Mar Tintoré

Rationale for early intervention with immunomodulatory treatments

■ **Abstract** The McDonald diagnostic criteria have allowed the formal diagnosis of multiple sclerosis in patients presenting with clinically isolated syndromes to be brought forward. Evidence from research suggests that many patients with clinically isolated syndromes or early multiple sclerosis should be treated with disease-modifying drugs at an early stage, since disease experience during the first few years are likely to have significant impact on the long-term evolution of the disease. Histopathological studies have demonstrated the presence of axonal transection in patients with less than five years of disease duration, and especially during the first twelve months. Natural history studies have shown that the number of relapses occurring during the first few years of the disease is related to the time to accrued disability. Moreover, longitudinal studies on patients with clinically isolated syndromes have shown that the presence of even a very small number of baseline MRI lesions is associated with an increased risk of developing clinically definite multiple sclerosis and, more importantly, that the increase in volume of the lesions seen in the first five years correlates with the degree of disability in the longer term. For example, long-term follow-up of a large cohort of patients presenting with a clinically isolated syndrome in Barcelona has shown that the number of Barkhof criteria fulfilled at baseline was correlated with the risk of relapse, EDSS disability scores at five years and the risk of reaching given EDSS disability thresholds. Three randomised clinical trials in patients with a clinically isolated syndrome and abnormal brain MRI have shown significant benefit of initiating early therapy with β-interferons, and a similar study is underway with glatiramer acetate. It is concluded that choosing the right time to introduce treatment is critically important for outcome and the earlier treatment is initiated, the better the outcome.

■ **Key words** Multiple sclerosis · glatiramer acetate · beta-interferon · disease progression · disability

Mar Tintoré (✉)
Unitat de Neuroimmunologia Clinica
(UNIC)
Edif. Escola d'Infermeria Planta 2
Hospital Universitari Vall d'Hebron
Pg Vall d'Hebron 119-129
08035 Barcelona, Spain
Tel.: +34-3/2746202
Fax: +34-3/2746084
E-Mail: mtintore@vhebron.net

Introduction

For the patient with multiple sclerosis, the decision to initiate treatment with a disease-modifying agent, such as a β-interferon or glatiramer acetate, has important consequences. Such treatments bring undoubted benefits in reducing the risk of relapse and, potentially, the risk of acquiring irreversible neurological disability, but also impose constraints on the patient due to the need for regular self-injection, and the risk of potential side-effects. It is therefore important to envisage initiating treatment when the relative benefit of so doing is the greatest. In this respect, it could be argued that treatment should be started as soon as a diagnosis has been made. The arguments in favour of such a strategy are reviewed in this article.

The possibilities for early treatment initiation have been greatly enhanced by advances in our ability to diagnose multiple sclerosis early, due essentially to developments in magnetic resonance imaging (MRI) technology. Diagnosis of multiple sclerosis requires evidence for dissemination of lesion activity in time (sequential appearance) and space (multiple brain regions in-

volved). Historically, this evidence was acquired from clinical observation of multiple attacks. However, MRI technology allows the demonstration of new or aggravated lesion activity within the nervous system, even when this is clinically silent. Consensus guidelines on standardised criteria for the diagnosis of multiple sclerosis which integrate the use of MRI have been established. These were published in 2001 [13] and have since been rapidly integrated into routine clinical practice. In particular, these specify that the appearance of a single new lesion visible on T2-weighted images or of a new gadolinium-enhancing lesion on T1-weighted images provides evidence for dissemination in time. Dissemination in space can be demonstrated by the observation of T2 lesion load fulfilling at least three of the Barkhof criteria or by the presence of at least two T2 lesions together with the presence of oligoclonal bands in the cerebrospinal fluid. The Barkhof criteria for MRI evidence for a diagnosis of multiple sclerosis involve presentation of (a) one Gadolinium-enhanced lesion or the presence of nine or more T2 lesions, (b) one infratentorial lesion, (c) one juxtacortical lesion and (d) three periventricular lesions [1].

