysine, alanine and tyrosine) in a specific molar ratio. So far, its immunological mechanisms of action are still not fully unravelled but some of them seem to be distinct from those of the interferons. It is suspected that GA treatment leads to a shift from a Th1 to a Th2 phenotype, induces antigen specific T suppressor cells that may cross-react with putative autoantigens in the CNS and that it also directly inhibits antigen presentation (29,41).

In a large, multicenter, randomized, double-blind and placebo-controlled trial with 251 RRMS patients half of them received 20 mg subcutaneous glatriamer acetate daily and half placebo. To be enrolled patients had to have an EDSS score between 0 and 5.0 and they had to have suffered from at least two clinical attacks in the previous 2 years. The study was initiated for 2 years with an extension phase of another third year (42). The relapse rate over 2 years was significantly lower in GA treated patients (-29%, $P = 0.007$). MRI parameters were not investigated in this clinical trial. However, a second short duration trial specifically addressed MRI findings upon GA treatment (14). 249 RRMS patients with a maximal EDSS score of 5.0 and at least one gadolinium-enhancing lesion on baseline MRI were enrolled and the treatment group showed a significant reduction in the total number of enhancing lesions (-35%, $P = 0.001$). Interestingly, the treatment effect only occurred after 6 months of treatment. This delay indicates that GA rather has a long-term immunomodulatory effect and rather no immediate immunosuppressive effect or effect on the blood-brain barrier. In an open-label extension trail all patients were assigned to GA for another 9 months. A reduction of 54% in the mean number of enhancing lesions for the previous placebo treated patients and an additional reduction of 25% for those always

© 2009 The Authors
Journal Compilation © 2009 John Wiley & Sons A/S

https://doi.org/10.1017/S092427080003266X Published online by Cambridge University Press

treated with GA was reported. These data suggest a sustained effect of glatiramer acetate over the period of one and a half years based on MRI parameters (43).

A recent study concerning the long-term clinical efficacy as well as long-term safety profile of GA over 22 years was published in 2008. A lower relapse rate and a slower EDSS progression was found in this open-label observational study in RRMS patients (44). However, the study cohort is self-selected and therefore a bias of this study towards treatment effects can not be excluded.

GA therapy generally causes only mild side effects and injection site reactions are usually minimal (45). In summary, GA reduces clinical relapses in patients with RRMS and therefore can be recommended for treatment of these patients.

Treatment of secondary progressive MS: Patients with SPMS are still a great challenge in terms of therapeutic treatment. It must be taken into account that the degree of disability and the inflammatory activity as determined by the annual relapse rate may vary widely in these patients. A successful therapeutic approach to patients with SPMS must therefore be personalized and especially weigh carefully between the expected clinical benefit and the adverse effects of the chosen therapy which might potentially occur.

Interferon beta: Effect of IFN beta treatment in SPMS patients has been tested in several large, randomized, placebo-controlled trials. One trial in Europe and one in North America investigating IFN beta-1b in SPMS have been reported.

718 patients with and EDSS of 3.0 to 6.5 were enrolled in the European trail. Patients also had to have either two relapses or more than a 1.0 point increase in the EDSS score in the previous 2 years. Half were treated with the standard dose of IFN beta-1b and half received placebo (46). IFN beta-1b treated patients had a significantly reduced 1-point EDSS progression rate (-33%, $P = 0.0008$) than placebo-treated patients and a significant improvement was also found concerning clinical and MRI attack rates and the volume of white-matter disease assessed by MRI. Subgroup analysis of patients with our without clinical attacks in the 2 years prior to study initiation or analysis of those patients who did or did not have attacks during the study all demonstrated similar therapeutical effects of IFN beta-1b. However, patients with an EDSS of at least 6.0 profited less and the North American trial failed to show any difference in time to confirmed progression of EDSS scores between both IFN beta-1b treatment groups and the placebo group (47).

A retrospective analysis was conducted to unravel the reason for the discrepancy between the European and the North American trial (48) and it was found out that the European patients were situated in an earlier phase of SPMS and that their disease was more active both pre-study (number of relapses, MRI data) as well as during the study (EDSS score, number of relapses, MRI data). This indicates that IFN beta is more effective in the relapsing phase of the disease course.

The Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-beta-1a in MS (SPECTRIMS) trial which tested the effect of subcutaneous IFN beta-1a in SPMS similarly failed to find a statistically significant reduction in the confirmed 1-point EDSS progression rate (49). Patients were post hoc separated into those with or without relapses and this analysis showed a beneficial therapeutic effect on the confirmed 1-point EDSS progression rate in the patient subgroup with attacks ($P = 0.027$). Such a re-analysis however gives raise to criticism about the validity of the results. The data would once more support the concept that IFN beta is most effective in patients with a residual inflammatory activity in early phases of SPMS.

The IMPACT trial investigated the effect of intramuscular IFN beta-1a in 436 patients with SPMS and an EDSS score of 3.5–6.5 (50). Patients either received 60 μg IFN beta-1a (twice the FDA-approved dose for RRMS) or placebo by intramuscular injection once a week over 2 years. The MS Functional Composite (MSFC) which includes quantitative tests of ambulation (timed 25-foot walk), arm function (nine-hole peg test) and cognition (paced auditory serial addition test) was chosen as a primary outcome measure. IFN beta-1a led to a significant amelioration of MSFC scale ($P = 0.033$) and this was mostly due to improvement in the nine-hole peg test. No difference was found in EDSS score. Patients treated with IFN beta-1a had significantly fewer relapses ($P = 0.008$) and it is therefore appropriate to consider IFN beta for treatment in SPMS patients who still experience relapses but not in those patients without clinical attacks.

IFN beta-1b was approved for the treatment of SPMS patients in the US by the FDA and the European agency (EMEA) also approved IFN beta-1b and subcutaneous IFN beta-1a for SPMS with superimposed relapses. The efficacy of IFN-beta in patients with SPMS who do not experience relapses any more is unclear at the moment.

Treatment of primary progressive MS: Primary progressive MS appears to be different from relapsing-remitting MS in terms of pathology and clinical appearance. So far, treatments for RRMS have failed in PPMS and neither the interferons nor glatiramer acetate have shown to be effective in this subform of MS and therefore can not be recommended (51,52).

Oral disease modifying treatments for MS:

Cladribine: The adenosine deaminase-resistant nucleoside analogue cladribine accumulates – after phosphorylation into the active triphosphate deoxynucleotide – in lymphocytes and monocytes causing DNA damage and subsequent cell death (53,54). Since 1993 the substance is approved for the treatment of hairy cell leukemia.

Smaller placebo-controlled trials in chronic progressive MS (55,56) and RRMS patients (57) demonstrated that cladribine delays disease progression, nearly completely eliminates gadolinium-enhanced T1 lesions and stabilizes T2 lesion volume. Anyhow, a multicenter, double-blind, placebo controlled trial of cladribine in 159 patients with SPMS and PPMS showed no significant clinical benefit after 1 year (0.7 mg/kg, 2.1 mg/kg vs. placebo) (58–60). Side effects included upper respiratory tract infarctions, muscle weakness and injection site reactions. 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 (60). Meanwhile the substance is available as an oral formulation and a randomized, double-blind, placebo controlled phase III trial (1290 RRMS patients) has been initiated (CLARITY). The outcome parameters include relapse rate, EDSS progression and MRI activity and results from this trial are expected in 2009.

Furthermore two other phase III trials investigate the substance in CIS patients (ORACLE) and pre-treated RRMS patients (ONWARD).

Teriflunomide: Teriflunomide belongs to a group of malononitrilamide agents blocking the mitochondrial enzyme dihydroorotatedehydrogenase, is an analogue of leflonomide (known from the therapy of rheumatoid arthritis) and inhibits T and B cell proliferation by energy reduction (61,62). Teriflunomide has been found to display beneficial effects on the EAE model probably by suppression of TNFα and IL2 (63,64). Results from a clinical phase II trial testing teriflunomide (7 or 14 mg/day vs. placebo over 36 weeks) in patients with RRMS and SPMS have recently been published (65). The primary endpoint of the study was met since subjects receiving verum of either dose had significantly less active MS lesions and a reduced number of new lesions on MRI. Furthermore EDSS progression was delayed (high dose group) and a trend towards reduction in relapses was observed. Besides respiratory tract infections and headache the substance was well tolerated. Anyhow, serious side effects (e.g. toxic liver necrosis and pancytopenia) have been described in

© 2009 The Authors

https://doi.org/10.1017/S092427080003266X Published online by Cambridge University Press

patients with rheumatoid arthritis. Therefore final appraisal of the substance has to wait for the results of an ongoing phase III trial investigating the safety and efficacy of the drug in MS.

