Disease activity in the first year predicts longer-term clinical outcomes in the pooled population of the phase 3 FREEDOMS and FREEDOMS II studies

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BACKGROUND

- Relapsing multiple sclerosis (RMS) is an inflammatory and neurodegenerative demyelinating disease of the central nervous system with both focal and diffuse pathology that can be measured by magnetic resonance imaging (MRI) techniques.
- The ability of focal MRI activity to do its own versus focal MRI activity in combination with different clinical parameters to predict future clinical events and disability has been debated.
- Early identification of patients at risk of suboptimal response to treatment is key for (re)considering therapeutic options in order to optimize long-term outcome.
- No evidence of disease activity (NEDA) is an aggregate measure of MRI and clinical parameters that is often used to determine overall benefit in MS.

OBJECTIVES

- To assess whether focal MRI activity and/or relapses during the first 12 months of treatment with fingolimod predicts subsequent disease activity over the following 36 months (M12-M24 and M12-M48) in the pooled extension populations of FREEDOMS and FREEDOMS II.
- To compare the strength of these predictors with that of baseline demographics/disease characteristics and other on-treatment disease activity measures.

METHODS

- This pooled analysis included patients who had initiated treatment with fingolimod in the 24-month FREEDOMS and FREEDOMS II studies and who entered the respective extension studies. All patients with at least one EDSS measurement following entry to the extension studies were included in the analysis.
- The definition of focal MRI activity used in this analysis was as proposed by Probst et al., i.e., Gd-enhancing or ≥2 new or newly enlarged T2 lesions on T2-weighted images.
- Unadjusted logistic regression was used to assess whether focal MRI activity and/or ≥1 confirmed relapses during M0-M12 of treatment, could predict the likelihood of the following clinical events during M12-M24 and M12-M48:
  - Confirmed relapses in ≥1 region-defined disability progression (6M-CDP), defined as a 1.5 point increase from baseline EDSS score ≥5.5 from M12–M24 and M12–M48
  - Number of confirmed relapses between baseline and months 12–24
  - EDSS score change from baseline to months 12–24
  - Number of relapses in 2 years prior to baseline of core study
  - Number of Gd-lesions at baseline of core study
- For continuous variables the odds ratio corresponds to a unit increase in the explanatory variable, for categorical variables, the last-mentioned category is used as a reference category. An odds ratio >1 implies a higher risk of relapses or 6M-CDP.

RESULTS

- In total, data for 1699 patients entering the extensions of FREEDOMS and FREEDOMS II studies were available for the M12-M24 period, while data for 1162 patients were available for the M12-M48 period.
- As shown in Figure 1, the analysis of potential baseline predictors yielded similar results for relapses or 6M-CDP and NEDA. Sex was not predictive of achievement for any of the outcomes.
- For disease activity during the first year, either focal MRI activity or ≥1 relapse were strongly and significantly predictive of relapses or 6M-CDP, while the combination of these disease activity measures was associated with the highest odds of relapses or 6M-CDP (Figure 3).
- All measures of disease activity during the first year, except for change in EDSS, were significantly predictive of not achieving NEDA (Figure 3).
- MRA activity was the strongest predictor, reducing the odds of achieving NEDA by 85% at M12-M24 and 82% at M12-M48.
- Combining focal MRI activity and relapses did not improve predictive ability above that of focal MRI activity alone.

CONCLUSIONS

- During the first year of fingolimod treatment, focal MRI activity (defined as ≥1 Gd+ lesion or ≥2 new or newly enlarged T2 lesions) or relapses, and their combination, were strongly predictive of subsequent relapses or 6-month confirmed disability progression.
- The strongest predictor for failure to achieve NEDA (absence of clinical relapses, disability progression and focal MRI activity) was focal MRI activity.

REFERENCES

6. Novartis Pharmaceuticals Corporation. The final responsibility for the content lies with the authors.

Disclosures

Aaron Boster has served on scientific advisory boards for Biogen Idec, Medtronic, Novartis Pharmaceuticals, Questcor and Teva Pharmaceuticals; has served as a consultant for Genzyme, Medtronic, Novartis Pharmaceuticals and Questcor; and has received research support from Actelion Therapeutics, Actelion Pharmaceuticals, Biogen Idec, CNS Therapeutics, Jazz Pharmaceuticals, Novartis Pharmaceuticals, Roche, Sanoften and Teva Pharmaceuticals. Kathleen Hawker, Shannon Ritter and Davorka Tomić are employees and stock holders of Novartis Pharmaceuticals. Till Springer has received research support for serving on scientific advisory boards or speaking for Actelion Pharmaceuticals, Allergan Pharma, Biogen, Genzyme, Janssen, Minopharma/Pharma Europe, Novartis Pharmaceuticals and Teva Pharmaceuticals.

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