The use of these diagnostic criteria has permitted the diagnosis of multiple sclerosis to be made more rapidly after the occurrence of a clinically isolated neurological syndrome (CIS) suggestive of a multiple sclerosis attack, since it is no longer necessary to wait for the occurrence of a second clinically manifest attack before making the diagnosis if the MRI criteria are fulfilled. In a cohort of 139 patients presenting in our clinic with a CIS [19], a diagnosis of multiple sclerosis could be assigned within twelve months of initial presentation to 37 % of patients using the new McDonald criteria, compared to only 11 % if diagnosis had been made on clinical criteria alone, as previously recommended [18]. The question then arises as to whether these patients who are being diagnosed earlier would benefit from earlier initiation of treatment. Evidence in support of this has come from pathological studies of the disease process in multiple sclerosis, from natural history studies and from randomised controlled trials of disease-modifying treatments in patients presenting with a CIS.

Lessons from histopathology

Considerable data have now accrued from histopathological studies suggesting that axonal damage occurs early in the disease process in multiple sclerosis and is intimately associated with the acute inflammatory phase of lesion development [11, 21]. Axonal damage is believed to represent the principal pathophysiological determinant of development of permanent neurological disability. A quantitative study of recent axonal damage using the immunocytochemical marker APP (amy-

loid precursor protein) has revealed that the density of damaged axons is around five times higher in plaques isolated from patients within the first year after disease onset compared to those from patients with a disease duration of ten years or more (Fig. 1; [11]). The same study also demonstrated a clear association between the extent of acute axonal injury and the inflammatory process, as measured by the extent of infiltration by CD3-positive T cells, in both plaques and adjacent white matter.

It should not be neglected that, although inflammation is a major mechanism of tissue damage in multiple sclerosis, it also may have beneficial aspects. In particular, infiltrating inflammatory cells have been demonstrated to release a cocktail of neurotrophic factors that may play a role in limiting the extent of axonal damage or in promoting axonal repair [7]. Harnessing this potential neuroprotective effect may represent a particularly attractive therapeutic strategy for attenuating irreversible accumulation of disability. As such, disease-modifying treatments aimed at enhancing natural neuroprotective immunity would need to be given early in the disease course, when acute axonal injury is at its most intense and when the density of neurotrophin-secreting immune cells in lesion sites is highest.

Lessons from natural history studies

Natural history studies can provide important information about the anticipated long-term outcome in multiple sclerosis and thus help guide treatment decisions. The key findings from these studies are that the early course of disease can influence long-term outcome and
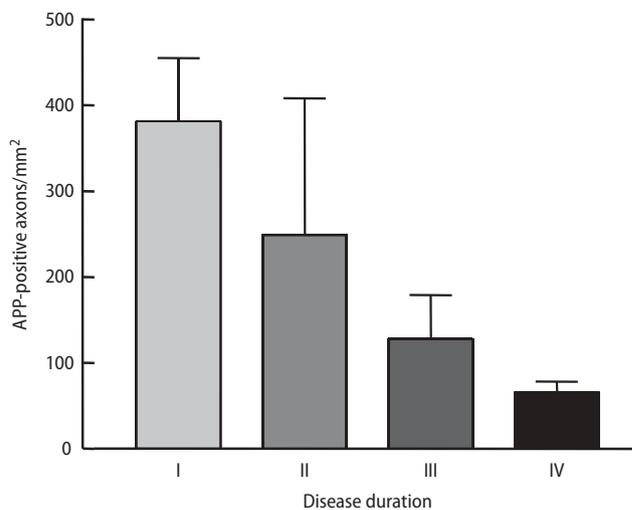

Fig. 1 Density of amyloid precursor protein (APP) staining axons in lesions from multiple sclerosis patients as a function of disease duration. I: less than one year; II: one to five years; III: five to ten years; IV: over ten years. Data are taken from Kuhlmann et al. [11], with permission from Oxford University Press. Copyright 2002

that there is a window of opportunity early on in treatment where it may be possible to inflect the long-term course of disease.