Laquinimod: Laquinimod (ABR-215062, SAIK-MS) is a novel orally active immunomodulator which is approximately 20 times more potent than its ''ancestor'' roquinimex (linomide), at least in EAE (66). The synthetic compound is characterized by a convincing oral bioavailability and it mediates immunoregulatory properties without general immunosuppressive actions. In a number of different animal models mimicking autoimmune or inflammatory diseases the sustained inhibitory activity of the immune system could be shown (67–69). In clinical phase II studies of MS linomide significantly reduced active MRI lesions, but a phase II trial had to be halted due to unexpected severe side effects (e.g. serositis and myocardial infarction) (70,71).

Two phase I studies indicated that laquinimod is well tolerated and results from a double-blind, randomized, multicenter proof-of principle study testing 0.1 mg/day and 0.3 mg/day vs. placebo in 180 patients with RRMS have recently been published (72). A significant difference between laquinimod 0.3 mg/day and placebo was observed for the primary outcome measure, i.e. the mean cumulative number of active MRI lesions (5.24 vs. 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.

Based on these data laquinimod has a good potential to become a safe and effective oral treatment in MS. The substance is currently tested in a large phase III trial.

Fingolimod: The orally available compound FTY720 (fingolimod, 2-amino-2-(2-(4-octylphenyl)ethyl)-propan-1,3-diole) is derived from the fungus *Isaria sinclairii* and exhibits profound and unique immunoregulatory effects by targeting sphingosine-1-phosphate (S1P) receptors (73). After *in vivo* phosphorylation FTY720 forms FTY720P which leads to internalization of the SIP1 receptor, resulting in a rapid and reversible inhibition of lymphocyte egress from peripheral lymph nodes, which prevents auto reactive T cells from sites of autoimmune inflammation (74). Further effects were demonstrated on dendritic, endothelial and glia cells (75–77). The therapeutic potency of this agent has already been demonstrated in acute and chronic EAE models (78,79). The results of an international, double-blind, placebo-controlled phase II study involving 281 subjects with active RR-MS have recently been released (80). The participants received one of two doses of oral FTY720 (1.25 mg/day or 5 mg/day, respectively) or placebo for 6 months. Both dosages of FTY720 significantly reduced the number of Gd-enhancing lesions and led to a 45% reduction in the annualized relapse rate. The 18-month extension phase of the trial included a switch of the placebo group to verum and demon stared sustained efficacy. Side effects included colds, sinusitis, mild headaches and gastrointestinal disorders. The underlying mechanism of drug action however warrants extensive safety analysis, especially with longer periods of administration. Two large phase III studies of FTY720 in MS are currently launched (2006). One study is testing the safety and efficacy of two doses (1.25 mg/day and 0.5 mg/day) against placebo (FREEDOMS I and II study), the other assesses the efficacy of FTY720 in a head-to-head design against an active comparator (IFNß-1a i.m. once weekly; TRANSFORMS study). Results are expected in 2009. In these trials, two fatal cases of viral encephalitis were recently reported (www.reuters.com/article/CHMMFG/idUSL058 6762720080605).

Fumaric acid: Oral application of fumaric acid esters (BG12, fumarate) represents an other strategy to induce beneficial immune modulation by enhancing Th2-driven responses in MS (81).

An exploratory, prospective, open-label study of fumaric acid esters was conducted in patients with RR-MS. In this small trial including 10 subjects, a reduction of relapse rate and volume of gadolinium-enhancing lesions as assessed by MRI was observed after 12 weeks (82). However, 3 patients discontinued treatment during the first 3 weeks of the study and several patients experienced mild to moderate gastrointestinal discomfort.

A double-blind, placebo-controlled phase II study was performed to further test the safety and effectiveness in controlling disease course and development of MS brain lesions. In January 2006, the product sponsor announced that the study met its primary endpoint by reducing the number of active MRI lesions with 6 month of treatment (http://www.FDA.org). Details about the secondary outcome measures have not been released so far.

