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History of modern multiple sclerosis therapy

Abstract Although the earliest recorded description of multiple sclerosis (MS) dates back to the 14th century, it was not until the latter years of the 20th that treatments for this disabling condition were found. However, the "road to success" has not been without hurdles. Trials with both interferon alpha and gamma proved unsuccessful, as did treatment with oral myelin, cladribine, sulfasalazine and inhibitors of tumour necrosis factor. In 1993, interferon beta-1b (IFNβ-1b) became the first therapy proven to be effective in altering the natural history of relapsing-remitting MS (RRMS). This was followed by successful trials with IFNβ-1a and glatiramer acetate. In 1998, a European trial showed IFNβ-1b to be also beneficial in the treatment of secondary progressive MS (SPMS). A similar trial in North America failed to reach its primary endpoint but was effective across secondary endpoints, highlighting how different methodology and patient populations can lead to inconsistent results and, thus, making comparisons across trials difficult. The trend for early intervention in MS with IFNβ was recently supported by the CHAMPS (Controlled High-risk Avonex MultiPle Sclerosis) and ETOMS (Early Treatment of Multiple Sclerosis) studies using once-weekly IFNβ-1a. Both trials demonstrated delayed conversion to clinically definite MS in patients with a clinically isolated syndrome and magnetic resonance imaging (MRI) findings suggestive of MS. Two directly comparative trials of high- (250 μg IFNβ-1b or 44 μg IFNβ-1a) and low-dose (30 μg IFNβ-1a) IFNβ (INCOMIN [INdependent COMparison of INterferons] and EVIDENCE [EVidence of Interferon Dose-response: European North American Comparative Efficacy]) support the superior efficacy of the higher dose and/or more frequent administration for treating RRMS. Since MS entered the treatment era in 1993, therapies for RRMS, SPMS and, more recently, progressive-relapsing MS have been developed. There is now a much better understanding of the pathogenesis of the disease, but new and improved therapeutic approaches are still needed.

Key words multiple sclerosis · therapy · interferon beta-1b

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Introduction

The earliest recorded description of multiple sclerosis (MS) dates back to the 14th century, but it was the French neurologist, Jean-Martin Charcot (1825–1893), who made the first definite links between the symptoms of MS and the pathological changes seen in post-mortem samples. He described the condition as "*sclerose en plaques*" and recognised MS as a distinct disease entity. Charcot's contribution extended to the development of diagnostic criteria, which included the now-famous triad of "nystagmus, tremor and scanning speech". He also identified many important histological features, including loss of myelin. This paper reviews the development of current treatment strategies for MS.

A brief history

In the 1960s, corticosteroids were introduced to reduce the severity of relapses. They are, however, not effective at reducing the number of relapses or the rate of disease progression. This was followed in the 1970s and 1980s by trials with a variety of immunosuppressant agents, including cyclophosphamide, cyclosporine, azathioprine, methotrexate and glatiramer acetate (GA) (copolymer 1) [2]. These studies examined the effect of treatment on exacerbations of MS, thus providing a useful platform for the development of assessment tools for use in later studies. However, it was not until the late 1980s that the concept of immunomodulation was extensively explored, and this was assisted by the development of non-invasive monitoring methods.

In 1981, the new imaging technique, magnetic resonance imaging (MRI), dramatically improved the visualisation of the brain and spinal cord, enabling lesions to be quantified in the living patient. The pioneering work of Ian Young in this field correctly predicted the future value of MRI scanning in the diagnosis and monitoring of MS [31]. He suggested that the technique may help measure the severity of the disease and, thus, be used to evaluate the effect of therapeutic regimens on disease progression. The technique was refined by Robert Grossmann in 1986, who discovered that gadolinium enhancement was a marker of inflammation [8]. Gadolinium-enhanced MRI scans provide a way of identifying new and active lesions. MRI has become an established method of monitoring disease progression in clinical trials.

The interferons have a unique place in the history of drug development in that studies in man preceded animal studies. In early trials, interferon gamma was found to provoke acute exacerbations of MS, which ceased when the drug was removed. Attention shifted to interferon alpha and interferon beta (IFNβ) as they were known inhibitors of interferon gamma, and IFNβ was shown to be well-tolerated when compared with interferon alpha. The pivotal IFNβ-1b trial was published in 1993 and heralded the start of the therapeutic era in MS and the introduction of IFNβ-1b into the USA – the first therapy proven effective in altering the natural history of relapsing-remitting MS (RRMS) [11, 29]. Although the pivotal trial did not use gadolinium in the imaging protocols, a study by Stone et al. clearly showed that IFNβ-1b had a dramatic effect at reducing gadolinium-enhancing lesions [26].

