

The 11-year long-term follow-up study from the randomized BENEFIT CIS trial

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Study question: In patients diagnosed with clinically isolated syndrome (CIS), does immediate treatment with interferon beta-1b reduce the long-term risk of conversion to clinically definite multiple sclerosis (CDMS) compared to delayed treatment?

Summary answer: After 11 years, risk of conversion to CDMS remained lower in those receiving immediate treatment.

What is known and what this paper adds: The results of the study support initiating treatment of CIS before conversion to CDMS, and provide Class IV evidence that such treatment may provide benefits over the long term compared to a delay in starting treatment.

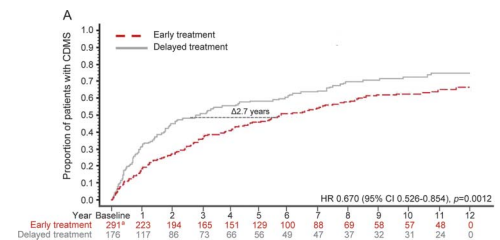
Design: As part of the phase 3, international, multicenter BENEFIT trial, patients with a CIS and 2 or more clinically silent MRI lesions were randomized (5:3) to 250 µg interferon beta-1b (early treatment group) or placebo (delayed treatment group) every other day for 2 years or until conversion to CDMS, after which patients receiving placebo could switch to interferon beta-1b. Results from a prospective, comprehensive follow-up at 11 years (BENEFIT-11) are reported here.

Participants and setting: Of the 468 patients in BENEFIT, 278 enrolled in BENEFIT-11, including 167 originally assigned to active treatment and 111 to placebo. Baseline characteristics between the 2 groups were similar. Sixty-two percent of patients were on a disease-modifying therapy, including 31% on interferon beta-1b.

Primary outcome(s): The primary outcome measure was the proportion of patients in each group converting to CDMS, assessed by modified Poser criteria, by the time of BENEFIT-11.

Main results and the role of chance: Early treatment was associated with a reduced risk of conversion to CDMS, with a hazard ratio of 0.670 (95% CI 0.526–0.854), $p = 0.0012$. Sixty-seven percent of all patients receiving early treatment had converted to CDMS by the time of BENEFIT-11, compared to 75% of those receiving delayed treatment. Early treatment

Kaplan-Meier estimates of probability of CDMS-Annualized Relapse Rate



was associated with a longer time to first relapse (median [Q1, Q3] days: 1,888 [540, not reached] vs 931 [253, 3296]; $p = 0.0005$), and lower overall annualized relapse rate (0.21 vs 0.26; $p = 0.0018$). The Kaplan-Meier estimate of 50% probability of CDMS indicated an average delay of conversion of 2.7 years for early vs delayed treatment (figure).

Harms: The reported adverse events were consistent with the known profile of interferon beta-1b, with no serious adverse effect during BENEFIT 11. No new safety signals were detected at year 11.

Bias, confounding, and other reasons for caution: Some patients from the original trial were unavailable for follow-up. However, the follow-up study included a large proportion of patients from the original trial, and the follow-up patient population was similar to the original trial. Treatment allocation was unblinded for all patients by 5 years after randomization.

Generalizability to other populations: Because of the international, multi-center design of the trial, the results are likely to be generalizable to other populations.

Study funding/potential competing interests: This study was funded by Bayer HealthCare Pharmaceuticals, the manufacturer of the study drug, and the analysis was performed by an employee of Bayer. Go to Neurology.org for full disclosures.

Trial registration number: NCT01795872.

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