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Early Intervention in Multiple Sclerosis

Better Outcomes for Patients and Society?

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Abstract

Multiple sclerosis (MS) is thought to be a chronic inflammatory disorder of the CNS. The past decade has seen the introduction of the new immunomodulatory drugs, interferon (IFN)-β and glatiramer acetate, that have considerably improved the therapeutic options for this often disabling disease. The efficacy of these treatments in terms of reducing relapse rate and slowing progression has been proven in several large, multicentre, randomised, controlled trials. Similarly, early IFNβ treatment of patients with clinically isolated syndromes suggestive of MS has been shown to lengthen time to conversion into definite MS. Cost-effectiveness has been questioned with the increasing use of these innovative and, therefore, costly therapies; however, modern studies with appropriate economic modelling suggest that treatment with IFNβ may indeed be cost-effective. Since increasing disability is associated with increasing costs, stabilisation of the disease at low functional grades of disability should aim at not only improving quality of life for the individual patient, but provide for prospective cost-benefit analysis focussing on the socioeconomic aspects of MS.

Multiple sclerosis (MS) is a chronic inflammatory disorder of the CNS that is thought to be a T-cell-mediated autoimmune process, which occurs in genetically susceptible individuals and is triggered by an exogenous agent. The disease results in injury to myelin sheaths, oligodendrocytes and axons which leads to permanent disability. With a lifetime risk of one in 400, affecting approximately 120 000 people in Germany, between 250 000 and 350 000 in the US, and more than 1 million worldwide, it is potentially the most common cause of neurological disability in young adults.[1]

The symptoms of MS vary depending on the site of the plaques within the CNS. The most common symptoms include optic neuritis, motor symptoms particularly in the lower extremities with walking difficulties, bladder and sexual dysfunction, sensory symptoms and ataxia.[2] Three main types of clinical course have been defined.[3] The first, relapsing-remitting MS (RR-MS), is characterised by episodes of neurological deterioration evolving over days to weeks. Over the next weeks to months, most patients experience a recovery which is often but not always complete. The second clinical course, primary-progressive MS (PP-MS) is characterised by a steady decline of neurological function without acute attacks. Secondary-progressive MS (SP-MS) begins with a relapsing-remitting course, but at some point relapse frequency is reduced and a steady progression unrelated to acute attacks occurs.

Table I. Modern immunomodulatory treatment of multiple sclerosis (MS)

Preparation	Trade name	Dosage	Route	RR	SP
IFNβ-1b	Betaferon®	8 MIU/2 days	SC	a	a
IFNβ-1a	Rebif®	22μg 3/week	SC	a	a
		44μg 3/week	SC	a	a
	Avonex™	30 μg/week	IM	a	
Glatiramer acetate	Copaxone®	20 mg/day	SC	a	
Mitoxantrone	Ralenova®	12 mg/m^2	IV		a

a Licensed in the US, Canada and throughout Europe.

IFN = interferon; **IM** = intramuscular; **IV** = intravenously; **RR** = relapsing-remitting MS; **SC** = subcutaneous; **SP** = secondary-progressive MS.

Initially, more than 85% of patients have the relapsing-remitting form. After 10–15 years, up to 50% of patients are in the secondary-progressive phase.[4] Natural history studies show that, on average, patients required unilateral assistance to walk about 100 metres after 15 years; at the same timepoint, about 10–15% required the use of a wheelchair, but 20–25% still remained unrestricted in their ambulation.[4]

These figures highlight the enormous burden of the disease for patients and society, and underline the necessity for the development and the initiation of appropriate disease-modifying therapies. However, given that 10–20% of patients have 'benign' MS (i.e., patients who were unrestricted after more than 15 years disease duration), the widely variable outcome and the lack of reliable prognostic markers for individual patients, the question is raised of when to start immunomodulatory treatment to prevent relapses and progression of disability.