It has been considered that some patients may have a 'benign' form of multiple sclerosis in which recovery from relapses is always complete and irreversible disability may never appear. It could be argued that treatment of such patients with current immunomodulatory treatment may not be necessary or desirable. However, such a decision would imply that disease always remains 'benign' in these patients and never evolves, an idea that is far from universally accepted. The interest of treating patients with 'benign' disease is thus controversial. A recent report [17] assessed disability outcome in a group of 49 patients in the Olmstead County survey who had been originally considered to present 'benign' multiple sclerosis since they had not reached an EDSS score of 4.5 ten years after their diagnosis. These patients were reassessed a further ten years on, and at this time, it was observed that 30 % of these patients had progressed (Fig. 2), and thus that 'benign' status was lost if the observation period was sufficiently long. This was especially relevant in patients with an EDSS at 10 years between 2.5 to 4.0. In the light of such findings, the notion of 'benign' multiple sclerosis may not be justified, at least in terms of orienting treatment decision-making, particularly since patients with 'benign' disease may evolve and develop disability.

The predictive value of the early clinical course of multiple sclerosis with respect to subsequent disease course and accrual of disability has also been controversial. Important information addressing this issue has come from cohorts o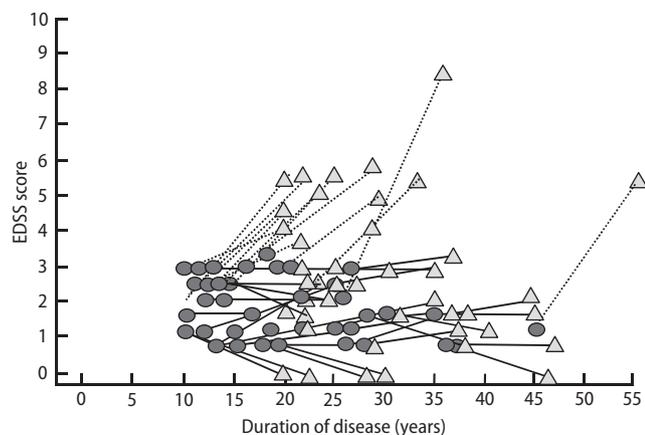f patients followed prospectively over the course of the disease. One of the best-studied cohorts was originally established in 1972 in London, Ontario, Canada which includes over one thousand patients [23]. An analysis of the clinical factors associated with disability progression has been performed in this cohort [22], which evaluated the influence of three variables, namely the initial relapse rate, the first inter-attack interval and the initial rate of disability progression, on the time taken to reach an EDSS score of six. This is a clinically important landmark, as it represents the moment when the patient is no longer able to walk unaided. Using actuarial survival analysis, significant differences in the survival distribution for this landmark, with respect to all three variables. The data obtained for the initial relapse rate are presented in Fig. 3. It can be seen that the median time to reach EDSS 6 is clearly related to the number of attacks during the first two years. Studies such as this suggest that the early disease course may determine long-term disability outcome, with the corollary that treatments that slow down the early course could have a potentially beneficial effect on long-term outcome if initiated sufficiently early.

A recent systematic review of predictors of long-term disability in patients with relapsing-remitting multiple sclerosis evaluated data from 27 studies that were selected on the basis that they enrolled at least forty subjects who were followed for at least five years with a retention rate of at least eighty percent [12]. The variable that was found to be the strongest predictor of prognosis was a short interval between the first and second attack. The most robust finding from the extensive number of randomised clinical trials performed with immunomodulatory treatments has been that these reduce relapse rate, thus increasing the interval between two successive attacks. Taking these two pieces of information
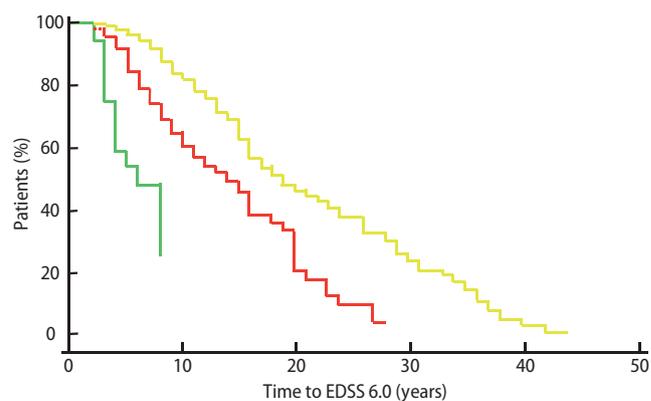

