ORIGINAL ARTICLE

Fingolimod Therapy in Early Multiple Sclerosis: An Efficacy Analysis of the TRANSFORMS and FREEDOMS Studies by Time Since First Symptom

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Received 13 August 2013; revision 9 January 2014; accepted 12 January 2014

SUMMARY

Aims: The phase 3 TRANSFORMS and FREEDOMS studies established the efficacy of fingolimod in reducing multiple sclerosis (MS) relapses and magnetic resonance imaging lesions compared with intramuscular (IM) interferon (IFN) β -1a and placebo over 12 and 24 months, respectively. **Methods:** To investigate the efficacy of fingolimod at the approved 0.5 mg dose in patients early in the MS disease course, post hoc subgroup analyses of TRANSFORMS ($n = 272$) and FREEDOMS ($n = 217$) data were conducted in patients who experienced their first MS symptom <3 years before randomization. **Results:** Fingolimod 0.5 mg reduced annualized relapse rate by 73.4% ($P = 0.0002$) versus IFN β -1a IM and by 67.4% ($P < 0.0001$) versus placebo in patients with <3 years since first symptom; respective reductions were 45.4% and 51.4% in subgroups of patients with ≥ 3 years since first symptom. For patients with <3 years since their first symptom, significantly fewer new/newly enlarged T2 lesions were observed with fingolimod versus IFN β -1a IM (mean number, 1.94 vs. 2.95; $P = 0.036$) or placebo (4.1 vs. 10.7; $P < 0.001$); the mean number of gadolinium-enhancing T1 lesions was significantly reduced versus placebo (0.3 vs. 1.1; $P < 0.001$). **Conclusion:** Fingolimod 0.5 mg is highly effective in reducing relapses and MRI activity in patients early in the MS disease course.

doi: 10.1111/cns.12235

Introduction

Studies of the natural history of multiple sclerosis (MS) have demonstrated the predictive value of the number of early relapses with respect to longer-term outcomes. A greater number of relapses within the first few years of MS onset are associated with more rapid progression of disability and earlier onset of a secondary progressive disease course [1–4]. Moreover, residual disability may accumulate with each exacerbation [5]. Thus, reducing relapses early in the MS disease course may be important to slowing disease progression and reducing overall disease burden.

The burden of disease at treatment initiation may affect treatment efficacy. An independent, prospective, 24-month study of natalizumab found that complete disease remission was more likely in patients with ≤ 2 versus >2 relapses in the year before natalizumab initiation and in patients with a baseline Expanded Disability Status Scale (EDSS) score <3.0 versus ≥ 3.0 [6]. This provides a further rationale for early treatment initiation.

Several studies have shown that ongoing disease activity during treatment predicts worse disability outcomes. In a study of interferon (IFN) β treatment, the presence of >2 active magnetic

resonance imaging (MRI) lesions (gadolinium-enhancing T1 or new/newly enlarged T2 lesions) during the first 12 months of treatment significantly increased the risk of disability progression over the following 2 years [7]. Further, the presence of relapse and active lesions with or without progression in the first 12 months significantly increased the risk of later progression [8]. A retrospective analysis of a 2-year trial comparing IFN β -1a intramuscular (IM) with placebo indicated that EDSS worsening of ≥ 1 point from baseline was a strong predictor of reaching disability milestones at an 8-year follow-up [9]. This suggests that therapies highly effective in reducing clinical and/or MRI exacerbation can slow disease progression. Other studies suggest a high interrelationship between treatment effects on relapse rates, MRI lesions, and disability [10–12]. For example, an analysis of individual patient data from a large, placebo-controlled trial of IFN β -1a IM demonstrated that the combined treatment effect on active MRI lesions and relapses accounted for 100% of the treatment effect on disability [12]. These observations, together with the demonstrated role of early relapses in disability progression, suggest that reducing relapses and MRI lesions with disease-modifying treatment (DMT) early in the MS disease course may improve disability outcomes.