1. Outcome Measures in Clinical Trials

Clearly, the most important therapeutic aim of any disease-modifying treatment is to prevent or postpone disability in the long term. However, long-term disability in MS generally evolves over several years but clinical trials are conducted for only short periods of time, generally over 2–3 years.[5] In most of these randomised, controlled trials, the clinical endpoints were either relapse rate (number of relapses per year) or progression of disability, as measured as an increase of one point on the Expanded Disability Status Scale (EDSS).[6] During the last decade, magnetic resonance imaging (MRI) has been increasingly used as an objective surrogate measure in clinical trials.[7] Despite the advantages of MRI in studying new treatment options in phase II clinical trials, clinical outcome measures remain the 'gold standard' in large, multicentre phase III clinical trials.

2. Disease-Modifying Therapies in Multiple Sclerosis (MS)

The therapeutic options for patients with MS have been improved with the introduction of new immunomodulating agents for the treatment of this disease. Currently, four treatment principles, recombinant human interferon (IFN)-β, glatiramer acetate, azathioprine and mitoxantrone, are licensed in the US, Canada and throughout Europe, with IFNβ, glatiramer acetate and mitoxantrone having been studied in modern, randomised, controlled trials. Three formulations of IFNβ (IFNβ-1b, Betaferon®[1], IFNβ-1a subcutaneously, Rebif® and IFNβ-1a intramuscularly, Avonex™ are approved for RR-MS, SP-MS and MS with relapses [table I]).

The efficacy of IFNβ for the treatment of RR-MS has been established in three pivotal, large, randomised, double-blind, placebo-controlled, multicentre studies representing class I evidence,[5,8] which were all successful in reaching their primary endpoints.[9-11] Although not directly comparable (mainly because of different dosages, routes of administration, selection of primary endpoints and patient

1 Use of tradenames is for product identification only and does not imply endorsement.

populations), these studies demonstrated reductions in relapse rate (about 30%), accumulation of disability and MRI lesion load.[5,8] Similar effects were obtained with glatiramer acetate, a randomised synthetic oligopeptide, for both clinical and MRI endpoints.[12-14] In agreement with consensus statements from Canada[15] and the US,[5] the Austrian-German-Swiss Multiple Sclerosis Therapy Consensus Group (MSTCG) thus regarded IFNβ and glatiramer acetate as first-line immunomodulatory treatment options for patients with RR-MS (figure 1).[8,16]

In patients with SP-MS, different studies have yielded controversial results concerning the efficacy of IFNβ. In the large European study using IFNβ-1b (Betaferon®), it was shown to be successful in delaying disease progression (in the magnitude of about 9–12 months) and reducing relapse frequency in all patient subgroups included.[17] In contrast, the North-American SP-MS study with IFNβ-1b failed to find a statistically significant reduction in the confirmed 1-point EDSS progression rate (the primary endpoint of the trial), although it did report significant reductions in relapse rate and various MRI parameters.[18] The clinical trial of IFNβ-1a (Rebif® 22μg and 44μg three times weekly) in patients with SP-MS also failed to demonstrate a significant effect on the primary endpoint, the reduction in the confirmed 1-point EDSS progression, but again showed significant reductions in relapse rate and MRI activity.[19,20] Recently, another study has shown that treatment with intramuscular IFNβ-1a (Avonex™ 60 μg/week) was beneficial when using the MS functional composite as the primary outcome criterion but not when using the criterion of confirmed 1-point EDSS progression.[21]

The reason for the apparent discrepancies between these trials is not clear but may be due to different patient populations with potentially different disease activity. In line with the findings of these studies is the final analysis of the European multicenter trial on IFNβ-1b in SP-MS, wherein patients with higher pre-study activity (more than two relapses or EDSS progression by more than 1 point) seemed to have a more pronounced treatment effect.[22] Thus, further treatment of SP-MS is not recommended in patients who progress slowly, particularly in those who no longer experience clinical attacks or do not show disease activity on MRI.[16]