The pivotal IFNβ-1b study was followed in subsequent years by successful trials in RRMS with IFNβ-1a and the non-interferon agent GA [11, 13, 15]. In 1998, a study undertaken in Europe showed that IFNβ-1b was also successful in the treatment of secondary progressive MS (SPMS) [7].

However, the "road to success" in the treatment of MS has not been without its challenges. Unsuccessful studies have included experimental treatment with a range of promising agents. Whilst we now have a much better understanding of the pathogenesis of the disease, there is a continued need for improved therapeutic approaches for MS.

MS and clinical trials

Exemplary clinical trials incorporate blinding to treatment, randomisation and the selection of appropriate patients and outcome measures. The classification of MS into four distinct clinical patterns (namely RRMS, SPMS, primary progressive and progressive-relapsing MS) has also played an important role in ensuring that homogeneous populations are assigned to clinical trials, even though precise biological definitions are not yet available [17].

Comparison between current treatments in clinical trials is made difficult by the lack of prospectively designed, fully-blinded, head-to-head trials. Interpretation of data obtained from different studies is fraught with difficulty because of differences in inclusion and exclusion criteria, different use of placebo control, and differences in duration of treatment, which impact upon measures of efficacy. Furthermore, there are no laboratory studies (including MRI findings) that meet Food and Drug Administration requirements for a surrogate marker of prognosis.

In terms of outcome variables, relapse rate in MS is a routine measure of disease activity that is easy to quantify and included in almost all trials. Assessment of disability as a measure of disease progression is equally, if not more, important. MRI assessment of gadolinium-enhancing lesions provides useful information about acute disease activity, but interpretation of T2 lesion load is more problematic because of the heterogeneous nature of these lesions, and because lesion load is a measure of disease burden rather than disease activity. Nevertheless, it still provides strong evidence of treatment effects.

An important principle when interpreting clinical trial data is that of coherence. A study in which all outcomes point to the same effect, even if they are not all statistically significant, provides confidence that the outcomes observed are real. It is also important that the treatment duration in a clinical trial is long enough to provide meaningful information about expected benefits. For example, in an early study with sulfasalazine, the results at 18 months showed a marked reduction in disease progression relative to placebo, but at the end of the planned 3-year study duration no differences were observed between placebo and active treatment [18].

Treatment of RRMS

The original IFNβ-1b study included 372 patients with RRMS who were randomised to receive placebo, or IFNβ-1b 50 µg or 250 µg (1.6 or 8.0 MIU) self-administered by subcutaneous injection every other day for 2 years, with an optional 1-year extension [11]. Due to staggered enrollment, some patients received treatment for 5 years or more. The results indicated that IFNβ-1b 250 µg was associated with a reduction in relapse rate of approximately 30 % compared with placebo over the 5 years of the study (Fig. 1) [12]. The reductions after 3–5 years (28–30 %), although comparable to those seen during the first 2 years of the study (28–33 %), failed to attain statistical significance because of the declining patient numbers in the study at each successive time point. The risk of progression at 2 years also showed a strong trend and magnitude of effect in favour of IFNβ-1b treatment, but the study was not powered to measure an effect on this outcome. Clinically important and statistically significant reductions in MRI T2 lesion load with IFNβ-1b in comparison with placebo were also achieved throughout the 5-year follow-up period (Fig. 2). These findings clearly demonstrate the clinically important benefit of treatment with IFNβ-1b in patients with RRMS.

