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

Aaron Boster[1], Kathleen Hawker[2], Shannon Ritter[2], Davorka Tomic[3], Till Sprenger[4,5]

[1]Department of Neurology, The Ohio State University Wexner Medical Center, Columbus, OH, USA; [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA; [3]Novartis Pharma AG, Basel, Switzerland; [4]Medical Image Analysis Center and Department of Neurology, University Hospital Basel, Basel, Switzerland; [5]Departments of Medicine, Clinical Research, and Biomedical Engineering, University Hospital Basel, Basel, Switzerland

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**

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[1]
- The ability of focal MRI disease activity on its own versus focal MRI disease activity in combination with different clinical parameters to predict future clinical events and disability has been debated[2–5]
- 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 treatment benefit in MS
  - For the purpose of this analysis, NEDA was defined as no evidence of (1) clinical relapses, (2) disability progression and (3) MRI lesion activity
- Here we investigate if focal MRI activity by itself in the first year, or in combination with clinical parameters, could predict clinical event rate or achievement of NEDA in the pooled extension populations of the FREEDOMS and FREEDOMS II clinical trials

OBJECTIVES

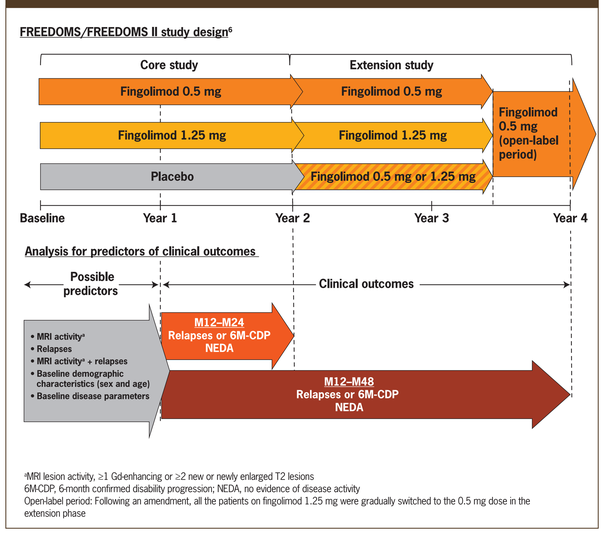
- To assess whether focal MRI activity and/or relapses during the first 12 months of treatment (M0–M12) predicts subsequent disease activity over the following 36 months (M12–M24 and M12–M48) in the pooled extension populations of FREEDOMS and FREEDOMS II
- To compare the strength of these predictors 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[6] and FREEDOMS II[7] 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 Prosperini et al. (≥1 Gd-enhancing or ≥2 new or newly enlarged T2 lesions)[5]
- Unadjusted logistic regression was used to assess whether focal MRI activity and/or ≥1 confirmed relapses[a] during M0–M12 of treatment, could predict the likelihood of the following clinical events during M12–M24 and M12–M48
  - Confirmed relapses[a] or 6-month confirmed disability progression (6M-CDP, defined as a 1.5 point increase from baseline EDSS score 0; 1.0 point increase from baseline EDSS scores between 1.0 and 5.0; or 0.5 point increase from baseline EDSS score ≥5.5) from M12–M24 and M12–M48
  - NEDA, defined as no relapses, no 6M-CDP, and no new and/or newly enlarged T2 lesion activity

[a]A relapse was confirmed when it was accompanied by an increase of at least half a point (0.5) on the EDSS, or an increase of 1 point on two different Functional Systems (FS) of the EDSS, or 2 points on one of the FS (excluding bowel/bladder or cerebral FS)

Figure 1. Study and analysis overview



[a]MRI lesion activity, ≥1 Gd-enhancing or ≥2 new or newly enlarged T2 lesions
6M-CDP, 6-month confirmed disability progression; NEDA, no evidence of disease activity
Open-label period: Following an amendment, all the patients on fingolimod 1.25 mg were gradually switched to the 0.5 mg dose in the extension phase