3. Early Intervention in MS

When analysing the 4-year data of the Prevention of Relapses and disability by Interferon-β/α Subcutaneously in Multiple Sclerosis (PRISMS) study with IFNβ-1a (Rebif®), it has been suggested that the early initiation of therapy may provide benefit over delayed treatment.[23] In this study, clinical and MRI outcomes were consistently better for patients treated for 4 years with IFNβ than for those who were initially assigned to placebo and then switched to active treatment after 2 years. At the same time, histopathological[24] and MRI studies[25] have consistently shown that both axonal transection and cerebral atrophy are present at the earliest stage of MS, and that irreversible damage occurs early in the course of the disease, thus providing the pathological argument for early intervention.[26]

Two studies have been published addressing the question whether early immunomodulatory treatment with IFNβ might indeed be beneficial in patients after the first clinical attack upon proof of disseminated MS-typical lesions on MRI of the brain. Both studies were randomised, placebo-controlled and multicentre using recombinant IFNβ once a week (Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study [CHAMPS]: Avonex™ 30μg intramuscularly,[27] and Early Treatment of MS Study [ETOMS]: Rebif® 22μg subcutaneously[28]). The time from the

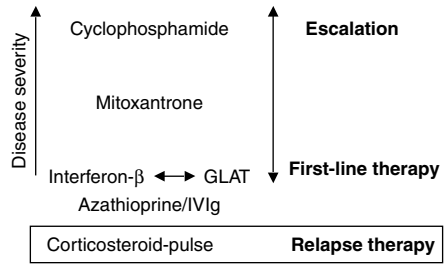

Fig. 1. Escalating immunotherapy in multiple sclerosis.[16] **GLAT** = glatiramer acetate; **IVIg** = intravenous immunoglobulin.

Table II. Summary of CHAMPS[27] and ETOMS[28] investigating the use of interferon (IFN)-β after first clinical episode suggestive of multiple sclerosis (MS)

Parameter	CHAMPS		ETOMS	
	Avonex® 30μg IM	placebo	Rebif® 22μg SC	placebo
Baseline data				
Inclusion criteria	Recent (<28 days) optic neuritis, brainstem or spinal cord lesion and more than two MRI lesions >3mm		Recent (<3 months) optic neuritis, brain stem or spinal cord lesion and MS-typical MRI lesions	
Patients (n)	193	190	154	155
Age (mean ± SD)	33 ± 8	33 ± 7	29 ± 6	28 ± 6
EDSS (mean ± SD)	1.3 ± 1.0	1.3 ± 1.1	1.2 ± 1.2	1.2 ± 1.2
Patients with Gd-MRI (%)	34	26	58	59
Results				
Patients converting to MS (%)	21	38	34	45
Days to conversion to MS	807 (25th percentile)	395 (25th percentile)	569 (30th percentile)	252 (30th percentile)
Patients with MRI activity (%)	19	42	84	94

CHAMPS = controlled high-risk subjects Avonex multiple sclerosis prevention study; **EDSS** = expanded disability status scale; **ETOMS** = early treatment of multiple sclerosis study; **Gd-MRI** = gadolinium-enhanced MRI; **IM** = intramuscularly; **MRI** = magnetic resonance imaging; **SC** = subcutaneously.

presentation of first clinical symptoms to inclusion into the study was <28 days in the CHAMPS study and <3 months in the ETOMS study (table II).

The relative risk of developing clinically definite MS was 0.56 (p = 0.002) indicating a 44% decrease in the rate of conversion to MS after administration of IFNβ-1a in the CHAMPS study.[27] In the ETOMS study, the proportion of patients converting to clinically definite MS was less in the treated group than placebo (−24%, p = 0.047).[28] Concurrently, both studies demonstrated that the time to appearance or the relative risk of a second attack can significantly be delayed for more than 9[28] and 13 months,[27] respectively, if treatment with IFNβ is implemented early. Furthermore, in both studies a significantly lower progression of subclinical disease activity on cranial MRI was recorded within an observation period of up to 2 years in the patient groups receiving IFNβ. Although both studies can not directly be compared because of different inclusion criteria and different observation periods, they concurrently demonstrated that in the early phase of MS the appearance of a second attack can be delayed and the course of the disease can be positively influenced by administering weekly injection of either IFNβ-1a preparation.[26,29]

