**INTERFERON BETA 1-B AND MORTALITY**

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Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) with a lifelong course. This long course means that clinicians need to be concerned about outcome over both the short and long term. Despite this, virtually all randomized controlled trials (RCTs) have focused only on short-term outcomes (e.g., relapse rate, disability after 2 years, and MRI measures). Nevertheless, what matters most to patients is going to happen to them in the long-term. Of all the possible long-term outcomes, survival is the ultimate long-term measure, and is therefore surprising that, to date, little attention has been directed to the mortality in MS patients treated with disease-modifying therapy (DMT).

Despite this, several independent studies have demonstrated that the standardized mortality rate (SMR) is 2–5 times higher for MS patients than it is for non-MS controls, with differences becoming apparent as early as 2–10 years after diagnosis. Although MS results in a significant survival disadvantage, the impact of DMTs on longevity remains unknown. We therefore conducted a long-term follow-up study to determine the impact of early treatment with interferon beta (IFNβ)-1b on survival up to 21.4 years after RCT-enrolment.

From October 1, 2009 to December 15, 2010, we attempted to identify each of the 372 randomized patients who participated in the pivotal, placebo-controlled RCT of IFNβ-1b in relapsing-remitting MS (RRMS). All patients enrolled in the pivotal IFNβ-1b trial were eligible to participate. Those included in the original RCT were treatment-naïve patients aged 18–50 years with an Expanded Disability Status Scale (EDSS) score ≤5.5 and with two or more clinical exacerbations within the previous 2 years. Patients were randomized to receive IFNβ-1b 50 μg, IFNβ-1b 250 μg, or placebo every other day. During the RCT, patients were treated and prospectively followed for a period of up to 5.1 years, with a median of 3.8 years (range 0.1–5.1) and a mean of 3.3 ± 1.4 years on assigned treatment. During the RCT, both clinical and magnetic resonance imaging (MRI) outcomes were assessed.

At the conclusion of the RCT in 1993, the subsequent use of DMTs was at the discretion of patients and their physicians. Only IFNβ-1b was available initially; after 1996, use of alternative DMTs was possible. The primary outcome, defined prior to data collection, was the comparison of all-cause mortality between the IFNβ-1b 250 μg and placebo groups from the time of randomization (intention-to-treat, log-rank test for Kaplan–Meier survival curves). All other survival outcomes were considered secondary.

After a median of 21.1 years from RCT enrolment, 98.4% (366/372) of patients were identified, and, of these, 81 deaths were recorded (22.1%; 81/366). Patients originally randomized to IFNβ-1b 250 μg showed a significant reduction in all-cause mortality over the 21-year period compared with placebo ($p$ = 0·0173), with a hazard ratio (HR) of 0.532 (95% confidence interval 0.314–0·902). The HR of death at LTF by Kaplan–Meier estimates was reduced by 46·8% among IFNβ-1b 250 μg-treated patients (46·5% among IFNβ-1b 50 μg-treated patients) compared with placebo.

Certain baseline parameters were associated with longer survival, using univariate Cox models with dichotomized variables. These included assignment to IFNβ-1b 250 μg (HR 0.532, 95% CI 0.314–0.902; $p$ = 0.0192); assignment to IFNβ-1b 50 μg (HR 0.533, 95% CI 0.314–0.903; $p$ = 0.0194); lower EDSS score (HR 0.630, 95% CI 0.400–0.993; $p$ = 0.0464); lower MRI T2 disease burden (HR 0.422, 95% CI 0.262–0.678; $p$ = 0.0004); and smaller MRI ventricle size (HR 0.573, 95% CI 0.351–0.935; $p$ = 0.0256).

Bivariate regression models (using dichotomized variables), which included treatment together with each individual baseline variable, showed that gender, MRI T2 disease burden, and MRI ventricle size, in addition to treatment, influenced the risk of dying. In these models, the HR for the treatment effect on mortality remained quite stable, ranging from 0.506 to 0.604 (table 1). Thus, the treatment-related HR was unchanged by the inclusion of baseline variables, even when these variables were themselves associated with an increased likelihood of mortality

Thus, in this study there was a significant survival advantage in this cohort of patients receiving early IFNβ-1b treatment, at either dose, compared with placebo. Near-complete ascertainment, together with confirmatory findings from both active treatment groups, strengthens the evidence for an all-cause mortality effect.