Long-term Predictors of Clinical Outcomes in Patients With Multiple Sclerosis Randomized to Fingolimod 0.5 mg in the Phase 3 FREEDOMS, FREEDOMS II and TRANSFORMS Studies

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Introduction

- The utility of patient and disease parameters measured in early multiple sclerosis (MS) (eg disease duration and number of relapses) to predict disability progression has been investigated previously, mainly in patients treated with interferons[1-3]
- Patients at risk of suboptimal response to first-line therapy may need treatment modification to slow accumulation of inflammation and neurodegeneration, and maximize long-term benefits[3]
- Fingolimod 0.5 mg is a once-daily oral therapy for the treatment of relapsing forms of MS[4]
- Since MS disease predictors in patients treated with fingolimod are not well characterized, we investigated which patient or disease parameters at baseline and during first year of treatment with fingolimod 0.5 mg could predict clinical outcomes in patients with MS in the short and long term

Objective

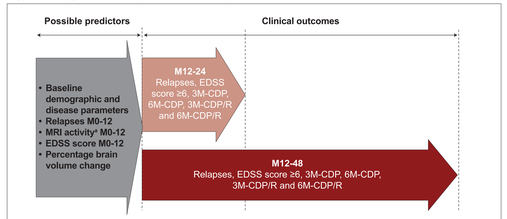
- Assess utility of patient and disease parameters (eg Expanded Disability Status Scale [EDSS] score and number of confirmed relapses) at baseline and during the first year of FREEDOMS/FREEDOMS II[5,6] and TRANSFORMS[7] and extensions,[8-14] to predict outcomes for patients randomized to fingolimod 0.5 mg:
  - Confirmed relapses, EDSS score ≥6 points, 3 month (M)-confirmed disability progression (3M-CDP), 6M-CDP, 3M-CDP or confirmed relapses (3M-CDP/R), and 6M-CDP or confirmed relapses (6M-CDP/R)

Methods

Analyses

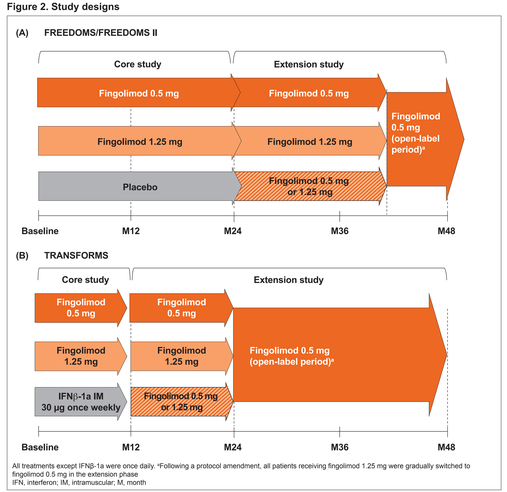
- Post hoc analyses of data from patients randomized to fingolimod 0.5 mg in FREEDOMS/FREEDOMS II (n=649) and TRANSFORMS (n=342) and extensions (**Figure 1**)
  - Data from FREEDOMS and FREEDOMS II were pooled; data from TRANSFORMS were analyzed separately
- Multiple logistic regression analyses assessed which parameters at baseline (M0), or during M0-12, predicted six clinical outcomes during M12-24 (short term) and M12-48 (long term)
- Patient and disease parameters used to predict clinical outcomes were:
  - M0: sex, age, duration of MS since diagnosis, previous treatment for MS (yes/no), number of relapses in the previous 2 years, EDSS score, number of gadolinium-enhancing (Gd+) lesions, T1 hypointense lesion volume, volume of T2 lesions and normalized brain volume
  - M0-12: confirmed relapses, change in EDSS score, number of new T2 lesions, magnetic resonance imaging (MRI) lesion activity (≥1 Gd+ lesions or ≥2 new T2 lesions),[15] MRI lesion activity and at least one confirmed relapse, and percentage brain volume change
- Clinical outcomes (**Figure 1**) were: confirmed relapses, EDSS score ≥6 points, 3M-CDP, 6M-CDP, 3M-CDP/R and 6M-CDP/R
  - Confirmed relapses: those accompanied by an increase in EDSS score of ≥0.5 points, or an increase of 1 point in two different functional systems (FS), or of 2 points in one FS (excluding bowel/bladder or cerebral FS)
  - CDP: increase from baseline EDSS score of 1.5 points for patients with a baseline score of 0, 1.0 point if baseline score was 1.0-5.0, or 0.5 points if baseline score was ≥5.5, confirmed 3 months later or 6 months later
- Odds ratios were derived from a multivariate regression model built from predictors significant in univariate regression models
- Only significant predictors (p<0.05) from the multivariate model are reported. All analyses were adjusted for study

