Does early (treatment in) BENEFIT lead to late MS benefit?

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Contemporary trends in treatment of multiple sclerosis (MS) have embraced the concept "time is brain" to emphasize the importance of utilizing disease-modifying treatments for MS to mitigate irreversible and usually silent damage to axons in early phases of the disease that may result in later progressive axonal degeneration with consequent disability. Recommendations that have emerged from this construct are the need for early treatment,[1] possibly with potent therapies ("induction treatment"),[2] with strict assessment and rigorous requirements for efficacy ("no evidence of disease activity")[3] to achieve better outcomes. Similar approaches are now espoused in other autoimmune diseases in which acute flares ultimately lead to chronic destructive disease, such as rheumatoid arthritis.[4]

A decision to begin long-term treatment very early is complex because uncertainty about the diagnosis is particularly troublesome in patients with clinically isolated syndromes, especially in those with relatively minor symptoms and nonspecific radiologic findings. Furthermore, it is difficult to determine whether treatment is beneficial to an individual patient given the variability of MS disease course. Accordingly, it is important to assemble a strong evidence base of benefit in relevant cohorts of patients, assessing not only short-term outcomes, such as new lesions on MRI and annualized rate of clinical attacks, but also long-term robust outcomes, such as secondary progressive MS, major disability milestones, employment, and death. Long-term robust endpoints are more difficult to assess for a variety of reasons: short duration of randomized clinical trials, despite a lengthy interval before secondary progression and long-term disability accumulates; biases of selection of patients for treatment and for patients to remain on treatment, which is influenced by feedback on indicators of short-term success; incomplete follow-up; and apparent shifts in the course of MS in the placebo groups of clinical trials and even in natural history studies.[5] The data for long-term benefit have been conflicting, in part determined on whether the analysis has been in "real world" studies[6] or in cohorts of patients that are generated at the time of randomization in a clinical trial.[7]

In this issue of *Neurology*®, Kappos et al.[8] report the long-term follow-up of a cohort comprising 60% of the persons originally enrolled in the BENEFIT (Betaferon/Betaseron in Newly Emerging MS for Initial Treatment) clinical trial with what was then defined as clinically isolated syndrome, who were randomized to immediate treatment vs delayed treatment until clinically definite MS was reached or 2 years had passed. The definition of clinically isolated syndrome has since been changed to exclude individuals who have radiologic evidence of dissemination in time and space, who are now designated as having MS rather than clinically isolated syndrome. Four previous publications of the BENEFIT trial have described a significant benefit of early treatment on the time to clinically definite MS with hazard ratios ranging from 0.50 in the earliest study[9] to 0.68 in the most recent.[10] Furthermore, these studies have shown a benefit of early treatment on a measure of cognitive dysfunction in MS, the Paced Auditory Serial Addition Test, at long-term follow-up points; however, there was no consistent benefit of treatment on disability accumulation as assessed by the Expanded Disability Status Scale (EDSS). The present study confirms these previous results by showing early treatment was associated with an increase in the time to clinically definite MS (hazard ratio = 0.67) and a decrease in the total relapse rate over 11 years. The difference in the first year rather than later time points was primarily responsible for the overall relapse benefit. The 2 treatment groups did not differ in EDSS score or change in EDSS score over the 11-year period. Although a larger proportion of participants seemed to develop secondary progressive MS in the delayed treatment group, this was not significant, attributable in part to a small number of events, suggesting that even longer follow-up may be required to establish a treatment benefit on this outcome. The previous benefit on the Paced Auditory Serial Addition Test was confirmed in this study, but no difference was observed on a different measure of

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processing speed (Symbol Digit Modalities Test) or on patient-reported outcomes. Finally, no significant group differences were observed on MRI outcomes of atrophy or lesion load. In summary, early treatment appears to have a benefit on relapses, especially early in the disease, but limited effects on other outcome measures.

Important strengths of the study are the retention rate, similarity between participants who contributed to this analysis and the original sample, and similarity between the 2 treatment groups in this analysis. Since BENEFIT 11 participants are comparable to those in the original trial, the results from this study would likely be unchanged had all participants contributed. Furthermore, since the treatment groups who are compared in BENEFIT 11 are balanced as in the original trial, it seems unlikely that the treatment group differences are driven solely by differential dropout between the 2 treatment arms. At the same time, unidentified biases could influence interpretation of the results.

Despite the excellent design and analysis of the study, comparisons of the disease course and disability accumulation in these patients with natural history studies must be considered cautiously. Although the disability accumulation 11 years after disease onset in BENEFIT 11 was notably more modest than in natural history studies, the explanation may not be early treatment alone. Furthermore, with many new therapeutic options for MS, obtaining comparable long-term outcome information on patients treated with several different agents at different points following diagnosis will be necessary to determine the best practices for managing recently diagnosed patients at what is emerging to be a critical point in their disease course.

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