The pivotal study of IFNβ-1a in RRMS included 301 patients who were randomly assigned to treatment with placebo or IFNβ-1a 30 µg administered by intra-muscular injection once a week [13]. This was the first study to use a sustained one-point change in Expanded Disability Status Scale (EDSS) score as a primary efficacy variable. Follow-up at 2 years indicated that treatment with IFNβ-1a reduced the risk of sustained EDSS progression in comparison with placebo (21.9 % vs. 34.9 %, respectively; $P = 0.02$) over the 2-year study period. The subgroup of patients treated with IFNβ-1a for at least 2 years also had significantly fewer exacerbations and fewer gadolinium-enhanced brain lesions than those treated with placebo. However, the concern over this

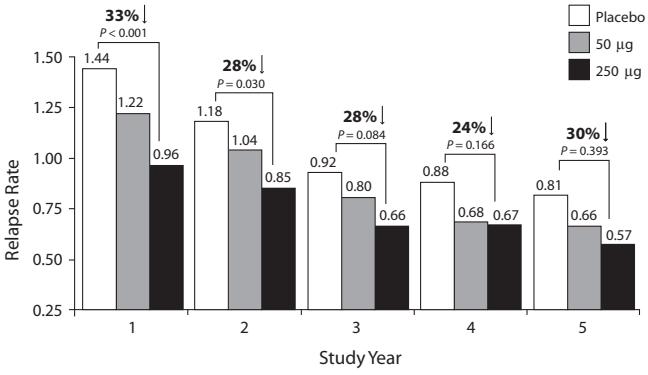

Fig. 1 Effect of IFNβ-1b on annual relapse rate in RRMS over 5 years [12]

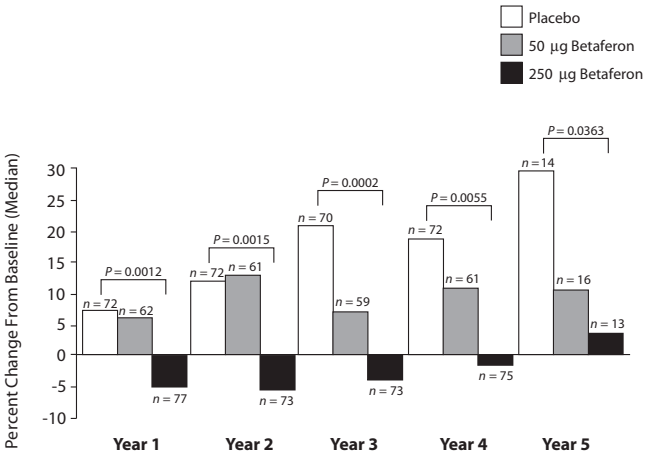

Fig. 2 Effect of IFNβ-1b on T2 MRI lesion area over 5 years in patients with RRMS (from [12] with permission of Lippincott Williams & Wilkins)

study was the substantial proportion of patients who did not complete 2 years of treatment, and intention-to-treat analysis showed an 18 % reduction in relapse rate.

Glatiramer acetate (copolymer 1) was investigated in a 2-year, double-blind, placebo-controlled study involving 251 patients with RRMS who were randomised to receive placebo ($n = 126$) or GA ($n = 125$) at a dosage of 20 mg by daily subcutaneous injection for 2 years, with an 11-month extension period [15]. The primary endpoint was a difference in the MS relapse rate. The mean number of documented relapses during the initial 2-year, double-blind phase of the study was 1.19 ± 0.13 for patients receiving GA and 1.68 ± 0.13 for those receiving placebo; a 29 % reduction in favour of GA ($P = 0.007$) [15]. Long-term follow-up at 6 years indicated that open-label treatment with GA continued to protect against worsening disability [30]. Between years 3 and 7, the patients initially receiving placebo were switched to active treatment, meaning there was no control against which to measure effect. However, although these patients benefited from active therapy, they failed to "catch up" with patients originally assigned to GA, demonstrating the importance of early treatment.

When to begin treatment

Pathological and MRI studies suggest that axonal damage may be an early event in the evolution of MS, and evidence is accumulating that, in the early phases of the disease, axonal damage is largely a consequence of inflammatory processes [4, 10, 27, 28]. As the mechanism of action of IFNβ in MS is anti-inflammatory, improved results could be predicted with earlier rather than later treatment of MS.

In the CHAMPS (Controlled High-risk subjects Avonex® MultiPle Sclerosis prevention) study, 383 pa-

tients who had a first acute clinical demyelinating event (optic neuritis, incomplete transverse myelitis or brainstem or cerebellar syndrome), and evidence of demyelination on MRI of the brain, were randomly assigned to receive weekly intra-muscular injections of IFNβ-1a 30 µg or placebo [14]. During 3 years of follow-up, the cumulative probability of developing clinically definite MS (CDMS) was significantly lower in the IFNβ-1a group than in the placebo group. The relative risk was 0.56 with a 95% confidence interval of 0.38–0.81 ($P = 0.002$). These findings showed that initiating treatment with IFNβ-1a at the time of a first demyelinating event was beneficial for patients with brain lesions on MRI that indicated a high risk of CDMS.