Conclusion: Both IFN beta and GA have proven efficacy in RRMS and represent first line treatment choices for those patients. Additionally, SPMS patients with superimposed relapses will profit from those treatments. IFN beta and GA still remain the most recognized therapeutic options for MS treatment but many novel treatment strategies are currently tested in clinical trials and some of them are expected to be approved in the following years, among them oral therapies. Various phase III clinical trials are currently being initiated or are already underway evaluating the efficacy of a variety of orally administered agents, including cladribine, teriflunomide, laquinimod, fingolimod and fumaric acid. Results from these studies are awaited from both, clinicians and patients, and promising new candidates will help to further improve therapeutic possibilities in MS treatment.

Références:

1. Compston A & Coles A. Multiple sclerosis. Lancet 2002;**359**:1221–1231.
2. Kieseier BC, Hemmer B, & Hartung HP. Multiple sclerosis–novel insights and new therapeutic strategies. Curr Opin Neurol 2005;**18**:211–220.
3. Brex PA, Ciccarelli O, O'Riordan JI, Sailer M, Thompson AJ, & Miller DH. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. N Engl J Med 2002;**346**:158–164.
4. Rodriguez M, Siva A, Cross SA, O'Brien PC, & Kurland LT. Optic neuritis: a population-based study in Olmsted County, Minnesota. Neurology 1995;45:244–250.
5. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, McFarland HF, Paty DW, Polman CH, Reingold SC, Sandberg-Wollheim M, Sibley W, Thompson A, van den Noort S, Weinshenker BY, & Wolinsky JS. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001;**50**:121–127.
6. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, Lublin FD, Metz LM, McFarland HF, O'Connor PW, Sandberg-Wollheim M, Thompson AJ, Weinshenker BG, & Wolinsky JS. Diagnostic criteria for multiple sclerosis: 2005 revisions to the ''McDonald Criteria''. Ann Neurol 2005;**58**:840–846.
7. Tintore M, Rovira A, Rio J, Tur C, Pelayo R, Nos C, Tellez N, Perkal H, Comabella M, Sastre-Garriga J, & Montalban X. Do oligoclonal bands add information to MRI in first attacks of multiple sclerosis? Neurology 2008;**70**:1079–1083.
8. Weinshenker BG, Bass B, Rice GP, Noseworthy J, Carriere W, Baskerville J, & Ebers GC. The natural history of multiple sclerosis: a geographically based study. 2. Predictive value of the early clinical course. Brain 1989;**112** (Pt 6):1419–1428.
9. Weinshenker BG, Bass B, Rice GP, Noseworthy J, Carriere W, Baskerville J, & Ebers GC. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. Brain 1989;**112** (Pt 1):133–146.

© 2009 The Authors
Journal Compilation © 2009 John Wiley & Sons A/S

https://doi.org/10.1017/S092427080003266X Published online by Cambridge University Press