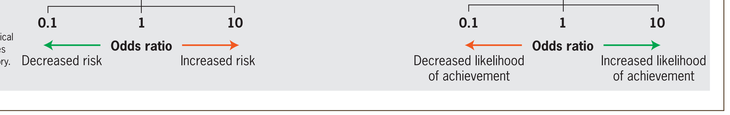
- Similarly, the predictive value of EDSS score change from baseline to M12 and number of active (new/enlarged) T2 lesions at M12 was determined
- The same procedure was used to assess the predictive ability of various baseline characteristics
  - Demographic characteristics (sex and age)
  - Baseline disease parameters (duration of relapsing–remitting multiple sclerosis [RRMS] since diagnosis; previous treatment for RRMS [yes/no]; number of relapses in the previous 2 years; EDSS score at baseline of core study; and number of Gd-enhancing lesions at baseline of core study)

RESULTS

- In total, data for 1969 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 2**, the analysis of potential baseline predictors yielded similar results for relapses or 6M-CDP and NEDA. Sex was not predictive for future clinical events (data not shown)
- 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 score from baseline, were significantly predictive of not achieving NEDA (**Figure 3**)
  - MRI 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

Figure 2. Baseline predictors of clinical event rate (relapses or 6M-CDP) or achievement of NEDA between M12 and M24, and M12 and M48

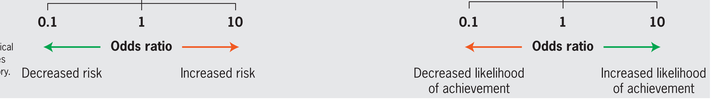
Variable		Relapses or 6M-CDP: Odds ratio (95% CI)	Relapses or 6M-CDP: p-value	NEDA: Odds ratio (95% CI)	NEDA: p-value
Age at baseline of core study (years)	M12–24	**0.985 (0.972; 0.998)**	**0.021**	**1.042 (1.031; 1.053)**	**<0.0001**
	M12–48	1.011 (0.996; 1.025)	0.142	**1.035 (1.020; 1.051)**	**<0.0001**
Duration of MS since diagnosis (years)	M12–24	**1.024 (1.005; 1.044)**	**<0.0001**	1.009 (0.992; 1.025)	0.299
	M12–48	**1.052 (1.030; 1.076)**	**0.014**	0.992 (0.970; 1.014)	0.476
Previous treatment for MS (yes/no)	M12–24	**1.523 (1.191; 1.946)**	**0.0008**	**0.791 (0.652; 0.959)**	**0.017**
	M12–48	**1.586 (1.230; 2.045)**	**0.0004**	**0.762 (0.590; 0.983)**	**0.037**
No. of relapses in 2 years prior to baseline of core study	M12–24	**1.135 (1.049; 1.228)**	**0.002**	**0.903 (0.842; 0.968)**	**0.004**
	M12–48	**1.154 (1.054; 1.263)**	**0.002**	0.911 (0.827; 1.004)	0.06
EDSS score at baseline of core study	M12–24	**1.209 (1.108; 1.319)**	**<0.0001**	**0.927 (0.864; 0.995)**	**0.035**
	M12–48	**1.366 (1.239; 1.505)**	**<0.0001**	**0.898 (0.816; 0.989)**	**0.029**
No. of Gd+ lesions at baseline of core study	M12–24	**1.209 (1.108; 1.319)**	**0.023**	**0.909 (0.877; 0.942)**	**<0.0001**
	M12–48	1.008 (0.972; 1.045)	0.68	**0.923 (0.878; 0.971)**	**0.002**
Volume of T1 hypointense lesions at baseline of core study	M12–24	**1.039 (1.003; 1.076)**	**0.035**	0.970 (0.940; 1.000)	0.0527
	M12–48	**1.092 (1.049; 1.137)**	**<0.0001**	**0.947 (0.904; 0.992)**	**0.023**



Odds ratios are derived from individual regression models with the respective variable as the only predictor. 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, or an increased likelihood of achieving NEDA, for the respective category compared to the reference category. For continuous variables the odds ratio corresponds to a unit increase in the explanatory variable

