Intrathecal Rituximab is not effective in progressive multiple sclerosis

Background

No treatments have been approved for primary progressive multiple sclerosis. Fingolimod, an oral sphingosine 1-phosphate receptor modulator, is effective in relapse-onset multiple sclerosis, but has not been assessed in primary progressive multiple sclerosis. We assessed the safety and efficacy of fingolimod in patients with primary progressive multiple sclerosis.

Methods

In INFORMS, a multicentre, double-blind, placebo-controlled parallel-group study, patients with primary progressive multiple sclerosis recruited across 148 centres in 18 countries were randomly allocated (1:1) with computer-generated blocks to receive oral fingolimod or placebo for at least 36 months and a maximum of 5 years. Patients were initially assigned to fingolimod 1·25 mg per day or placebo (cohort 1); however, after a protocol amendment on Nov 19, 2009, patients were switched in a masked manner to fingolimod 0·5 mg, whereas those on placebo continued on matching placebo. From then onwards, patients were assigned to receive fingolimod 0·5 mg/day or placebo (cohort 2). Key inclusion criteria were age 25–65 years, clinical diagnosis of primary progressive multiple sclerosis, 1 year or more of disease progression, and two of the following criteria: positive brain MRI; positive spinal cord MRI; or positive cerebrospinal fluid. Additional eligibility criteria included disease duration of 2–10 years and objective evidence of disability progression in the previous 2 years. Patients and study investigators were masked to group assignment. We used a novel primary composite endpoint based on change from baseline in Expanded Disability Status Scale (EDSS), 25' Timed-Walk Test, or Nine-Hole Peg Test to assess time to 3-month confirmed disability progression in study participants treated for at least 3 years. All randomised patients took at least one dose of study drug. The primary efficacy analysis included all patients in cohort 2 and those assigned to placebo in cohort 1. The safety analysis included all patients in cohorts 1 and 2. This study is registered with ClinicalTrials.gov, number NCT00731692. The study is now closed.

Findings

970 patients were randomly assigned between Sept 3, 2008, and Aug 30, 2011 (147 to fingolimod 1·25 mg and 133 to placebo in cohort 1; 336 to fingolimod 0·5 mg and 354 to placebo in cohort 2). The efficacy analysis set (n=823) consisted of 336 patients randomly allocated to fingolimod 0·5 mg and 487 to placebo. Baseline characteristics were similar across groups and representative of a primary progressive multiple sclerosis population (48% women, mean age 48·5 years [SD 8·4], mean EDSS 4·67 [SD 1·03], 87% free of

gadolinium-enhancing lesions). By end of study, 3-month confirmed disability progression had occurred in 232 and 338 patients in the fingolimod and placebo groups, respectively, resulting in Kaplan-Meier estimates of 77·2% (95% CI 71·87–82·51) of patients in the fingolimod group versus 80·3% (73·31–87·25) of patients in the placebo group (risk reduction 5·05%; hazard ratio 0·95, 95% CI 0·80–1·12; p=0·544). Safety results were generally consistent with those of studies of fingolimod in patients with relapse-onset multiple sclerosis. Lymphopenia occurred in 19 (6%) patients in the fingolimod group versus none in the placebo group, bradycardia in five (1%) versus one (<1%), and first-degree atrioventricular block in three (1%) versus six (1%). Serious adverse events occurred in 84 (25%) patients in the fingolimod group and 117 (24%) in the placebo group, including macular oedema in six (2%) versus six (1%), and basal-cell carcinoma in 14 (4%) versus nine (2%).

Interpretation

The anti-inflammatory effects of fingolimod did not slow disease progression in primary progressive multiple sclerosis. Therapeutic strategies for primary progressive multiple sclerosis might need different approaches to those used for relapse-onset multiple sclerosis.