Management of Early Multiple Sclerosis

a report by
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Relapsing remitting multiple sclerosis (RRMS) accounts for approximately 90% of MS cases and first presents with a demyelinating neurological attack, the clinically isolated syndrome (CIS). Despite full clinical recovery from CIS in most patients, subclinical tissue damage may persist and accumulate over time. Supported by histopathological and radiological data demonstrating active disease with potentially irreversible damage even at early disease stages, the beneficial impact of early immunomodulatory intervention on subsequent disease evolution can now be demonstrated. Here I will review the pathological, radiological and clinical data supporting early therapy of MS and also the ongoing controversy on early immunomodulatory treatment.

Histopathological and Radiological Studies – Early Multiple Sclerosis Is Not Silent

Axonal pathology in MS was described as early as the 19th century. However, it was only in the late 1990s that methodologically advanced histopathological studies led to a reappraisal of the concept of irreversible axonal damage underlying persistent disability.

A series of elegant studies demonstrated that axonal transection occurs early during the disease and is at least initially associated with ongoing tissue inflammation.[1] Using different non-conventional magnetic resonance (MR) techniques, such as magnetisation transfer and MR spectroscopy, widespread tissue damage and axonal dysfunction can also be identified radiologically during early MS, even in areas without overt lesions on conventional MR imaging (MRI).

Functional re-organisation of neuronal networks and/or compensation by redundant mechanisms are thought to contribute to rapid clinical recovery after CIS, again emphasising widespread alterations during this early disease phase.[2] This initially subclinical tissue damage can accumulate over time and pose a substantial risk for disease progression and disability during later disease stages. Clinically, this may be reflected by the impact of the early course of established MS on long-term prognosis. Thus, several longitudinal natural history studies demonstrate that the number of relapses during the first two to five years is associated with the rate of accrual of permanent disability, with greater numbers of early episodes leading to a shorter interval to reach disability landmarks.[3]

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Surrogate Parameters – Initial Cranial Magnetic Resonance Imaging Identifies Clinically Isolated Syndrome Patients Who Are 'At Risk'

While the majority of CIS patients experience further relapses, defining MS, the disease remains monophasic in a proportion of patients. Given this population on the one hand, but early irreversible tissue damage in other patients, a major aim is to identify parameters that can predict risk of further relapses and accrual of disability after CIS. Currently, cranial (c)MRI is the best validated method of identifying CIS patients with a high risk of experiencing further relapses. Long-term observation of a CIS cohort reported by the group from the National Hospital for Neurology and Neurosurgery (NHNN) at Queen's Square, London corrobated the predictive value of the initial cMRI. Here, the risk of suffering further relapses is related to the initial cMRI lesion load, which may also be associated with the degree of long-term disability.[4]

Similar findings have been reported for other cohorts. Thus far, no other biological markers characterising CIS patients who are 'at risk' have been unequivocally identified. Initial high expectations after a report on the value of serum antibodies against components of central myelin to predict the risk of suffering further relapses after CIS were not met due to lack of reproduction of these findings in other cohorts.[5,6] However, the role of antimyelin antibodies as surrogate parameters and optimal detection methods and their potential pathogenetic implications are currently still under investigation.

Clinical Studies – Evidence in Favour of Early Immunomodulatory Treatment

Given the data demonstrating highly active disease even at early stages, it was soon suggested that immunotherapy initiated immediately after disease onset could have an impact on subsequent clinical course. Three phase III randomised, placebo-controlled trials have investigated the effects of initiating immunomodulatory therapy in CIS patients with abnormal cranial MRI, thus selecting for patients at risk of undergoing further relapses. One major end-point common to all studies was the conversion to 'clinically definite multiple sclerosis' (CDMS) according to the Poser criteria, with the demonstration of clinical temporospatial dissemination, e.g. a second relapse affecting a different site in the central nervous system.

The Controlled High-Risk Subjects Avonex® Multiple Sclerosis Prevention Study (CHAMPS) demonstrated that interferon-beta (IFN-β) 1a (30µg intramuscular once weekly; Avonex) was efficacious in delaying the development of a second relapse in 383 CIS patients with at least two lesions on T2-weighted cMRI suggestive of MS.[7] While for the placebo group the risk of developing CDMS at three years was 50%, IFN-β1a treatment reduced the risk to 35%.