Whereas the National Multiple Sclerosis Society of the US[30] and the Canadian Multiple Sclerosis Clinical Network[15] stated that therapy should be started 'as soon as possible' without giving a clear definition for a time frame, the MSTCG recommends in the light of these findings that immunomodulatory therapy should be started after the first attack if, upon proof of intrathecal IgG synthesis and after exclusion of other diseases mimicking MS, a subclinical dissemination can be demonstrated on MRI and:

- a functionally significant symptom is not regressing sufficiently within 2 months after high-dose corticosteroid treatment or
- a high lesion burden of greater than six lesions on cranial MRI is present or
- active inflammatory lesions (gadolinium enhancement or definite increase of T_2 lesions) can be proven in a follow-up MRI examination within 6 months.[16]

Similarly, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council of Clinical Prac-

tice Guidelines in the US concluded that it is appropriate to consider IFNβ for treatment in any patient who is at high risk for developing MS, besides those who already have either RR-MS or SP-MS and are still experiencing relapses.[5]

Although CHAMPS and ETOMS both used single weekly doses, an increase in dose or frequency of administration, as well as a change of therapeutic agent, should be considered if further attacks occur during early treatment (figure 1). Indeed, once the diagnosis of relapsing MS is made, that is, the second attack has occurred, on-label use would be: (i) once weekly intramuscular injections of IFNβ-1a (Avonex™) 30μg; (ii) three times weekly IFNβ-1a (Rebif®) 22μg or 44μg per dose; or (iii) IFNβ-1b (Betaferon®) 8 MIU every other day. No data are available for the application of other immunomodulatory agents after the first episode suggestive of MS. However, it can be assumed that the general considerations on early treatment may also be extended to the other available therapies included in figure 1. There are at least some hints from the 6-year observation period of the glatiramer acetate study in the US that starting treatment at an earlier timepoint is associated with a reduced risk for disease progression.[31]

4. Cost of Illness

Several cost-of-illness studies have been performed in patients with MS in different countries.[32-37] Most of them have some limitations for use in cost-effectiveness analysis as a result of a number of methodological problems such as small sample sizes, different designs (i.e., 'top-down', by using available statistical databases and registries, vs 'bottom-up', with collecting data primarily from the patients through patient charts and questionnaires), or the type of costs included or excluded.[38] In particular, the major focus of 'top down analysis' (which represents the 'payer's perspective') is often on diagnostic and therapeutic procedures, but the relationship of this cost with the overall socioeconomic impact of the disease itself, including indirect costs, is under represented. This 'societal perspective' is generally preferred in economic studies.

Given this background, three cost-of-illness studies have been performed, one each in Sweden,[39] Germany[40] and the UK.[41] All three studies were prevalence-based, observational studies using a 'bottom-up' approach, with direct collected data on resource utilisation from the patients. The questionnaires provided information on both medical and non-medical resource consumption, sickness leave and informal care due to MS. Furthermore, the MS-related costs were correlated to disability (EDSS) and quality of life. In Germany, six centres (five outpatient clinics in university hospitals and one rehabilitation clinic) studied a total of 737 patients. To estimate the accuracy of the data, the medical charts were also abstracted in a subsample of 202 patients showing a high degree of agreement between recorded data and answers in the questionnaires. In Sweden and in the UK, 413 and 619 patients, respectively, filled in the questionnaires.