Fig. 2 Evolution of Expanded Disability Summary Scale (EDSS) score in 38 patients designated as presenting 'benign' multiple sclerosis on the basis of an EDSS score of three or less ten years after diagnosis. ●: EDSS assessment made in 1991, at least ten years after the original diagnosis; ▲: EDSS assessment made in 2001, ten years after attribution of 'benign' status. Reprinted from Pittock et al. [17] with permission from John Wiley & Sons, Inc. Copyright 2004 American Neurological Association

Fig. 3 Kaplan-Meier analysis of the time to reach an Expanded Disability Summary Scale (EDSS) score of six as a function of the number of attacks in the first two years following diagnosis in a Canadian cohort of 1099 patients with relapsing remitting multiple sclerosis. Yellow: less than two attacks; red: two to four attacks; green: more than four attacks. The survival curves are significantly different ($p < 0.0001$: logrank test). Adapted from Weinshenker et al. [22], with permission

together, there is thus a cogent reason for initiating immunomodulatory treatment early in the disease course.

A cohort of patients presenting with a clinically isolated syndrome has been followed for over twenty years at the Institute of Neurology in London. Analyses of outcome have been made at time horizons of five [14], ten [16], fourteen [2] and twenty years [6]. The sequential analyses of this database revealed that the proportion of patients who acquire a diagnosis of clinically definite multiple sclerosis at a given time point is related to the MRI lesion load at initial presentation. Of the patients with more than three visible lesions at presentation, 85 % have converted to clinically definite multiple sclerosis within five years, whereas this proportion is only achieved after ten years for those with less than three lesions (Table 1). Furthermore, a moderate association was also observed between a higher lesion load at initial presentation with a higher probability reaching an EDSS score of six, corresponding to loss of the ability to walk unaided (Fig. 4).

Similarly, we have followed a cohort of 175 consecutive patients presenting with a clinically isolated syndrome at our multiple sclerosis centre in Barcelona [20].

We assessed the MRI features observed at original presentation and subsequent acquisition of disability, which we defined as reaching an EDSS score of three. The maximum possible follow-up period at the time of the analysis was ten years. When patients were categorised according to the number of Barkhof criteria fulfilled at baseline, a clear association with the probability of acquiring disability was observed (Fig. 5). Patients with a baseline MRI fulfilling three or four Barkhof criteria presented an adjusted hazard ratio of 3.9 (1.1 to 13.6) for reaching an EDSS score ≥ 3.0 compared to those fulfilling none of the Barkhof criteria. Consistent with this, the EDSS score at year five correlated with the number of Barkhof criteria fulfilled at baseline ($r = 0.46, p < 0.0001$). Another important point to emerge from these data is that these patients did not start to develop disability until relatively late. In the highest risk group (three or four Barkhof criteria fulfilled at baseline), only 10 % had reached this disability threshold at year five, but thereafter disability emerged rapidly, with 40 % reaching this threshold at eight years (Fig. 5). The first five years thus represent the time frame where we could expect that initiation of an effective treatment would allow subsequent accumulation of disability to be minimised.

Patients presenting with a CIS between 1995 and 2001 and belonging to the referred cohort were invited to initiate β-interferon therapy after a second attack, provided this occurred within the first three years after the CIS. Patients were then followed prospectively for two more years on treatment with β-interferon. After this period, patients with an EDSS progression of one point confirmed at six months and sustained until the end of follow up were identified. There were no significant differences between patients with confirmed increase of disability and those without in terms of age, sex

Table 1 Proportion of patients presenting with a clinically isolated syndrome to convert to clinically definite multiple sclerosis as a function of the number of T2 lesions observed on baseline MRI. Data have been compiled from Brex et al., Morrissey et al., O'Riordan et al. [2, 14, 16]