Similarly, the Early treatment of Multiple Sclerosis (ETOMS) study, which also included CIS patients with cMRI abnormalities suggestive of MS, demonstrated an effect on the likelihood to progress to CDMS. While 45% of the placebo patients converted to CDMS during the two-year follow-up, the risk was reduced to 34% in patients treated with IFN-β 1a (22µg subcutaneously once weeky; Rebif®).[8] The potential impact of this early treatment on the underlying accrual of tissue damage was also demonstrated in this trial. Patients treated with IFN-β1a showed significantly less brain volume decrease/atrophy on cMRI compared with placaebo patients after 24 months.[9] However, the dose and frequency employed in this trial differ from the formulations currently approved for therapy. In the Betaferon®/Betaseron® in Newly Emerging Multiple Sclerosis For Initial Treatment (BENEFIT) study, a positive effect of early treatment was shown in 468 CIS patients with at least two clinically silent cMRI lesions.[10] In patients treated with IFN-β 1b (250µg subcutaneously; Betaferon/Betaseron), the probability of developing CDMS over two years was 28% compared with 45% in the placebo group. At the 25th percentile, IFN-β 1b treatment prolonged the time to CDMS by 363 days: from 255 days in the placebo group to 618 days in the treated group.

> Taken together, positive results obtained in all the studies support a robust biological effect of early immunomodulatory treatment.

This study also incorporated new diagnostic guidelines where validation of temporospatial dissemination by MRI can also fulfil the original McDonald diagnostic criteria, which have recently been revised.[11] In this study, 51% of the patients in the placebo arm fulfilled the original McDonald criteria after six months and 85% after two years, emphasising considerable disease activity during early disease. IFN-β 1b treatment reduced the probability of converting to McDonald MS at these timepoints to 28 and 69%, respectively.

Although these studies focused on analogous clinical contexts, individual differences deserve further comment. Despite similar risks of developing CDMS in the placebo groups, differences in study conduction preclude direct comparison of the substances in terms of efficacy. Analyses of the CHAMPS and ETOMS trials indicate a better treatment effect for patients with more inflammatory activity on initial MRI. Initial subgroup analyses of the BENEFIT study indicating a stronger treatment effect in patients with less MRI activity and monofocal clinical presentation were not confimed in a long-term follow-up (see below). However, these data point to different baseline characteristics of the investigated cohorts. Taken together, positive results obtained in all of the studies support a robust biological effect of early immunomodulatory treatment. Consequently, after initial approval of Avonex for use in "patients with an initial demyelinating event and high risk of occurrence of clinically definite MS" by the European Medicines Agency (EMEA), more recently Betaferon has also received approval for early therapy with the same restrictions. Rebif was recently approved for treatment of MS according to the McDonald criteria, extending the previous approval for clinically confirmed MS according to the Poser criteria. A placebo-controlled phase III study examining glatiramer acetate after CIS is currently under way (PreCISe study). An interim analysis of the PreCISe study has been reported to demonstrate efficacy of early treatment using glatiramer acetate. However, these data have not been presented in a peer-reviewed fashion yet.

Long-term Data – Further Corroboration of the Effect of Early Therapy

More recently, extended observations of the initial phase III trials were published that allow a better assessment of long-term outcome. Open-label follow-up of the CHAMPS study indicates treatment effects over five years after the initial randomisation. Thus, patients treated with IFN-β1a (Avonex) from the beginning were less likely to develop CDMS than those who crossed from placebo to IFN-β1a only after the blinded phase of the study.[12] Similar, but extended, results were also reported from the prospective three-year follow-up analysis of the BENEFIT trial.[13] Here, patients initially randomised to placebo were treated with IFN-β1b after two years or after conversion to CDMS (delayed treatment) and compared with the cohort that had received Betaferon from the beginning (early treatment). Blinding was maintained for the initial treatment randomisation. After three years, 37% in the early treatment group converted to CDMS compared with 51% in the delayed treatment group. Most importantly, early treatment also had an impact on further disability: 16% in the early group but 40% in the delayed treatment group experienced deterioration on the expanded disability status scale by at least one point over three years.

These data are indeed the first to demonstrate a beneficial effect of early therapy on subsequent disability progression. Interestingly, immediate treatment in a relatively young patient cohort after the first clinical episode was nevertheless associated with high treatment adherence, at least under study conditions. The use of a titration scheme and acetaminophen or ibuprofen at the start of therapy may have contributed to these favourable findings and may have helped to enhance initial treatment compliance in the critical time before the frequency of drug-related adverse reactions spontaneously decreases. Additionally, the use of an autoinjector may have contributed to lowering the rate of injecion-site reactions.

> Parameters are needed to identify subpopulations that will benefit most from early therapy.