Figure 1. Analysis for predictors of clinical outcomes



[a]MRI lesion activity defined as: ≥1 Gd+ or ≥2 new or newly enlarged T2 lesions
CDP, confirmed disability progression; CDP/R, confirmed disability progression or confirmed relapses; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; M, month; MRI, magnetic resonance imaging

Figure 2. Study designs

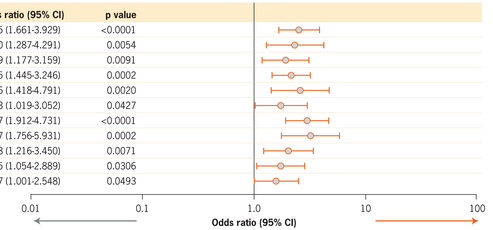


All treatments except IFNß-1a were once daily. [a]Following a protocol amendment, all patients receiving fingolimod 1.25 mg were gradually switched to fingolimod 0.5 mg in the extension phase
IFN, interferon; IM, intramuscular; M, month

Figure 3. Odds ratios for patient and disease parameters in predicting worsening clinical outcomes during M12-24 (short term) and M12-48 (long term) in FREEDOMS/FREEDOMS II and TRANSFORMS data sets. Non-significant predictors not shown

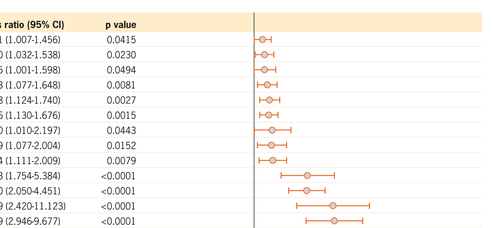
(A) Relapse parameters

Predictive parameter	Clinical outcome	Data set	Phase	Odds ratio (95% CI)	p value
Confirmed relapses (M0-12)	6M-CDP/R	FREEDOMS/FREEDOMS II	Short term	2.555 (1.661-3.929)	<0.0001
Confirmed relapses (M0-12)	6M-CDP/R	FREEDOMS/FREEDOMS II	Long term	2.350 (1.287-4.291)	0.0054
Confirmed relapses (M0-12)	6M-CDP/R	TRANSFORMS	Short term	1.929 (1.177-3.159)	0.0091
Confirmed relapses (M0-12)	3M-CDP/R	FREEDOMS/FREEDOMS II	Short term	2.165 (1.445-3.246)	0.0002
Confirmed relapses (M0-12)	3M-CDP/R	FREEDOMS/FREEDOMS II	Long term	2.606 (1.418-4.791)	0.0020
Confirmed relapses (M0-12)	3M-CDP/R	TRANSFORMS	Short term	1.763 (1.019-3.052)	0.0427
Confirmed relapses (M0-12)	Confirmed relapses	FREEDOMS/FREEDOMS II	Short term	3.007 (1.912-4.731)	<0.0001
Confirmed relapses (M0-12)	Confirmed relapses	FREEDOMS/FREEDOMS II	Long term	3.227 (1.756-5.931)	0.0002
Confirmed relapses (M0-12)	Confirmed relapses	TRANSFORMS	Short term	2.048 (1.216-3.450)	0.0071
Confirmed relapses (M0-12)	Confirmed relapses	TRANSFORMS	Long term	1.745 (1.054-2.889)	0.0306
Relapses in 2 years before study	Confirmed relapses	TRANSFORMS	Short term	1.597 (1.001-2.548)	0.0493