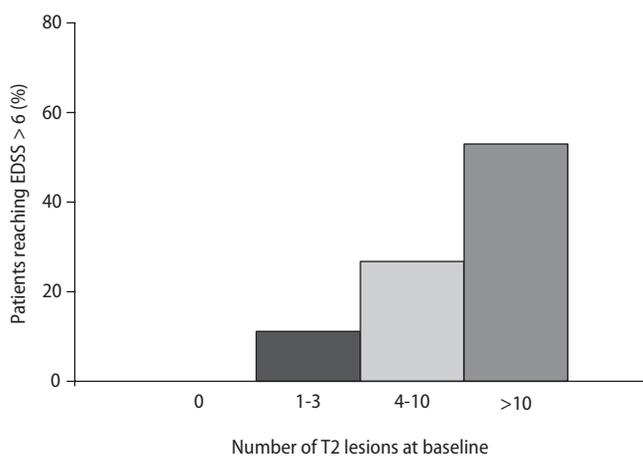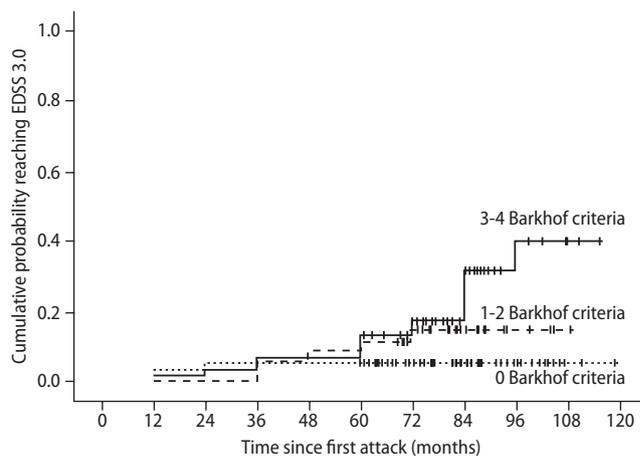| Follow-up duration	N° of patients	Number of T2 lesions at baseline		
		None	One to three	More than three
Five years	89	6 %	55 %	85 %
Ten years	81	11 %	79 %	86 %
Fourteen years	71	19 %	89 %	88 %

Fig. 4 Association between number of T2 lesions observed on baseline MRI in 71 patients presenting with an initial attack and the proportion of patients reaching a score of at least six on the Expanded Disability Summary Scale (EDSS) after a mean follow-up period of 14.1 years. Adapted from Brex et al. [2]

Fig. 5 Association between number of Barkhof criteria fulfilled on baseline MRI in patients presenting with an initial attack and probability of acquiring disability. The definition of disability was a score of at least three on the Expanded Disability Summary Scale (EDSS). Reproduced from Tintoré et al. [20], with permission

disease duration, number of relapses and disability before interferon or MRI baseline characteristics. Patients with a confirmed increase of disability after 24 months of therapy with interferon-β presented a higher number of new lesions on MRI over the first twelve months after the CIS. Regression analysis also confirmed that the only factor that predicted disability progression was the number of new T2 lesions 12 months after the CIS. These data seem to indicate that early MRI changes appearing after a CIS may have a prognostic value (manuscript in preparation).

Lessons from clinical trials

A number of clinical trials have been performed to investigate the potential benefit associated with the use of immunomodulatory treatments in patients presenting a CIS. Three of these have been completed and published and two more clinical trials are still underway.

The CHAMPS study [8] evaluated interferon β 1a *im* in a randomised, double-blind, placebo-controlled trial of 383 patients who had undergone a first clinically manifest acute demyelinating event and presented MRI evidence for previous subclinical demyelination. The treatment follow-up period was three years. Outcome measures were conversion to clinically definite multiple sclerosis and changes in MRI parameters. The CHAMPS study demonstrated a significantly ($p = 0.002$) lower cumulative probability of conversion to clinically definite multiple sclerosis in the interferon β 1a *im* treatment group, with a relative risk of conversion compared to the placebo group of 0.56 [95% confidence interval, 0.38–0.81]. With respect to MRI measures, a reduced T2 lesion volume ($p < 0.001$), fewer new or enlarging T2 lesions ($p < 0.001$), and fewer gadolinium-enhancing T1 lesions ($p < 0.001$) were observed in patients treated with interferon β 1a *im* after eighteen months follow-up compared to the placebo group. An extension study with a five year follow-up (CHAMPIONS) appeared to confirm the significant benefit conferred by early treatment in terms of relapses and MRI activity, though no differences in mean EDSS were seen (Kinkel et al., 2006).