Figure 3. Disease activity during the first year as predictors of clinical event rate (relapses or 6M-CDP) or achievement of NEDA between M12 and M24, and M12 and M48

Variable		Relapses or 6M-CDP: Odds ratio (95% CI)	Relapses or 6M-CDP: p-value	NEDA: Odds ratio (95% CI)	NEDA: p-value
No. of confirmed relapses between baseline of core study and month 12	M12–24	**2.367 (1.990; 2.815)**	**<0.0001**	**0.501 (0.419; 0.598)**	**<0.0001**
	M12–48	**2.812 (2.182; 3.623)**	**<0.0001**	**0.525 (0.394; 0.700)**	**<0.0001**
EDSS score change from baseline of core study to month 12	M12–24	1.077 (0.958; 1.211)	0.215	0.922 (0.839; 1.013)	0.0921
	M12–48	1.014 (0.887; 1.158)	0.842	0.967 (0.847; 1.105)	0.623
No. of active T2 lesions at month 12 compared to baseline of core study	M12–24	**1.045 (1.027; 1.064)**	**<0.0001**	**0.672 (0.636; 0.711)**	**<0.0001**
	M12–48	**1.036 (1.011; 1.061)**	**0.004**	**0.696 (0.641; 0.756)**	**<0.0001**
MRI activity[a] from baseline of core study to month 12 (yes/no)	M12–24	**1.787 (1.420; 2.248)**	**<0.0001**	**0.152 (0.123; 0.186)**	**<0.0001**
	M12–48	**1.505 (1.179; 1.922)**	**0.001**	**0.182 (0.135; 0.244)**	**<0.0001**
MRI activity[a] and ≥1 relapse for baseline of core study to month 12 (yes/no)	M12–24	**3.285 (2.454; 4.397)**	**<0.0001**	**0.176 (0.125; 0.249)**	**<0.0001**
	M12–48	**2.953 (2.022, 4.312)**	**<0.0001**	**0.288 (0.173; 0.479)**	**<0.0001**



[a]MRI activity: ≥1 T1 Gd-enhancing lesion or ≥2 new or enlarged T2 lesions

Odds ratios are derived from individual regression models with the respective variable as the only predictor. 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, or an increased likelihood of achieving NEDA, for the respective category compared to the reference category. For continuous variables the odds ratio corresponds to a unit increase in the explanatory variable

References

1. Filippi M et al. Lancet Neurol. 2012;11:349–360.
2. Prosperini L et al. Eur J Neurol. 2009;16:1202–1209.
3. Rio J et al. Mult Scler. 2009;15:848–853.
4. Dobson R et al. Neurology 2014;82:248–254.
5. Prosperini L et al. Mult Scler. 2014;20:566–576.
6. Kappos L et al. N Engl J Med. 2010;362:387–401.
7. Calabresi PA et al. Lancet Neurol. 2014;13:545–556.

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 Acorda Therapeutics, Actelion Pharmaceuticals, Biogen Idec, CNS Therapeutics, Jazz Pharmaceuticals, Novartis Pharmaceuticals, Roche, Serono and Teva Pharmaceuticals. **Kathleen Hawker**, **Shannon Ritter** and **Davorka Tomic** are employees and stock holders of Novartis Pharmaceuticals. **Till Sprenger** has received research support for serving on scientific advisory boards or speaking for Actelion Pharmaceuticals, ATI Pharma, Biogen Idec, Genzyme, Janssen, Mitsubishi Pharma Europe, Novartis Pharmaceuticals and Teva Pharmaceuticals.

Acknowledgments

The authors acknowledge Oxford PharmaGenesis, Oxford, UK, for editorial support, which was funded by Novartis Pharmaceuticals Corporation. The final responsibility for the content lies with the authors.

Scan to download a reprint of this poster

This study was funded by Novartis Pharmaceuticals Corporation | Poster presented at the 2015 Annual Meeting of the Consortium of Multiple Sclerosis Centers (CMSC) | May 27–30, 2015 | Indianapolis, Indiana, USA