Studies comparing early versus delayed DMT have shown a benefit of early therapy initiation. A 7-year observational study (median follow-up 4.5 years) of 2570 patients with relapsing-remitting MS treated with IFN β showed that patients who began therapy within 1 year of disease onset had a significantly reduced risk of a 1-point increase in EDSS score and of progressing to an EDSS score of 4.0 during the study compared with patients who delayed treatment initiation [13]. Another study showed that in patients with a first neurological event suggestive of MS and at least two clinically silent T2 lesions, early initiation of IFN β -1b reduced the risk for EDSS progression after 3 years of follow-up by 40% compared with a 2-year delay in treatment [14]. Although the precise mechanisms underlying the benefits of early treatment are unknown, it is thought that it might help to preserve neuronal function by limiting inflammation [15]. The enhanced response to immune therapy in patients with early disease may reflect a smaller repertoire of activated autoreactive T cells [16,17], a lower disease burden [6], and younger age [18].

Fingolimod is a once-daily oral therapy approved for the treatment of patients with relapsing forms of MS. In the phase 3, randomized, double-blind, double-dummy Trial Assessing Injectable Interferon Versus Fingolimod Oral in Relapsing-Remitting Multiple Sclerosis (TRANSFORMS), treatment with fingolimod 0.5 mg significantly reduced the annualized relapse rate (ARR) by 52% compared with IFN β -1a IM over 12 months (0.16 vs. 0.33; $P < 0.001$) [19]. In the phase 3, randomized, double-blind

Fingolimod Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis (FREEDOMS), treatment with fingolimod 0.5 mg significantly reduced the ARR by 54% compared with placebo over 24 months (fingolimod, 0.18; placebo, 0.40; $P < 0.001$) [20].

The objective of this post hoc analysis of TRANSFORMS and FREEDOMS data was to test the hypothesis that fingolimod effectively lowers ARR compared with IFN β -1a IM or placebo in patients early in the disease course. We assessed fingolimod efficacy in subgroups of patients based on the time since their first MS symptom (SFS).

Patients and methods

Study Design and Patients

Study methods for FREEDOMS and TRANSFORMS were previously described in detail [19,20]. In the current analyses, the main analysis cohort comprised patients in the intent-to-treat population with <3 years SFS at the time of randomization, similar to a threshold used previously to define early disease [21]. The FREEDOMS and TRANSFORMS studies were conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki. The protocols were approved by each site's institutional review board, and patients gave written, informed consent before any study procedures were performed [19,20].

Table 1 Demographics and clinical characteristics in patients by time since first MS symptom (randomized populations)*

	Time SFS <3 years		Time SFS ≥ 3 years	
	Fingolimod 0.5 mg (n = 132)	IFN β -1a IM 30 μ g (n = 140)	Fingolimod 0.5 mg (n = 297)	IFN β -1a IM 30 μ g (n = 291)
TRANSFORMS				
Age, years	33.2 (9.6)	33.5 (8.2)	38.3 (8.0)	37.1 (8.1)
Women, n (%)	86 (65.2)	90 (64.3)	195 (65.7)	202 (69.4)
Duration of MS, [†] years	0.88 (0.72)	0.94 (0.73)	6.57 (4.95)	6.84 (5.68)
Relapses in previous 1 years, n	1.6 (0.8)	1.4 (0.8)	1.5 (1.3)	1.5 (0.8)
Relapses in previous 2 years, n	2.2 (1.1)	2.2 (1.1)	2.3 (2.5)	2.3 (1.3)
EDSS score	1.83 (1.12)	1.75 (1.07)	2.42 (1.37)	2.40 (1.29)
Gadolinium-enhancing lesions, n	1.02 (3.78)	1.36 (3.81)	0.96 (2.26)	0.92 (2.16)
T2 lesion volume, mm ³	3178 (4071)	3863 (4678)	6058 (7344)	5428 (6084)
FREEDOMS	Fingolimod 0.5 mg (n = 113)	Placebo (n = 104)	Fingolimod 0.5 mg (n = 312)	Placebo (n = 314)
Age, years	32.1 (9.0)	33.5 (8.8)	38.2 (8.1)	38.5 (8.2)
Women, n (%)	72 (63.7)	68 (65.4)	224 (71.8)	230 (73.2)
Duration of MS, [†] years	0.95 (0.74)	0.91 (0.71)	6.22 (5.32)	6.61 (5.23)
Relapses in previous 1 years, n	1.6 (0.8)	1.6 (0.8)	1.4 (0.8)	1.4 (0.7)
Relapses in previous 2 years, n	2.3 (0.9)	2.2 (0.9)	2.1 (1.2)	2.1 (1.3)
EDSS score	1.84 (1.18)	1.88 (1.06)	2.46 (1.28)	2.68 (1.30)
Gadolinium-enhancing lesions, n	2.63 (9.07)	1.37 (3.31)	1.29 (3.50)	1.22 (2.80)
T2 lesion volume, mm ³	4797 (7354)	4538 (5896)	6611 (7673)	6704 (7368)

EDSS, Expanded Disability Status Scale; FREEDOMS, Fingolimod Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis; IFN, interferon; IM, intramuscular; SFS, since first MS symptom; TRANSFORMS, Trial Assessing Injectable Interferon Versus Fingolimod Oral in Relapsing-Remitting Multiple Sclerosis. *All values are mean (SD) unless otherwise noted. [†]Since diagnosis.