The ETOMS trial [4] was a randomised, double-blind trial comparing interferon β 1a *sc* 22 µg to placebo in 308 patients who had presented a first episode of neurological dysfunction suggesting multiple sclerosis within the three months prior to inclusion, accompanied by MRI findings consistent with demyelination. Patients were treated for two years and evaluated clinically every six months and with MRI every twelve months. The ETOMS trial also showed that immunomodulatory treatment was useful in preventing or delaying a second attack. Fewer patients developed clinically definite multiple sclerosis in the interferon β 1a *sc* 22 µg treatment group (34%) compared to the placebo group (45%; p = 0.047). Accord-
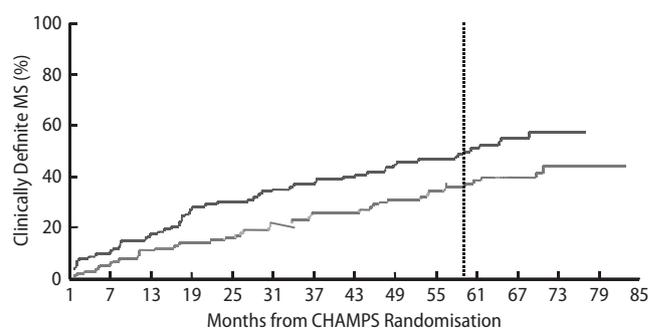

Fig. 6 Proportion of patients receiving a diagnosis of clinically definite multiple sclerosis in the CHAMPIONS study. Blue: 100 patients initially randomised to interferon β 1a *im*; red: 103 patients switched to interferon β 1a *im* after the interim analysis. At five years, the adjusted relative risk of conversion to clinically definite multiple sclerosis in the immediate treatment group compared to the delayed initiation group was 0.57 (95% confidence intervals: 0.38–0.86: p = 0.008). Adapted from Kinkel et al. [10], with permission

ing to actuarial survival analysis, the time by which 30% of patients had converted to clinically definite multiple sclerosis was also significantly longer (569 days) in the interferon β 1a *sc* 22 µg group compared to the placebo group (252 days; p = 0.034). The hazard ratio for conversion was 0.69. The study also found the number of new T2 lesions and the increase in lesion burden to be significantly lower with interferon β 1a *sc* 22 µg treatment. Additional data on brain volume have demonstrated that patients treated with interferon β 1a *sc* showed a significant slowing in the loss of brain tissue at two years compared with patients on placebo reducing the accumulation of brain atrophy by about 30% in 2 years [5].

Interferon β 1b *sc* was evaluated in 468 patients with a first clinical demyelinating event and at least two clinically silent brain MRI lesions in the BENEFIT study [9]. Over the two year treatment period, 45% of patients receiving placebo converted to clinically definite multiple sclerosis, compared to 28% in the interferon β 1b *sc* treatment group. This represents a reduction in risk corresponding to an adjusted hazard ratio of 0.50 ($p < 0.0001$). Interferon β 1b prolonged the time to clinically definite multiple sclerosis by 1 year based on the 25th percentiles.

Two further studies are underway in patients with recent-onset disease. The first is the REFLEX (REbif FLEX-ible dosing in early multiple sclerosis) study to evaluate the effect of two dosage regimens of interferon β 1a *sc* 44 µg, three times a week or once a week on the time to conversion to multiple sclerosis in people with first clinical symptoms suggestive of the disease. This trial will involve 480 patients considered at risk of developing multiple sclerosis because of a recently experienced isolated demyelinating event and of typical MRI brain scans. The treatment period is planned to be two years, with six-monthly clinical evaluations and three-monthly MRI scans.
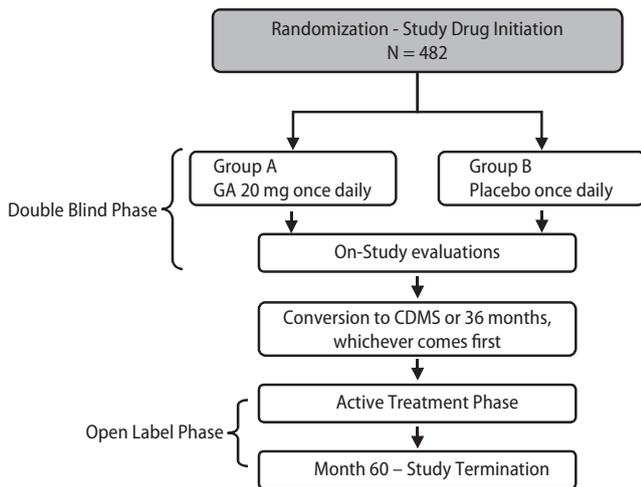
Fig. 7 Design of the PreCISe study of glatiramer acetate (GA) in patients with a clinically isolated syndrome. CDMS: clinically definite multiple sclerosis