Similar findings were achieved in the ETOMS (Early Treatment Of MS) study, in which IFNβ-1a was given subcutaneously at a dose of 22 µg once a week to patients who had initial findings suggestive of MS within the previous 3 months [5]. In this study, the time to the occurrence of the second relapse (i. e. MS according to Poser's criteria) in 30% of patients (i. e. the 30th centile) was used to define conversion to CDMS; this was 569 days in the IFNβ-1a group compared with 252 days in the placebo group. The hazard ratio (0.65) showed a statistically significant benefit with IFNβ-1a relative to placebo ($P = 0.023$) when adjusted for baseline lesion count and time from first attack to randomisation. Importantly, in this study the therapeutic benefit on relapses was supported by MRI findings showing that both lesion activity and the accumulation of lesion burden were reduced compared with placebo. The efficacy of IFNβ-1a in these two studies in RRMS reinforces the concept of early intervention.

Treatment intensification

In addition to starting treatment early in the course of the disease, there is good evidence to suggest that better results are obtained with high-dose (250 µg IFNβ-1b, 44 µg IFNβ-1a) IFNβ rather than with low-dose IFNβ-1a. A study of two IFNβ-1b doses (50 µg and 250 µg every other day) against placebo found that the 250 µg dose improved the reduction in annual relapse rate by 34% relative to placebo, while the reduction with 50 µg was 8% [11]. The effect was not as substantial in the subcutaneous IFNβ-1a efficacy trial, with improvements in annual relapse rates relative to placebo of 29% and 33% for 22 µg and 44 µg IFNβ-1a, respectively [23].

The INCOMIN (INdependent COMparison of INterferon) trial showed the benefit of high-dose, high-frequency IFNβ-1b (250 µg every other day) over once-weekly IFNβ-1a (30 µg) in the prevention of relapse in patients with RRMS [6]. A higher proportion of patients receiving 250 µg IFNβ-1b (51%) remained free from relapse (the primary outcome measure) for the duration of the study compared with patients receiving IFNβ-1a once weekly (36%). This corresponded to a significant increase of 42%, favouring IFNβ-1b-treated patients ($P = 0.036$).

Similar findings were obtained in the EVIDENCE (EVidence for Interferon Dose Effect: European-North American Comparative Efficacy) study, which compared IFNβ-1a at 44 µg given subcutaneously 3 times a week with a once-weekly regimen of IFNβ-1a given intra-muscularly at 30 µg to patients with RRMS [21]. The results at week 48 show that the more frequent, high-dose (44 µg) regimen was associated with a 23% reduction in the number of patients suffering a first relapse (Fig. 3).

Not all studies have shown an increase in efficacy with increased dosing. Data from a study comparing once-weekly single (30 µg) with double-dose (60 µg) intra-muscular IFNβ-1a in 802 patients with RRMS for at least 3 years failed to show a reduction in disease progression with the higher dose at any point during the 3-year study [3]. It is possible, therefore, that frequency of dosing may be as important as the actual dose.

Studies in SPMS

The European study with IFNβ-1b in SPMS included 718 patients (EDSS score 3.0–6.5), of whom 360 were randomly assigned to receive IFNβ-1b 250 µg by subcutaneous injection every other day, and 358 patients were assigned to receive placebo [7]. Patients were followed up for 3 years after the start of treatment. IFNβ-1b was shown to delay disease progression by between 9 and 12 months. In the placebo group, 49.7% of patients had confirmed progression at 3 years compared with 38.9% in the IFNβ-1b group ($P = 0.005$), representing a relative reduction of 21.7%.