10. Kieseier BC & Wiendl H. Oral disease-modifying treatments for multiple sclerosis: the story so far. CNS Drugs 2007;**21**:483–502.
11. Stuve O, Bennett JL, Hemmer B, Wiendl H, Racke MK, Bar-Or A, Hu W, Zivadinov R, Weber MS, Zamvil SS, Pacheco MF, Menge T, Hartung HP, Kieseier BC, & Frohman EM. Pharmacological treatment of early multiple sclerosis. Drugs 2008;**68**:73–83.
12. Wiendl H & Hohlfeld R. Therapeutic approaches in multiple sclerosis: lessons from failed and interrupted treatment trials. BioDrugs 2002;**16**:183–200.
13. Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownscheidle CM, Murray TJ, Simonian NA, Slasor PJ, & Sandrock AW. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. N Engl J Med 2000;**343**:898–904.
14. Comi G, Filippi M, Barkhof F, Durelli L, Edan G, Fernandez O, Hartung H, Seeldrayers P, Sorensen PS, Rovaris M, Martinelli V, & Hommes OR. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. Lancet 2001;**357**:1576–1582.
15. Beck RW, Chandler DL, Cole SR, Simon JH, Jacobs LD, Kinkel RP, Selhorst JB, Rose JW, Cooper JA, Rice G, Murray TJ, & Sandrock AW. Interferon beta-1a for early multiple sclerosis: CHAMPS trial subgroup analyses. Ann Neurol 2002;**51**:481–490.
16. Kinkel RP, Kollman C, O'Connor P, Murray TJ, Simon J, Arnold D, Bakshi R, Weinstock-Gutman B, Brod S, Cooper J, Duquette P, Eggenberger E, Felton W, Fox R, Freedman M, Galetta S, Goodman A, Guarnaccia J, Hashimoto S, Horowitz S, Javerbaum J, Kasper L, Kaufman M, Kerson L, Mass M, Rammohan K, Reiss M, Rolak L, Rose J, Scott T, Selhorst J, Shin R, Smith C, Stuart W, Thurston S, & Wall M. IM interferon beta-1a delays definite multiple sclerosis 5 years after a first demyelinating event. Neurology 2006;**66**:678–684.
17. Kappos L, Polman CH, Freedman MS, Edan G, Hartung HP, Miller DH, Montalban X, Barkhof F, Bauer L, Jakobs P, Pohl C, & Sandbrink R. Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology 2006;**67**:1242–1249.
18. Kappos L, Freedman MS, Polman CH, Edan G, Hartung HP, Miller DH, Montalban X, Barkhof F, Radu EW, Bauer L, Dahms S, Lanius V, Pohl C, & Sandbrink R. Effect of early vs. delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study. Lancet 2007;**370**:389–397.
19. Barkhof F, Filippi M, Miller DH, Scheltens P, Campi A, Polman CH, Comi G, Ader HJ, Losseff N, & Valk J. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. Brain 1997;**120** (Pt 11):2059–2069.
20. Brex PA, O'Riordan JI, Miszkiel KA, Moseley IF, Thompson AJ, Plant GT, & Miller DH. Multisequence MRI in clinically isolated syndromes and the early development of MS. Neurology 1999;**53**:1184–1190.
21. Dalton CM, Brex PA, Miszkiel KA, Hickman SJ, MacManus DG, Plant GT, Thompson AJ, & Miller DH. Application of the new McDonald criteria to patients with clinically isolated syndromes suggestive of multiple sclerosis. Ann Neurol 2002;**52**:47–53.
22. Fazekas F, Barkhof F, Filippi M, Grossman RI, Li DK, McDonald WI, McFarland HF, Paty DW, Simon JH, Wolinsky JS, & Miller DH. The contribution of magnetic resonance imaging to the diagnosis of multiple sclerosis. Neurology 1999;**53**:448–456.
23. McFarland HF, Barkhof F, Antel J, & Miller DH. The role of MRI as a surrogate outcome measure in multiple sclerosis. Mult Scler 2002;**8**:40–51.
24. The 5-year risk of MS after optic neuritis. Experience of the optic neuritis treatment trial. Optic Neuritis Study Group. Neurology 1997;**49**:1404–1413.
25. Fisniku LK, Brex PA, Altmann DR, Miszkiel KA, Benton CE, Lanyon R, Thompson AJ, & Miller DH. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. Brain 2008;**131**:808–817.
26. Coyle PK & Hartung HP. Use of interferon beta in multiple sclerosis: rationale for early treatment and evidence for dose- and frequency-dependent effects on clinical response. Mult Scler 2002;**8**:2–9.
27. Corboy JR, Goodin DS, & Frohman EM. Disease-modifying Therapies for Multiple Sclerosis. Curr Treat Options Neurol 2003;**5**:35–54.
28. Kieseier BC, Seifert T, Giovannoni G, & Hartung HP. Matrix metalloproteinases in inflammatory demyelination: targets for treatment. Neurology 1999;**53**:20–25.
29. Yong VW. Differential mechanisms of action of interferon-beta and glatiramer acetate in MS. Neurology 2002;**59**:802–808.
30. Yong VW, Chabot S, Stuve O, & Williams G. Interferon beta in the treatment of multiple sclerosis: mechanisms of action. Neurology 1998;**51**:682–689.
31. Paty DW & Li DK. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. II. MRI analysis results of a multicenter, randomized, double-blind, placebo-controlled trial. UBC MS/MRI Study Group and the IFNB Multiple Sclerosis Study Group. Neurology 1993;**43**:662–667.
32. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. The IFNB Multiple Sclerosis Study Group. Neurology 1993;**43**:655–661.
33. Interferon beta-1b in the treatment of multiple sclerosis: final outcome of the randomized controlled trial. The IFNB Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group. Neurology 1995;**45**:1277–1285.
34. Jacobs LD, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, Fischer JS, Goodkin DE, Granger CV, Simon JH, Alam JJ, Bartoszak DM, Bourdette DN, Braiman J, Brownscheidle CM, Coats ME, Cohan SL, Dougherty DS, Kinkel RP, Mass MK, Munschauer FE, 3rd, Priore RL, Pullicino PM, Scherokman BJ, Whitham RH, & et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Ann Neurol 1996;**39**:285–294.
35. Rudick RA, Goodkin DE, Jacobs LD, Cookfair DL, Herndon RM, Richert JR, Salazar AM, Fischer JS, Granger CV, Simon JH, Alam JJ, Simonian NA, Campion MK, Bartoszak DM, Bourdette DN, Braiman J, Brownscheidle CM, Coats ME, Cohan SL, Dougherty DS, Kinkel RP, Mass MK, Munschauer FE, Priore RL, Whitham RH, & et al. Impact of interferon beta-1a on neurologic disability in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group (MSCRG). Neurology 1997;**49**:358–363.
36. Simon JH, Jacobs LD, Campion M, Wende K, Simonian N, Cookfair DL, Rudick RA, Herndon RM, Richert JR, Salazar AM, Alam JJ, Fischer JS, Goodkin DE, Granger CV, Lajaunie M, Martens-Davidson AL, Meyer M, Sheeder J, Choi K, Scherzinger AL, Bartoszak DM, Bourdette DN, Braiman J, Brownscheidle CM, Whitham RH, & et al. Magnetic resonance studies of intramuscular interferon beta-1a for relapsing