The second ongoing study is the PreCISe study (cited in [15] which is evaluating the benefit of glatiramer acetate in patients presenting with a CIS. Four hundred and eighty-two patients presenting with a single unifocal clinical attack in the previous three months and at least two MRI lesions suggestive of multiple sclerosis have been enrolled. The study uses a randomised, placebo-controlled, double-blind parallel group design (Fig. 7). The double-blind treatment period is planned to last for three years and will be followed by an open-label extension until five years from randomisation, when all patients will receive glatiramer acetate. Patients will be evaluated every six months. The primary outcome measure will be conversion to clinically definite multiple sclerosis. All patients converting during the double blind treatment period will have reached a predefined study endpoint and will be proposed entry into the open-label extension. The PreCISe study started in 2004 and an interim analysis will be conducted at the time when approximately 80 % of the three-year placebo controlled

study exposure will be accumulated. Given previous results with β-interferons in CIS and the fact that glatiramer acetate has shown efficacy in patients with confirmed multiple sclerosis, this treatment is expected also to be effective in a less severe type of MS such as patients presenting with a CIS.

Conclusions

What happens very early on in the disease course has an important impact in the development in disability in the long term, since irreversible axonal damage sets in from the earliest stages of disease. The window of opportunity may thus increase when immunomodulatory treatments are given early. This indeed could be expected from what we now know about the evolving pathogenetic role of the immune system along the disease course in multiple sclerosis (discussed by Wiener elsewhere in this volume). It is clear from the different clinical trials that, if immunomodulatory drugs are used in the first attack, their efficacy range is in the order of 40–60 %, whereas when these same agents are used in established relapsing remitting disease, their efficacy range has fallen to around 30 %. In secondary progressive multiple sclerosis, their efficacy, if there is any, has fallen still further to 5–10 %. Similar observations have been made for the anti-CD52 monoclonal antibody alemzutumab, which is clearly highly efficacious in reducing disease activity in relapsing remitting patients, but seems to have little, if any, beneficial effect once disease has evolved to a secondary progressive course [3]. The inescapable conclusions from this clinical research are that choosing the right time to introduce treatment is critically important for outcome and the earlier treatment is initiated, the better the outcome.

References

1. Barkhof F, Filippi M, Miller DH, Scheltens P, Campi A, Polman CH, Comi G, Ader HJ, Losseff N, Valk J (1997) Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. Brain 120(Pt 11):2059–2069
2. Brex PA, Ciccarelli O, O'Riordan JI, Sailer M, Thompson AJ, Miller DH (2002) A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. N Engl J Med 346: 158–164
3. Coles AJ, Cox A, Le Page E, Jones J, Trip SA, Deans J, Seaman S, Miller DH, Hale G, Waldmann H, Compston DA (2006) The window of therapeutic opportunity in multiple sclerosis: evidence from monoclonal antibody therapy. J Neurol 253:98–108
4. Comi G, Filippi M, Barkhof F, Durelli L, Edan G, Fernandez O, Hartung H, Seeldrayers P, Sorensen PS, Rovaris M, Martinelli V, Hommes OR (2001) Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. Lancet 357: 1576–1582
5. Filippi M, Rovaris M, Inglese M, Barkhof F, De Stefano N, Smith S, Comi G (2004) Interferon beta-1a for brain tissue loss in patients at presentation with syndromes suggestive of multiple sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet 364:1489–1496
6. Fisniku L, Brex P, Altmann D, Miszkiel K, Thompson A, Miller D (2006) Disability status and the relationship between the T2-MRI abnormalities in CIS patients and the long-term outcome in a 20-year follow-up. Mult Scler 12(Suppl 1):S1