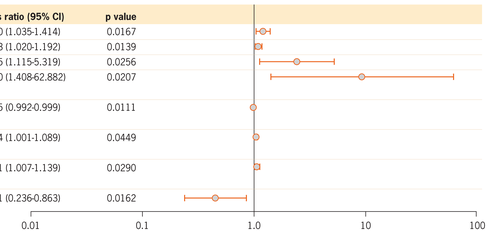
(B) EDSS parameters

Predictive parameter	Clinical outcome	Data set	Phase	Odds ratio (95% CI)	p value
EDSS at baseline	6M-CDP/R	FREEDOMS/FREEDOMS II	Short term	1.211 (1.007-1.456)	0.0415
EDSS at baseline	6M-CDP/R	FREEDOMS/FREEDOMS II	Long term	1.260 (1.032-1.538)	0.0230
EDSS at baseline	6M-CDP/R	TRANSFORMS	Short term	1.265 (1.001-1.598)	0.0494
EDSS at baseline	6M-CDP/R	TRANSFORMS	Long term	1.333 (1.077-1.648)	0.0081
EDSS at baseline	3M-CDP/R	TRANSFORMS	Short term	1.398 (1.124-1.740)	0.0027
EDSS at baseline	3M-CDP/R	TRANSFORMS	Long term	1.376 (1.130-1.676)	0.0015
EDSS at baseline	6M-CDP	TRANSFORMS	Short term	1.490 (1.010-2.197)	0.0443
EDSS at baseline	6M-CDP	TRANSFORMS	Long term	1.469 (1.077-2.004)	0.0152
EDSS at baseline	3M-CDP	TRANSFORMS	Short term	1.494 (1.111-2.009)	0.0079
EDSS at baseline	EDSS ≥6	FREEDOMS/FREEDOMS II	Short term	3.073 (1.754-5.384)	<0.0001
EDSS at baseline	EDSS ≥6	FREEDOMS/FREEDOMS II	Long term	3.020 (2.050-4.451)	<0.0001
EDSS at baseline	EDSS ≥6	TRANSFORMS	Short term	5.189 (2.420-11.123)	<0.0001
EDSS at baseline	EDSS ≥6	TRANSFORMS	Long term	5.339 (2.946-9.677)	<0.0001
EDSS at baseline	Confirmed relapses	FREEDOMS/FREEDOMS II	Long term	1.309 (1.058-1.619)	0.0131
EDSS change (M0-12)	6M-CDP	FREEDOMS/FREEDOMS II	Short term	0.555 (0.350-0.881)	0.0124
EDSS change (M0-12)	6M-CDP	FREEDOMS/FREEDOMS II	Long term	0.687 (0.492-0.962)	0.0286
EDSS change (M0-12)	3M-CDP	FREEDOMS/FREEDOMS II	Short term	0.649 (0.471-0.895)	0.0084
EDSS change (M0-12)	3M-CDP	FREEDOMS/FREEDOMS II	Long term	0.658 (0.496-0.874)	0.0038
EDSS change (M0-12)	3M-CDP	TRANSFORMS	Long term	0.595 (0.397-0.890)	0.0115
EDSS change (M0-12)	EDSS ≥6	FREEDOMS	Short term	4.094 (1.954-8.578)	0.0002
EDSS change (M0-12)	EDSS ≥6	TRANSFORMS	Short term	3.356 (1.567-7.185)	0.0018
EDSS change (M0-12)	EDSS ≥6	TRANSFORMS	Long term	3.217 (1.773-5.837)	0.0001



(C) MRI and disease parameters

Predictive parameter	Clinical outcome	Data set	Phase	Odds ratio (95% CI)	p value
T1 hypointense volume (cm³)[a]	6M-CDP	FREEDOMS/FREEDOMS II	Long term	1.210 (1.035-1.414)	0.0167
T1 hypointense volume (cm³)[a]	3M-CDP	FREEDOMS/FREEDOMS II	Long term	1.103 (1.020-1.192)	0.0139
MRI lesion activity (M0-12)	3M-CDP/R	FREEDOMS/FREEDOMS II	Long term	2.435 (1.115-5.319)	0.0256
MRI lesion activity and ≥1 relapse (M0-12)	EDSS ≥6	TRANSFORMS	Short term	9.410 (1.408-62.882)	0.0207
Normalized brain volume at baseline (cm³)[a,b]	3M-CDP	FREEDOMS/FREEDOMS II	Short term	0.995 (0.992-0.999)	0.0111
Duration of MS since diagnosis (years)[a]	6M-CDP/R	FREEDOMS/FREEDOMS II	Short term	1.044 (1.001-1.089)	0.0449
Duration of MS since diagnosis (years)[a]	Confirmed relapses	TRANSFORMS	Short term	1.071 (1.007-1.139)	0.0290
Sex (male)[c]	Confirmed relapses	FREEDOMS/FREEDOMS II	Short term	0.451 (0.236-0.863)	0.0162