© 2009 The Authors

https://doi.org/10.1017/S092427080003266X Published online by Cambridge University Press

multiple sclerosis. The Multiple Sclerosis Collaborative Research Group. Ann Neurol 1998;**43**:79–87.
37. Li DK & Paty DW. Magnetic resonance imaging results of the PRISMS trial: a randomized, double-blind, placebo-controlled study of interferon-beta1a in relapsing-remitting multiple sclerosis. Prevention of Relapses and Disability by Interferon-beta1a Subcutaneously in Multiple Sclerosis. Ann Neurol 1999;**46**:197–206.
38. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. PRISMS (Prevention of Relapses and Disability by Interferon beta-1a Subcutaneously in Multiple Sclerosis) Study Group. Lancet 1998;352:1498–1504.
39. PRISMS-4: Long-term efficacy of interferon-beta-1a in relapsing MS. Neurology 2001;56:1628–1636.
40. Evidence of interferon beta-1a dose response in relapsing-remitting MS: the OWIMS Study. The Once Weekly Interferon for MS Study Group. Neurology 1999;**53**:679–686.
41. Farina C, Weber MS, Meinl E, Wekerle H, & Hohlfeld R. Glatiramer acetate in multiple sclerosis: update on potential mechanisms of action. Lancet Neurol 2005;**4**:567–575.
42. Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, Myers LW, Panitch HS, Rose JW, & Schiffer RB. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology 1995;**45**:1268–1276.
43. Wolinsky JS, Comi G, Filippi M, Ladkani D, Kadosh S, & Shifroni G. Copaxone's effect on MRI-monitored disease in relapsing MS is reproducible and sustained. Neurology 2002;**59**:1284–1286.
44. Miller A, Spada V, Beerkircher D, & Kreitman RR. Long-term (up to 22 years), open-label, compassionate-use study of glatiramer acetate in relapsing-remitting multiple sclerosis. Mult Scler 2008;**14**:494–499.
45. Ziemssen T, Neuhaus O, & Hohlfeld R. Risk-benefit assessment of glatiramer acetate in multiple sclerosis. Drug Saf 2001;**24**:979–990.
46. Placebo-controlled multicentre randomised trial of interferon beta-1b in treatment of secondary progressive multiple sclerosis. European Study Group on interferon beta-1b in secondary progressive MS. Lancet 1998;**352**:1491–1497.
47. Panitch H, Miller A, Paty D, & Weinshenker B. Interferon beta-1b in secondary progressive MS: results from a 3-year controlled study. Neurology 2004;**63**:1788–1795.
48. Kappos L, Weinshenker B, Pozzilli C, Thompson AJ, Dahlke F, Beckmann K, Polman C, & McFarland H. Interferon beta-1b in secondary progressive MS: a combined analysis of the two trials. Neurology 2004;**63**:1779–1787.
49. Randomized controlled trial of interferon- beta-1a in secondary progressive MS: Clinical results. Neurology 2001;**56**:1496–1504.
50. Cohen JA, Cutter GR, Fischer JS, Goodman AD, Heidenreich FR, Kooijmans MF, Sandrock AW, Rudick RA, Simon JH, Simonian NA, Tsao EC, & Whitaker JN. Benefit of interferon beta-1a on MSFC progression in secondary progressive MS. Neurology 2002;59:679–687.
51. Miller DH & Leary SM. Primary-progressive multiple sclerosis. Lancet Neurol 2007;**6**:903–912.
52. Wolinsky JS, Narayana PA, O'Connor P, Coyle PK, Ford C, Johnson K, Miller A, Pardo L, Kadosh S, & Ladkani D. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. Ann Neurol 2007;**61**:14–24.
53. Beutler E. Cladribine (2-chlorodeoxyadenosine). Lancet 1992;**340**:952–956.
54. Sipe JC. Cladribine for multiple sclerosis: review and current status. Expert Rev Neurother 2005;**5**:721–727.
