Long-term effect of fingolimod on disability: a categorical trend analysis over 8 years

Shannon Ritter1, Anthony T Reder2, Daniela Piani Meier3, Davorka Tomic4, Bruce A.C. Cree5
1Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States; 2Department of Neurology, University of Chicago, Chicago, IL, United States; 3Novartis Pharma AG, Basel, Switzerland; 4University of California San Francisco, San Francisco, CA, United States

CONCLUSIONS
• Over 2 years, disability changed minimally or fluctuated in most patients with RMSs enrolled in the FREEDOMS trials
• Hence, longer follow-up periods are required to detect meaningful changes in disability evolution
• After 8 years, disability was stable or had improved in the majority of patients who received fingolimod continuously

BACKGROUND
• Disability progression is a major clinical outcome in patients with multiple sclerosis (MS), and even moderate levels of disability can be highly disruptive to normal living. It is important to identify disease-modifying therapies that can slow or halt accrual of disability in the long term
• Disability progression is most commonly measured in clinical trials by analyzing changes in the Expanded Disability Status Scale (EDSS) score, confirmed after 3 or 6 months, typically over periods of 2-3 years
• In the 2-year, phase 3 FREEDOMS trials, fingolimod reduced confirmed disability progression compared with placebo in patients with relapsing-remitting MS (RRMS)
• However, MS is a Hitting disease, so evaluating disability evolution over longer periods is important to determine the real impact of treatment and to minimize bias from short-term fluctuations in EDSS score that are not sustained in the longer term
• Changes in disability that are sustained in the longer term are likely to be a more meaningful measure of outcome than those observed in the short term. Categorizing trends in EDSS score changes may be a good means of assessing long-term disability progression, as these may capture the true impact of treatment
• In this analysis of the pooled FREEDOMS RRMS population, we examined trends in changes in EDSS scores over a maximum of 8 years to investigate the impact of early continuous treatment with fingolimod on long-term disability progression

OBJECTIVES
• To investigate over 96 months how patterns of disability evolved and the impact of fingolimod treatment on long-term disability, in the pooled FREEDOMS RRMS population, based on categorical analysis of change in EDSS score

METHODS
Analysis population
• Post hoc analyses were conducted using data collected for up to 96 months from baseline patients randomized to fingolimod 0.5 mg (n=783) or to placebo (n=773) in the two 2-year FREEDOMS trials, those who continued or switched to fingolimod 0.5 mg in the trial extensions, and those who continued to receive fingolimod 0.5 mg in the observational LONGTERMs trial
• Analyses were conducted in the full analysis set (FAS; individuals with values at baseline and at month 24, 48 or 96) in the complete subgroup ICS; individuals with complete values at baseline and at months 24, 48 and 96

Analyses
• Building on previously published work, trends in disability progression observed at intervals up to 96 months were categorized as:
  - minimal (an increase or decrease of 0.5 points from baseline EDSS score if the baseline score was ≤3.5, or no change if score if the baseline score was ≥3.5)
  - improving (a decrease of ≥1.0 point from baseline EDSS score, either confirmed at 6 months only or confirmed at 6 months and sustained until months 24, 48 or 96)
  - worsening (an increase of ≥1.0 point from baseline EDSS score, either confirmed at 6 months only or confirmed at 6 months and sustained until months 24, 48 or 96)

RESULTS
Evolution of disability patterns over 8 years
• Categorical trend analysis of disability at 24 months and at 96 months supported the notion that meaningful changes are more likely to be observed over longer periods
• In both the FAS (Figure 1) and CS (Figure 2), disability had fluctuated or changed minimally in most patients at 24 months (categories combined, 64.7-79.1%), but the proportions of patients in these categories had decreased by almost half at 96 months (categories combined, 34.5-43.3%)
• Among patients in the CS whose disability had fluctuated or changed minimally at 24 months:
  - in the continuous fingolimod group (n=106), 22.6% were improving, 22.6% were worsening and 54.7% had changed minimally or were still fluctuating at 96 months
  - in the placebo group (n=77), 20.0% were improving, 28.4% were worsening and 54.7% had changed minimally or were still fluctuating at 96 months
• Overall, the proportions of patients in either the improving or worsening categories were greater at 96 months (26.1-34.5%) than at 24 months (6.7-18.5%)

Impact of delaying fingolimod treatment on long-term disability
• Between-group trends in the proportions of patients with worsening disability over 96 months supported the benefit of early fingolimod treatment
(Figures 1 and 2)
  - Proportionally fewer patients had worsening disability in the continuous fingolimod group than in the switch group at 24 months (FAS, 13.3% vs 18.5%, p=0.01; CS, 6.7% vs 17.2%, p=0.01)
  - At 96 months, there were still proportionally fewer patients with worsening disability in the continuous fingolimod group than in the switch group, although differences were not significant (FAS, 26.7% vs 34.5%, p=0.18; CS, 26.1% vs 34.5%, p=0.15)

Disclosure
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References