7. Hohlfeld R, Kerschensteiner M, Stadelmann C, Lassmann H, Wekerle H (2000) The neuroprotective effect of inflammation: implications for the therapy of multiple sclerosis. J Neuroimmunol 107:161–166

8. Jacobs LD, Beck RW, Simon JH, Kinkel RP, Brownscheidle CM, Murray TJ, Simonian NA, Slasor PJ, Sandrock AW (2000) Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. N Engl J Med 343:898–904

9. Kappos L, Polman CH, Freedman MS, Edan G, Hartung HP, Miller DH, Montalban X, Barkhof F, Bauer L, Jakobs P, Pohl C, Sandbrink R (2006) Treatment with interferon beta-1b delays conversion to clinically definite and McDonald MS in patients with clinically isolated syndromes. Neurology 67:1242–1249

10. 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 (2006) IM interferon beta-1a delays definite multiple sclerosis 5 years after a first demyelinating event. Neurology 66:678–684

11. Kuhlmann T, Lingfeld G, Bitsch A, Schuchardt J, Bruck W (2002) Acute axonal damage in multiple sclerosis is most extensive in early disease stages and decreases over time. Brain 125:2202–2212

12. Langer-Gould A, Popat RA, Huang SM, Cobb K, Fontoura P, Gould MK, Nelson LM (2006) Clinical and demographic predictors of long-term disability in patients with relapsing-remitting multiple sclerosis: a systematic review. Arch Neurol 63:1686–1691

13. 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 (2001) Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 50: 121–127

14. Morrissey SP, Miller DH, Kendall BE, Kingsley DP, Kelly MA, Francis DA, MacManus DG, McDonald WI (1993) The significance of brain magnetic resonance imaging abnormalities at presentation with clinically isolated syndromes suggestive of multiple sclerosis. A 5-year follow-up study. Brain 116(Pt 1):135–146

15. Multiple Sklerose Therapie Konsensus Gruppe (MSTKG), Rieckmann P (2006) Immunmodulatorische Stufentherapie der Multiplen Sklerose. Der Nervenarzt 77:1506–1518

16. O'Riordan JI, Thompson AJ, Kingsley DP, MacManus DG, Kendall BE, Rudge P, McDonald WI, Miller DH (1998) The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up. Brain 121(Pt 3): 495–503

17. Pittock SJ, McClelland RL, Mayr WT, Jorgensen NW, Weinshenker BG, Noseworthy J, Rodriguez M (2004) Clinical implications of benign multiple sclerosis: a 20-year population-based follow-up study. Ann Neurol 56:303–306

18. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, Johnson KP, Sibley WA, Silberberg DH, Tourtellotte WW (1983) New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 13:227–231

19. Tintoré M, Rovira A, Rio J, Nos C, Grive E, Sastre-Garriga J, Pericot I, Sanchez E, Comabella M, Montalban X (2003) New diagnostic criteria for multiple sclerosis: application in first demyelinating episode. Neurology 60:27–30

20. Tintoré M, Rovira A, Rio J, Nos C, Grive E, Tellez N, Pelayo R, Comabella M, Sastre-Garriga J, Montalban X (2006) Baseline MRI predicts future attacks and disability in clinically isolated syndromes. Neurology 67:968–972

21. Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mork S, Bo L (1998) Axonal transection in the lesions of multiple sclerosis. N Engl J Med 338:278–285

22. Weinshenker BG, Bass B, Rice GP, Noseworthy J, Carriere W, Baskerville J, Ebers GC (1989) The natural history of multiple sclerosis: a geographically based study. 2. Predictive value of the early clinical course. Brain 112(Pt 6):1419–1428

23. Weinshenker BG, Bass B, Rice GP, Noseworthy J, Carriere W, Baskerville J, Ebers GC (1989) The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. Brain 112(Pt 1):133–146