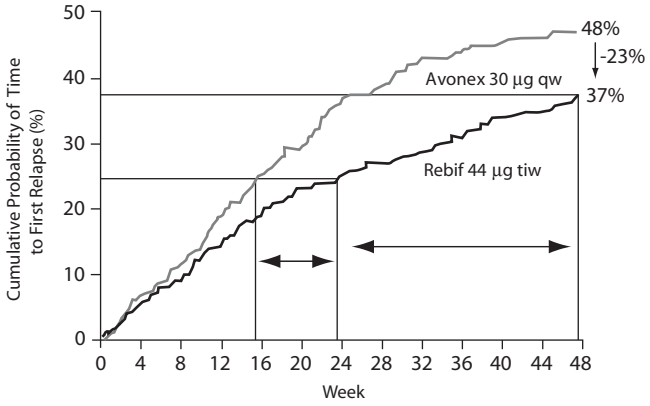

Fig. 3 Kaplan-Meier estimates of cumulative probability of relapse during the EVIDENCE trial (from [21] with permission of Lippincott Williams & Wilkins)

In the North American study in SPMS (a 3-year, multicentre, double-blind, placebo-controlled trial) 939 patients were randomised to receive IFNβ-1b 250 μg every other day, 160 μg/m^2 every other day or placebo. Treatment with IFNβ-1b resulted in significant improvement (compared with placebo) on all outcome measures involving clinical relapses, newly active MRI lesions and accumulated burden of disease on T2-weighted images [22]. However, the study failed to show a difference between active treatment and placebo in terms of disease progression – the primary outcome measure. There are several possible explanations for the difference between the primary outcomes of the European and North American trials, but one is that the North American study appeared to enrol patients at a more advanced stage of their disease. An analogous study that examined the effect of IFNβ-1a treatment in SPMS revealed similar findings [25]. This may imply that IFNβ may be more effective at preventing accumulation of disability in earlier stages of the disease or in patients experiencing more exacerbations.

Finally, mitoxantrone 12 mg/m^2 has been shown to significantly reduce the probability of EDSS progression in patients with SPMS when compared with placebo over a period of 2 years [9]. However, given the potential cumulative cardiotoxicity of mitoxantrone, it should be reserved for patients in whom disease progression cannot be controlled by established immunomodulatory therapeutics.

Other therapeutic approaches

A number of unsuccessful Phase II studies have been undertaken with a variety of agents. Although negative, some of this work nevertheless provides valuable information that may guide future research. Studies with cladribine in primary progressive MS and SPMS, for example, showed evidence for a good response in terms of gadolinium-enhancing lesions in the absence of any benefit on clinical parameters, suggesting a dissociation between inflammatory changes and relapses in progressive MS [24].

Studies with altered peptide ligand showed that administration of this substance was associated with a potentiation of exacerbations of MS, suggesting the possibility that myelin basic peptide is involved in the pathogenesis of MS [1].

Oral tolerance has been tested as a therapeutic strategy in MS using the oral administration of myelin. A multicentre trial controlled for patient gender and steroid treatment was conducted in which myelin was administered orally to over 500 early RRMS patients. Individuals received either 300 mg of bovine myelin or casein daily and were monitored for exacerbation, EDSS and MRI. Contrary to studies in experimental autoimmune encephalomyelitis animals, daily administration of bovine myelin did not significantly improve disease in MS patients.

Results from a number of small studies show that the administration of tumour necrosis factor (TNF) alpha inhibitors also appears to exacerbate MS [16, 20]. These findings are paradoxical – TNF inhibitors are clearly effective in animal models of MS, and are also widely used in the treatment of other autoimmune conditions such as rheumatoid and psoriatic arthritis and inflammatory bowel disease. Further research is, therefore, required to fully understand the role of TNF in the pathogenesis of MS.

A Phase III, placebo-controlled trial of linomide in 715 patients with RRMS ($n = 90$) or SPMS ($n = 625$) found that the drug caused coronary artery disease in a number of patients, and the trial was halted 1 month after completion of enrollment [19].

Conclusions

Interferon beta-1b was the first immunomodulatory therapy to be approved for the treatment of RRMS, and is the only IFNβ to receive a licence for SPMS therapy. The development of new agents is a long, drawn-out, often unsuccessful process, as the number of recent failures illustrates. However, the long-term safety and efficacy of IFNβ treatment is unquestionable, with over 10 years of clinical experience as evidence. Future studies will focus on going beyond the currently approved dosages and earlier intervention to prevent initial neuronal damage with the proven disease-modifying therapies. Furthermore, opportunities for pharmacological intervention into the immune processes contributing to MS exist for future research, offering the possibility of more effective therapies. It is hoped that ongoing research will expand our knowledge of the appropriate targets for intervention, enabling more effective therapies to be developed.

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