Credit: imageBROKER/Alamy Stock Photo

MILESTONE 1

The dawn of the therapeutic era in MS

The therapeutic era in multiple sclerosis (MS) began with the approval of interferon-β-1b (IFNβ-1b) by the FDA for the treatment of relapsing–remitting multiple sclerosis (RRMS) in 1993. Glatiramer acetate and additional formulations of IFNβ soon followed, and these injectable therapies were the mainstays of MS therapy for the following decade.

For more than a century, a limited understanding of the pathological mechanisms of MS in combination with the highly variable course of the disease hindered the development of treatments. In the late 1980s, however, an increased appreciation that aberrant immunological responses were associated with exacerbation of the disease sparked an interest in the potential of immunomodulatory therapies for MS. In addition, the development of MRI facilitated assessment of potential therapies by enabling brain and spinal cord lesions to be monitored non-invasively over time.

Therapeutic development focused on interferons — cytokines released in response to pathogens — on the basis of the hypothesis that MS is caused or exacerbated by viral infection. The first such therapies to be trialled were based on IFNγ, but it quickly became clear that this cytokine exacerbates relapses in patients with MS. Consequently, attention turned to IFNα and IFNβ, which were known to be inhibitors of IFNγ.

Evidence suggested that the safety profile of IFNβ was superior to that of IFNα. Isoforms of IFNβ that were derived from mammals (IFNβ-1a) and bacteria (IFNβ-1b) were tested in patients with RRMS in several small trials. These studies, although inconclusive, showed promise of therapeutic efficacy.

In 1993, a landmark multicentre, randomized, double-blind, placebo-controlled trial that included 372 patients with RRMS demonstrated that subcutaneous injection of IFNβ-1b significantly reduced annual relapse rates. The highest dose of IFNβ-1b reduced the number of annual relapses by 34% compared with placebo at 2 years. These results demonstrated the first successful modification of the disease course of MS, although IFNβ-1b had no detectable effect on disability progression.

Subsequent trials of IFNβ-1a did reveal an effect on disability progression in RRMS. A study published in 1996 showed that intramuscular IFNβ-1a not only reduced annual relapse rates by 18% compared with placebo, but also reduced sustained disability progression, measured with the Expanded Disability Status Scale (EDSS), after 2 years. Some uncertainty remained owing to early termination of the trial, the small number of patients included and the small, delayed effect, but a large double-blind, placebo-controlled study of subcutaneous IFNβ-1a in 560 patients with RRMS mitigated these concerns in 1998. In this trial, the time to sustained disability progression was significantly increased in patients who received IFNβ-1a compared with individuals who received placebo. This effect was in addition to a 27–33% reduction in relapse rate, depending on the dose.

> “success with injectable therapies in the 1990s transformed attitudes towards MS treatment”

In the midst of the interferon trials, glatiramer acetate became the second injectable therapy to be approved for RRMS in 1997. Glatiramer acetate is a mixture of peptides composed of four amino acids. The peptides are thought to mimic myelin basic protein and competitively inhibit the interaction between immune cells and myelin.

Following promising results in a pilot study of glatiramer acetate, a landmark trial published in 1995 showed that subcutaneous glatiramer acetate reduced annual relapse rates in patients with RRMS by 29% compared with placebo. Measurement of disability with the EDSS showed that glatiramer acetate reduced the chance of disability progression and increased the chance of disability improvement.

The success with injectable therapies in the 1990s transformed attitudes towards MS treatment. Previously, treatment had focused on symptomatic therapy, but the new drugs demonstrated that the disease course is amenable to therapeutic modification. Furthermore, the strong safety profiles of IFNβ and glatiramer acetate mean that these first injectable agents remain a crucial part of the clinician's toolbox for MS treatment today.

Charlotte Ridler, Associate Editor,
Nature Reviews Neurology

ORIGINAL ARTICLES The IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing–remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology* **43**, 655–661 (1993) | Johnson, K. P. et al. Copolymer 1 reduces relapse rate and improves disability in relapsing–remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. *Neurology* **45**, 1268–1276 (1995) | Jacobs, L. D. et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. *Ann. Neurol.* **39**, 285–294 (1996) | PRISMS study group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. *Lancet* **352**, 1498–1504 (1998)