[a]For continuous variables (T1 hypointense volume, normalized brain volume at baseline and duration of MS since diagnosis), odds ratios correspond to a unit increase in explanatory variable. Previous treatment (yes/no) refers to whether patients had received treatment before study initiation. [b]Less brain volume loss was associated with decreased risk of relapse or disability progression. [c]Male sex was associated with decreased risk of developing further confirmed relapses
MRI lesion activity defined as: ≥1 T1 Gd+ lesion or ≥2 new or newly enlarged T2 lesions at any post-baseline assessment up to M12. Odds ratios are derived from one multivariate regression model built from predictors that were significant in univariate regression models. All analyses are adjusted for study
CDP, confirmed disability progression; CDP/R, confirmed disability progression or confirmed relapses; CI, confidence interval; EDSS, Expanded Disability Status Scale; Gd+, gadolinium-enhancing; M, month; MRI, magnetic resonance imaging; MS, multiple sclerosis

Study design

FREEDOMS/FREEDOMS II

- 2-year, randomized, double-blind, Phase 3 FREEDOMS/FREEDOMS II compared fingolimod with placebo in patients with relapsing MS (**Figure 2A**)[5,6]
  - Patients were randomized 1:1:1 to oral fingolimod 0.5 mg or 1.25 mg, or placebo once daily
- All patients then received fingolimod 0.5 mg in an ongoing open-label extension[8,14]

TRANSFORMS

- 1-year, randomized, double-blind, Phase 3 TRANSFORMS compared fingolimod with intramuscular interferon (IFN) β-1a in patients with relapsing MS (**Figure 2B**)[7]
  - Patients were randomized 1:1:1 to fingolimod 0.5 mg or 1.25 mg once daily, or IFNβ-1a 30 µg once weekly
- Patients receiving IFNβ-1a who entered the 1-year extension were re-randomized to fingolimod 0.5 mg or 1.25 mg once daily[8,12]
  - All patients then received fingolimod 0.5 mg in an ongoing open-label extension[8,10]

Results

- Data were collected from 649 patients from FREEDOMS/FREEDOMS II and 342 from TRANSFORMS, who were randomized to fingolimod 0.5 mg and had not switched treatment

Predictors of clinical outcomes

- Confirmed relapses (M0-12; **Figure 3A**), baseline EDSS score, and change in EDSS score (M0-12; **Figure 3B**) in the short-term phase were consistent predictors of worsening clinical outcomes
- Change in EDSS score (M0-12) was predictive of decreased risk of 6M-CDP and 3M-CDP in the short and long term in FREEDOMS/FREEDOMS II, and of 3M-CDP in the long term in TRANSFORMS (**Figure 3B**)
  - Large changes in EDSS score might be indicative of recent relapses, which may be followed by a period of remission; this may warrant further investigation
- MRI lesion activity in the short-term phase (M0-12) was a predictor of long-term progression to 3M-CDP/R (FREEDOMS/FREEDOMS II), and MRI lesion activity plus ≥1 relapse was a predictor of short-term progression to EDSS ≥6 (TRANSFORMS (**Figure 3C**))
- Other baseline characteristics were predictive of certain clinical outcomes:
  - Relapses in 2 years before study was predictive of confirmed relapses in the short term in TRANSFORMS (**Figure 3A**)
  - T1 hypointense volume was predictive of both 3M- and 6M-CDP in the long term in FREEDOMS/FREEDOMS II (**Figure 3C**)
  - Normalized brain volume was predictive of 3M-CDP in the short term in FREEDOMS/FREEDOMS II (**Figure 3C**)
  - Duration of MS since diagnosis was predictive in the short term of 6M-CDP/R in FREEDOMS/FREEDOMS II and of confirmed relapses in TRANSFORMS (**Figure 3C**)
  - Being male was predictive of a decreased risk of confirmed relapses in the short term in FREEDOMS/FREEDOMS II (**Figure 3C**)
- The following patient and disease parameters were not predictive of any of the clinical outcomes assessed:
  - M0: age, previous treatment for MS, number of Gd+ lesions, volume of T2 lesions
  - M0-12: number of new T2 lesions and percentage brain volume change

Conclusions

- In FREEDOMS/FREEDOMS II and TRANSFORMS, confirmed relapses (M0-12), baseline EDSS score and short-term change in EDSS score (M0-12) were consistent predictors of worsening clinical outcomes for patients receiving fingolimod 0.5 mg for up to 4 years
  - Number of relapses occurring early on treatment can be used to predict long-term relapses
  - EDSS score at baseline and change in EDSS score within first year of treatment are predictive of long-term EDSS outcomes
- These findings support use of routine clinical parameters as tools to predict long-term outcomes in clinical practice

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