Who and When to Treat – An Ongoing Controversy

Common objections to early treatment include the low magnitude of clinical benefit, the concept of 'benign MS', adverse effects of immunomodulators and the consideration of pharmacoeconomical aspects.[14] Incomplete efficacy of current immunotherapy may well reflect the presumed pathogenetic heterogeneity of the disease, and

may support the idea of therapy tailored to underlying pathomechanisms and disease stages.[15] Thus, parameters are needed to identify subpopulations that will benefit most from early therapy. In addition, data from ongoing trials on the long-term prevention of disability will, ultimately, better delineate the extent of clinical benefit. Benign MS implies a favourable disease course without substantial disability, possibly even for decades. However, in the individual patient this may be difficult to ascertain as current clinical definitions do not preclude severe deterioration after long stable intervals and, thus far, no biological parameter predicts such a 'natural' long-term outcome. In addition, the impact of neuropsychological and cognitive defects that are highly prevalent in these patients is not accounted for.

Immunomodulatory treatment appears to be safe even after decades, and low drop-out rates in the phase III trials and their respective extensions demonstrate the feasibility of early treatment, at least under study conditions, characterised by continous supervision and support of patients. However, given the high non-adherence rate for current immunomodulatory drugs outside of clinical studies, close follow-up of a patient left untreated due to a high risk of non-adherence may, on occasion, be a valid alternative.[16]

Conclusion

In the past few years there has been considerable progress in our understanding of early MS. Despite incomplete treatment effects, patients with clinically or radiologically active disease profit from early immunomodulatory treatment. However, in addition to more efficacious treatment options, further research needs to focus on predictors that identify those CIS patients who will benefit most from immediate treatment. ■

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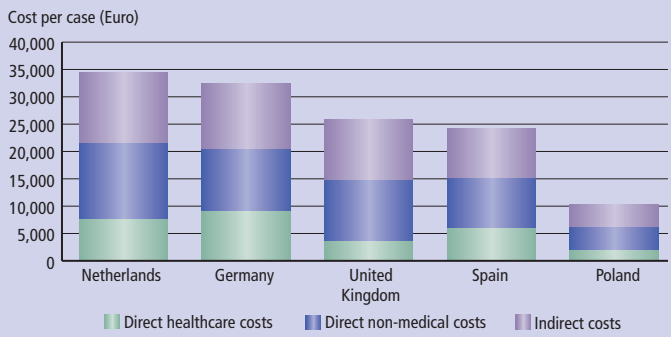
Multiple Sclerosis – The Facts

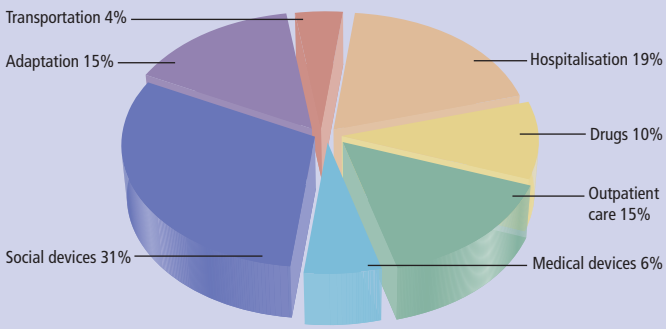
- Multiple sclerosis (MS) is one of the most common diseases of the central nervous system. In the EU, over 400,000 people have MS.
- Worldwide, MS occurs with much greater frequency in higher latitudes (above 40° latitude away from the Equator) than in lower latitudes, closer to the Equator.
- Women are more likely to develop MS than men, with MS occurring 50% more frequently in women than in men (i.e. three women for every two men).

Cost per Case of Multiple Sclerosis, Selected European Countries



Source: Andlin-Sobocki P et al., Cost of Disorders of the Brain in Europe, European Journal of Neurology, *2005, Supplement I.*

Total Direct Costs of Multiple Sclerosis in Europe



Source: Andlin-Sobocki P et al., Cost of Disorders of the Brain in Europe, European Journal of Neurology, *2005, Supplement I.*

- MS is a disease of young adults; the mean age of onset is 29–33 years, but the range of onset is extremely broad, from approximately 10 to 59 years.
- While MS is not strictly hereditary, having a first-degree relative such as a parent or sibling with MS increases an individual's risk of developing the disease several-fold above the risk for the general population.

Sources: European Multiple Sclerosis Platform, Multiple Sclerosis International Federation and National Multiple Sclerosis Society.