55. Beutler E, Sipe JC, Romine JS, Koziol JA, McMillan R, & Zyroff J. The treatment of chronic progressive multiple sclerosis with cladribine. Proc Natl Acad Sci U S A 1996;**93**:1716–1720.
56. Sipe JC, Romine JS, Koziol JA, McMillan R, Zyroff J, & Beutler E. Cladribine in treatment of chronic progressive multiple sclerosis. Lancet 1994;**344**:9–13.
57. Romine JS, Sipe JC, Koziol JA, Zyroff J, & Beutler E. A double-blind, placebo-controlled, randomized trial of cladribine in relapsing-remitting multiple sclerosis. Proc Assoc Am Physicians 1999;**111**:35–44.
58. Filippi M, Rovaris M, Iannucci G, Mennea S, Sormani MP, & Comi G. Whole brain volume changes in patients with progressive MS treated with cladribine. Neurology 2000;55:1714–1718.
59. Filippi M, Rovaris M, Rice GP, Sormani MP, Iannucci G, Giacomotti L, & Comi G. The effect of cladribine on T(1) 'black hole' changes in progressive MS. J Neurol Sci 2000;**176**:42–44.
60. Rice GP, Filippi M, & Comi G. Cladribine and progressive MS: clinical and MRI outcomes of a multicenter controlled trial. Cladribine MRI Study Group. Neurology 2000;**54**:1145–1155.
61. Korn T, Magnus T, Toyka K, & Jung S. Modulation of effector cell functions in experimental autoimmune encephalomyelitis by leflunomide–mechanisms independent of pyrimidine depletion. J Leukoc Biol 2004;**76**:950–960.
62. Kaplan MJ. Leflunomide Aventis Pharma. Curr Opin Investig Drugs 2001;**2**:222–230.
63. Korn T, Toyka K, Hartung HP, & Jung S. Suppression of experimental autoimmune neuritis by leflunomide. Brain 2001;**124**:1791–1802.
64. Smolen JS, Emery P, Kalden JR, Van Riel PL, Dougados M, Strand CV, & Breedveld FC. The efficacy of leflunomide monotherapy in rheumatoid arthritis: towards the goals of disease modifying antirheumatic drug therapy. J Rheumatol Suppl 2004;**71**:13–20.
65. O'Connor PW, Li D, Freedman MS, Bar-Or A, Rice GP, Confavreux C, Paty DW, Stewart JA, & Scheyer R. A Phase II study of the safety and efficacy of teriflunomide in multiple sclerosis with relapses. Neurology 2006;**66**:894–900.
66. Brunmark C, Runstrom A, Ohlsson L, Sparre B, Brodin T, Astrom M, & Hedlund G. The new orally active immunoregulator laquinimod (ABR-215062) effectively inhibits development and relapses of experimental autoimmune encephalomyelitis. J Neuroimmunol 2002;**130**:163–172.
67. Jonsson S, Andersson G, Fex T, Fristedt T, Hedlund G, Jansson K, Abramo L, Fritzson I, Pekarski O, Runstrom A, Sandin H, Thuvesson I, & Bjork A. Synthesis and biological evaluation of new 1,2-dihydro-4-hydroxy-2-oxo-3-quinolinecarboxamides for treatment of autoimmune disorders: structure-activity relationship. J Med Chem 2004;**47**:2075–2088.
68. Runstrom A, Leanderson T, Ohlsson L, & Axelsson B. Inhibition of the development of chronic experimental autoimmune encephalomyelitis by laquinimod (ABR-215062) in IFN-beta k.o. and wild type mice. J Neuroimmunol 2006;**173**:69–78.
69. Yang JS, Xu LY, Xiao BG, Hedlund G, & Link H. Laquinimod (ABR-215062) suppresses the development of experimental autoimmune encephalomyelitis, modulates the Th1/Th2 balance and induces the Th3 cytokine TGF-beta in Lewis rats. J Neuroimmunol 2004;**156**:3–9.
70. Andersen O, Lycke J, Tollesson PO, Svenningsson A, Runmarker B, Linde AS, Astrom M, Gjorstrup P, & Ekholm S. Linomide reduces the rate of active lesions in relapsing-remitting multiple sclerosis. Neurology 1996;**47**:895–900.