Analysis

Annualized relapse rate was defined as the number of confirmed relapses per year. Criteria for a confirmed relapse were new or worsening neurological symptoms that occurred ≥ 30 days after the onset of a preceding relapse, that lasted ≥ 24 h without fever or infection, and that were accompanied by an increase of ≥ 0.5 point in the EDSS score or an increase of ≥ 1 point in two functional systems scores or of ≥ 2 points in one functional system score (excluding scores for the bowel/bladder and cognition functions). The number of relapses was analyzed using a negative binomial model adjusted for treatment, time SFS, and the treatment-by-time SFS interaction. Time to first confirmed relapse was estimated using the Kaplan–Meier method and a Cox proportional hazard model, with treatment, country, number of relapses in the previous 2 years, and baseline EDSS score as explanatory variables. The number of gadolinium-enhancing T1 lesions was analyzed using a ranked analysis of covariance model with treatment and country as factors and number of gadolinium-enhancing T1 lesions at baseline as a covariate; the number of new/newly enlarged T2 lesions was analyzed using a negative binomial model adjusted for treatment and country (FREEDOMS) or treatment, country, number of relapses in the previous 2 years, and baseline EDSS score (TRANSFORMS). All analyses were post hoc, and there were no adjustments for multiple comparisons.

Results

Demographics and Clinical Characteristics

A total of 272 patients in TRANSFORMS and 217 patients in FREEDOMS had a time SFS of <3 years. In both studies, mean age was lower for this subgroup compared with that of the ≥ 3 years SFS (approximately 33 vs. 38 years in both studies; all $P < 0.0001$; Table 1). In addition, in both studies the overall burden of disease was lower in the subgroup with time SFS <3 years compared with the subgroup with time SFS ≥ 3 years, as reflected in the baseline EDSS score and T2 lesion volume ($P < 0.0001$ for all comparisons). Other baseline demographics and clinical characteristics were generally well balanced across subgroups. In FREEDOMS, the only notable difference by treatment group was a higher number of gadolinium-enhancing T1 lesions with fingolimod 0.5 mg versus placebo in patients with <3 years SFS. In both studies, the number of relapses in the previous 1–2 years was similar in patients with ≥ 3 versus <3 years SFS.

Relapses

In TRANSFORMS, in patients with <3 years SFS, fingolimod 0.5 mg significantly reduced ARR over 12 months by 73.4% versus IFN β -1a IM (Table 2; Figure 1). In comparison, fingolimod reduced the ARR by 45.4% versus IFN β -1a IM in patients with ≥ 3 years SFS. In addition, in patients with <3 years SFS, the proportion who were relapse-free after 12 months of treatment was higher with fingolimod 0.5 mg than with IFN β -1a IM (Table 3). In FREEDOMS, fingolimod 0.5 mg significantly reduced the ARR over 24 months versus placebo by 67.4% ($P < 0.0001$) in patients with <3 years SFS and by 51.4% in patients with ≥ 3 years SFS

(Table 2; Figure 1). The proportion of patients who were relapse-free at study end was greater in the fingolimod 0.5 mg versus placebo group (Table 3).

MRI Endpoints

Over the 12-month TRANSFORMS study period, in patients with <3 years SFS, treatment with fingolimod 0.5 mg resulted in the development of fewer new/newly enlarged T2 lesions ($P = 0.036$) and numerically fewer gadolinium-enhancing T1 lesions ($P = 0.079$) compared with IFN β -1a IM treatment (Table 3). Over the 24-month FREEDOMS study period, the number of new/newly enlarged T2 lesions and gadolinium-enhancing T1 lesions was significantly lower in patients with <3 years SFS treated with fingolimod 0.5 mg compared with placebo (both $P < 0.001$; Table 3).

