Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial.

The anti-CD52 monoclonal antibody alemtuzumab reduces disease activity in previously untreated patients with relapsing-remitting multiple sclerosis. We aimed to assess efficacy and safety of alemtuzumab compared with interferon beta 1a in patients who have relapsed despite first-line treatment.

In our 2 year, rater-masked, randomised controlled phase 3 trial, we enrolled adults aged 18-55 years with relapsing-remitting multiple sclerosis and at least one relapse on interferon beta or glatiramer. Eligible participants were randomly allocated in a 1:2:2 ratio by an interactive voice response system, stratified by site, to receive subcutaneous interferon beta 1a 44 μg, intravenous alemtuzumab 12 mg per day, or intravenous alemtuzumab 24 mg per day. Interferon beta 1a was given three-times per week and alemtuzumab was given once per day for 5 days at baseline and for 3 days at 12 months. The 24 mg per day group was discontinued to aid recruitment, but data are included for safety assessments. Coprimary endpoints were relapse rate and time to 6 month sustained accumulation of disability, comparing alemtuzumab 12 mg and interferon beta 1a in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT00548405.202 (87%) of 231 patients randomly allocated interferon beta 1a and 426 (98%) of 436 patients randomly allocated alemtuzumab 12 mg were included in the primary analyses. 104 (51%) patients in the interferon beta 1a group relapsed (201 events) compared with 147 (35%) patients in the alemtuzumab group (236 events; rate ratio 0·51 [95% CI 0·39-0·65]; p<0·0001), corresponding to a 49·4% improvement with alemtuzumab. 94 (47%) patients in the interferon beta 1a group were relapse-free at 2 years compared with 278 (65%) patients in the alemtuzumab group (p<0·0001). 40 (20%) patients in the interferon beta 1a group had sustained accumulation of disability compared with 54 (13%) in the alemtuzumab group (hazard ratio 0·58 [95% CI 0·38-0·87]; p=0·008), corresponding to a 42% improvement in the alemtuzumab group. For 435 patients allocated alemtuzumab 12 mg, 393 (90%) had infusion-associated reactions, 334 (77%) had infections (compared with 134 [66%] of 202 patients in the interferon beta 1a group) that were mostly mild-moderate with none fatal, 69 (16%) had thyroid disorders, and three (1%) had immune thrombocytopenia. For patients with first-line treatment-refractory relapsing-remitting multiple sclerosis, alemtuzumab could be used to reduce relapse rates and sustained accumulation of disability. Suitable risk management strategies allow for early identification of alemtuzumab's main adverse effect of secondary autoimmunity. Genzyme (Sanofi) and Bayer Schering Pharma.