The mean total cost per patient per year of MS in Germany was €33 438, adjusted for use of interferons which was higher in this sample than the current average use in Germany. When this cost was extrapolated to an estimated patient population of 120 000, the total costs to society were estimated €4 billion, which was 7-fold higher than earlier estimates.[35] Indirect costs due to sickness leave, premature retirement or loss of income contributed to almost half the overall costs (43%) and informal care, that is help provided by family members or friends not financed by the professional system, accounted for 12% of these costs. Direct costs represented 57%. Medication, including the innovative and expensive immunomodulatory therapies, contributed only 7% of the overall cost of illness (figure 2). Public payers paid for an estimated €12 680 per patient (or only 38% of total costs). As expected, costs increased with increasing disability levels and rose from €14 210 for mildly disabled patients (EDSS ≤3.0) to €36 430 for patients who are moderately disabled (EDSS 3.5–6.0) and to €61 230 for patients who are severely disabled (EDSS ≥6.5) [figure 3].[40] Similar results were obtained in Sweden,[39] Italy,[42] Canada[43] and in the UK.[41]

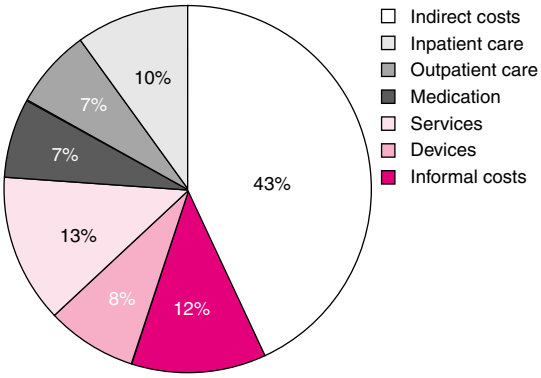

Fig. 2. Share of total costs (%) per patient and year of multiple sclerosis from the societal perspective. Mean total costs per year were €33 438 for one patient and over €4 billion for the estimated prevalence of 120 000 patients with multiple sclerosis in Germany.[40]

5. Is Treatment of MS Cost-Effective?

Economic considerations play a more and more important role in the decision making of healthcare providers, particularly in Europe. In addition to safety and efficacy, innovative technologies are now increasingly assessed for their economic consequences resulting in an additional barrier to the availability of new therapies (figure 4). An economic evaluation in healthcare is defined as 'a comparative analysis of alternative courses of action in terms of both their cost and their consequences (cost-effectiveness)'.[44,45] Thus, cost-effectiveness analyses are always comparative, and a treatment cannot be cost-effective by itself but only in relation to one or several alternatives.

Interest in the economic evaluation of the new and relatively expensive immunomodulatory therapies for MS was stimulated by the cost-utility analysis (a type of cost-effectiveness analysis that incorporates both length of life and quality of life into the outcome measure) of Forbes et al.[46] claiming that the cost per 'quality-adjusted life year' (QALY) gained from IFNβ-1b in patients with SP-MS is as high as £1 024 667 (€1 702 104; 2001 values) and, therefore, access to IFNβ-1b should be restricted. Although the concept of cost-utility analysis is generally accepted in the economic evaluation of healthcare, this study has been widely criticised, mainly because it focused on the benefit of avoiding a wheelchair, which represents only one aspect of reduced disease progression, and because it did not take into account that disease progression and future relapse rate are affected by the intervention.[47]

One of the economic models that integrates both relapse rate and disease progression is the Markov model. For this purpose, transition probabilities were directly calculated from the European SP-MS study with IFNβ-1b (Betaferon®) data[17] for the first 3 years and then extrapolated to 10 years, and mean costs and utilities for each Markov state were calculated from the cost-of-illness study in Sweden.[48] With this approach, the incremental cost per QALY were SEK 342 700 (€37 913; 2001 values) when all costs are included.[48] When natural history data from a geographically based epidemiological study in Canada were used to extrapolate beyond the clinical trial data, the incremental cost per QALY even decreased to SEK 257 000 (€28 432), an amount that appeared to be well within the acceptable range.[49] In patients with more active MS, the incremental cost per QALY gained with IFNβ-1b treatment was even lower, as shown by a recent cost-utility analysis in a subgroup of patients from two controlled trials.[50] On the other hand, the incremental cost per QALY was £51 582 (€85 684) in the UK, when clinical data from several multicentre, randomised clinical trials in patients with RR-MS and SP-MS were used to construct the model, and