Discussion

These post hoc subgroup analyses of TRANSFORMS and FREEDOMS data demonstrate a high level of efficacy of fingolimod 0.5 mg starting at the early stages of MS. Fingolimod 0.5 mg significantly reduced the ARR compared with IFN β -1a IM (-73.4% ; $P = 0.0002$) and placebo (-67.4% ; $P < 0.0001$) in patients with <3 years SFS and significantly increased the proportion of patients who were relapse-free versus IFN β -1a IM (91.5% vs. 77.9% over 12 months) or placebo (73.5% vs. 40.8% over

Table 2 Annualized relapse rates in patients with <3 years or ≥ 3 years since first MS symptom (ITT populations)

	Time SFS <3 years		Time SFS ≥ 3 years	
	Fingolimod 0.5 mg (n = 132)	IFN β -1a IM 30 μ g (n = 140)	Fingolimod 0.5 mg (n = 297)	IFN β -1a IM 30 μ g (n = 291)
TRANSFORMS				
ARR [†]	0.084	0.317	0.266	0.487
Percentage reduction versus IFN β -1a IM	73.4		45.4	
P	0.0002		0.0002	
	Fingolimod 0.5 mg		Fingolimod 0.5 mg	
	(n = 113)	Placebo (n = 104)	(n = 312)	Placebo (n = 314)
FREEDOMS				
ARR [*]	0.163	0.499	0.232	0.478
Percentage reduction versus placebo	67.4		51.4	
P	<0.0001		<0.0001	

ARR, annualized relapse rate; FREEDOMS, Fingolimod Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis; IFN, interferon; IM, intramuscular; ITT, intent to treat; SFS, since first MS symptom; TRANSFORMS, Trial Assessing Injectable Interferon Versus Fingolimod Oral in Relapsing-Remitting Multiple Sclerosis. ^{*}Negative binomial model adjusted for treatment, time SFS, and treatment-by-time SFS interaction.

Figure 1 Annualized relapse rate in the (A) subgroups with <3 years since first MS symptom[†] and (B) overall study populations. [‡],[§]EDSS, Expanded Disability Status Scale; FREEDOMS, Fingolimod Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis; IFN, interferon; IM, intramuscular; SFS, since first MS symptom; TRANSFORMS, Trial Assessing Injectable Interferon Versus Fingolimod Oral in Relapsing-Remitting Multiple Sclerosis.

[†]Negative binomial model adjusted for treatment, time SFS, and treatment-by-time SFS interaction.
[‡]Negative binomial model adjusted for treatment, country, number of relapses within the previous 2 years, and baseline EDSS score.
[§]Overall study results were analyzed separately and previously published.^{19,20}

24 months). In addition, fingolimod 0.5 mg significantly reduced MRI activity in the early MS subgroup. New/newly enlarged T2 lesions and inflammatory gadolinium-enhancing T1 lesions were reduced by fingolimod 0.5 mg compared with placebo. New/newly enlarged T2 lesions were also reduced with fingolimod 0.5 mg compared with IFN β -1a IM. Fingolimod 0.5 mg was also effective in patients with ≥ 3 years SFS, significantly reducing the ARR compared with IFN β -1a IM (-45.4%; $P = 0.0002$) and placebo (-51.4%; $P < 0.0001$).

Because patients early in the disease course tend to have a lower disease burden, and lower disease burden at initiation is correlated with greater treatment efficacy [6], patients with early MS may reap more benefit from treatment compared with those with more advanced disease. The present results may support this hypothesis, given the numerically higher ARR reductions observed with fingolimod versus IFN β -1a IM or placebo in patients with <3 years SFS compared with ≥ 3 years SFS. Further supporting this idea, a 5-year follow-up of the phase 2 alemtuzumab trial suggested an association between reduced relapse frequency and lower risk for a sustained increase in EDSS score in treatment-naïve patients with highly active disease and <3 years SFS [21]. Although the current analysis did not assess EDSS score changes through extended follow-up, the marked reduction in relapses observed with fingolimod in patients with

<3 years SFS may lead to improved longer-term disability outcomes. More prospective studies are needed to further establish the long-term impact of effective immunomodulatory therapy at MS onset.