© 2009 The Authors
Journal Compilation © 2009 John Wiley & Sons A/S

https://doi.org/10.1017/S092427080003266X Published online by Cambridge University Press

71. Karussis DM, Meiner Z, Lehmann D, Gomori JM, Schwarz A, Linde A, & Abramsky O. Treatment of secondary progressive multiple sclerosis with the immunomodulator linomide: a double-blind, placebo-controlled pilot study with monthly magnetic resonance imaging evaluation. Neurology 1996;**47**:341–346.
72. Polman C, Barkhof F, Sandberg-Wollheim M, Linde A, Nordle O, & Nederman T. Treatment with laquinimod reduces development of active MRI lesions in relapsing MS. Neurology 2005;**64**:987–991.
73. Hiestand PC, Rausch M, Meier DP, & Foster CA. Ascomycete derivative to MS therapeutic: S1P receptor modulator FTY720. Prog Drug Res 2008;**66**:361, 363–381.
74. Linker RA, Kieseier BC, & Gold R. Identification and development of new therapeutics for multiple sclerosis. Trends Pharmacol Sci 2008;**29**:558–565.
75. Coelho RP, Payne SG, Bittman R, Spiegel S, & Sato-Bigbee C. The immunomodulator FTY720 has a direct cytoprotective effect in oligodendrocyte progenitors. J Pharmacol Exp Ther 2007;**323**:626–635.
76. Miron VE, Jung CG, Kim HJ, Kennedy TE, Soliven B, & Antel JP. FTY720 modulates human oligodendrocyte progenitor process extension and survival. Ann Neurol 2008;**63**:61–71.
77. Mullershausen F, Craveiro LM, Shin Y, Cortes-Cros M, Bassilana F, Osinde M, Wishart WL, Guerini D, Thallmair M, Schwab ME, Sivasankaran R, Seuwen K, & Dev KK. Phosphorylated FTY720 promotes astrocyte migration through sphingosine-1-phosphate receptors. J Neurochem 2007;**102**:1151–1161.
78. Balatoni B, Storch MK, Swoboda EM, Schonborn V, Koziel A, Lambrou GN, Hiestand PC, Weissert R, & Foster CA. FTY720 sustains and restores neuronal function in the DA rat model of MOG-induced experimental autoimmune encephalomyelitis. Brain Res Bull 2007;**74**:307–316.
79. Fujino M, Funeshima N, Kitazawa Y, Kimura H, Amemiya H, Suzuki S, & Li XK. Amelioration of experimental autoimmune encephalomyelitis in Lewis rats by FTY720 treatment. J Pharmacol Exp Ther 2003;**305**:70–77.
80. Kappos L, Antel J, Comi G, Montalban X, O'Connor P, Polman CH, Haas T, Korn AA, Karlsson G, & Radue EW. Oral fingolimod (FTY720) for relapsing multiple sclerosis. N Engl J Med 2006;**355**:1124–1140.
81. Lee DH, Linker RA, & Gold R. Spotlight on fumarates. Int MS J 2008;**15**:12–18.
82. Schimrigk S, Brune N, Hellwig K, Lukas C, Bellenberg B, Rieks M, Hoffmann V, Pohlau D, & Przuntek H. Oral fumaric acid esters for the treatment of active multiple sclerosis: an open-label, baseline-controlled pilot study. Eur J Neurol 2006;**13**:604–610.

© 2009 The Authors

https://doi.org/10.1017/S092427080003266X Published online by Cambridge University Press