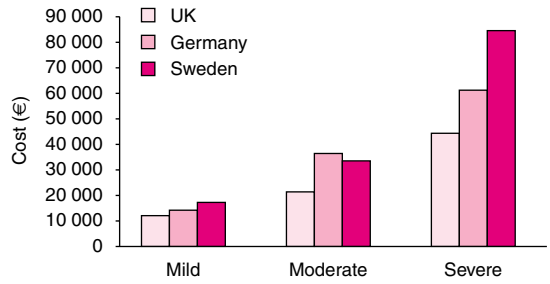

Fig. 3. Mean total costs per patient and year in three 'bottom-up' cost of illness studies in the UK,[41] Germany[40] and Sweden,[39] according to level of disability: mild (EDSS ≤3.0), moderate (EDSS 3.5–6.0) and severe (EDSS ≥6.5). Costs were adjusted to average interferon-β usage in the countries and transformed into Euros at the commercial exchange rates on 1 June 2001 (1 euro = 9.039 Swedish kronor, 0.602 pounds sterling and 1.956 Deutsche mark). **EDSS** = expanded disability status scale.

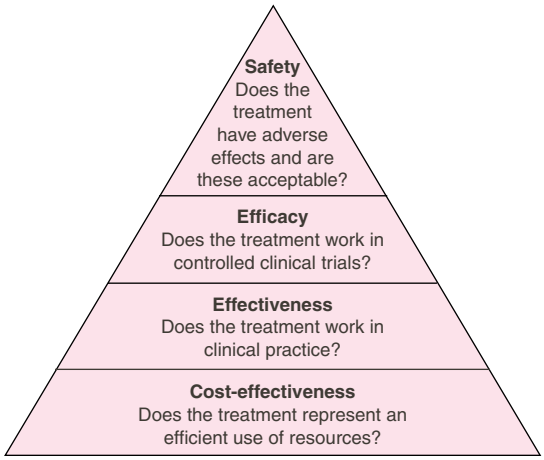

Fig. 4. Assessment criteria for new therapies for multiple sclerosis

costs (from the 'payer's perspective' only) were obtained from the National Health Service.[51] The differences between these studies demonstrate that both the data used to describe disability and to estimate costs and the method of extrapolation clearly affect the results of the economic consequences of an intervention, and underline the necessity to develop appropriate economic models that could exactly describe the complex disease process of MS.

Recently, preliminary data using an econometric time series regression model from the PRISMS 4-year data[23] showed that treatment with IFNβ-1a 44μg three times weekly (Rebif®) prevented 121 EDSS months of additional disability (a measure that integrates disability over time) at a cost of €732 per EDSS month over 10 years. Over 20 years, 321 EDSS months were saved at a cost of €359 each suggesting that IFNβ-1a is increasingly cost-effective over time.[52]

6. Conclusion

IFNβ and glatiramer acetate are effective in reducing relapse rate and slowing progression in patients with MS, and, early IFNβ treatment of patients with clinically isolated syndromes suggestive of MS, could lengthen time to conversion into definite MS. Despite some limitations and uncertainties of the economic models to available evaluate cost-effectiveness, numerous studies have unequivocally demonstrated that increasing disability is associated with increasing costs. As a consequence of these studies, stabilisation of the disease at low functional grades of disability should aim to not only improve quality of life for the individual patients, but also provide for prospective cost-benefit analysis focussing on the socio-economic aspects, particularly in patients with early MS in whom cost-effectiveness studies are not yet available. If progression can be delayed as early as possible in the course of the disease, quality of life and functional independence of patients will improve, and costs to healthcare systems, society and patients will also be diminished. In the long term, disease cost will only be reduced if the progression of MS is not only postponed, but if more effective therapies could halt the progression or even induce remission in patients with long-term disability.

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