The mechanisms by which patients with early disease appear to be more responsive to treatment compared with those in later stages of MS are not understood. Possible contributing factors include patient age [18], burden of disease [6], and possibly qualitative and quantitative aspects of the activated immune system [16,17,22]. In the current study, the patient subgroup with <3-years SFS was younger and had a lower disease burden than the subgroup with ≥ 3 years SFS. Furthermore, as disease duration becomes more prolonged, there is generally more extensive target tissue damage. Experimental models of MS have implicated such damage in furthering the autoimmune response, with the observation that as disease progresses, the repertoire of antigen-specific activated T cells expands [23]. Tissue damage exposes previously cryptic antigenic epitopes, which may then activate new lymphocyte specificities [23]. Evidence for epitope spreading has also been reported in patients with MS [16,17,22]. Reducing tissue damage early in the disease process may limit the recruitment of new T cell clones into the autoimmune response and thereby the escalation of inflammation. The data presented in this analysis—showing that gadolinium-enhancing T1 lesions and T2

Table 3 Relapse-free patients and focal MRI activity in patients with <3 years since first MS symptom (randomized populations)

	Fingolimod 0.5 mg (n = 132)	IFN- β -1a IM 30 μ g (n = 140)
TRANSFORMS		
Relapse-free patients at month 12, %	91.5	77.9
Hazard ratio (95% CI) [†]	0.37 (0.18–0.76)	
New/newly enlarged T2 lesions, ^{‡,§} mean (SD)	1.94 (3.68)	2.95 (7.04)
P value [¶]	0.036	
Gadolinium-enhancing T1 lesions, ^{‡,***} mean (SD)	0.18 (0.622)	0.31 (0.843)
P value [§]	0.079	
FREEDOMS	Fingolimod 0.5 mg (n = 113)	Placebo (n = 104)
Relapse-free patients at month 24, %	73.5	40.8
Hazard ratio (95% CI) [†]	0.31 (0.19–0.50)	
New/newly enlarged T2 lesions, ^{††,‡‡} mean (SD)	4.1 (12.14)	10.7 (12.78)
P value [¶]	<0.001	
Gadolinium-enhancing T1 lesions, ^{††,***} mean (SD)	0.3 (0.93)	1.1 (2.27)
P value [¶]	<0.001	

FREEDOMS, Fingolimod Research Evaluating Effects of Daily Oral Therapy in Multiple Sclerosis; IFN, interferon; IM, intramuscular; TRANSFORMS, Trial Assessing Injectable Interferon Versus Fingolimod Oral in Relapsing-Remitting Multiple Sclerosis. *Kaplan–Meier estimate. [†]Cox proportional hazard model adjusted for treatment, country, number of relapses in the previous 2 years, and baseline Expanded Disability Status Scale (EDSS) score. [‡]Month 0 to month 12. [§]Negative binomial model adjusted for treatment, country, number of relapses in the previous 2 years, and baseline EDSS score. [¶]No adjustment for multiple comparisons. ^{**}Ranked analysis of covariance model with treatment and country as factors and number of gadolinium-enhancing T1 lesions at baseline as a covariate. ^{††}Month 0 to month 24. ^{‡‡}Negative binomial model adjusted for treatment and country.

lesions were reduced with fingolimod treatment compared with placebo—are consistent with effective inhibition of inflammation and tissue damage in patients with early MS.

This study has several limitations. TRANSFORMS and FREEDOMS were not powered for these post hoc analyses. No adjustments were made for multiplicity, so findings are considered hypothesis generating rather than conclusive. Outcomes were limited to relapse and active MRI lesions; disability reduction, an important objective of MS therapy, was not analyzed. Finally, the impact of early treatment with fingolimod on long-term disease progression was not assessed in these studies and requires additional long-term evaluation. These data demonstrate that fingolimod is effective in reducing relapses and the development of new/newly enlarged MRI lesions in patients with early MS as well as ≥ 3 years SFS. Taken together with the evidence that fewer relapses early in the disease course are associated with slower long-term disability progression, these data suggest that the use of highly effective and well tolerated DMTs early in the disease process may lead to more favorable outcomes in patients with MS.

Acknowledgments

This study was supported by Novartis Pharmaceuticals Corporation. Editorial support for the preparation of this manuscript was provided by Valerie P. Zediak, PhD, and Erica S. Wehner, RPh, CMPP, from Complete Healthcare Communications, Inc. and funded by Novartis Pharmaceuticals Corporation.

Conflict of Interest

M. Agius has received compensation for consulting from Novartis, Biogen Idec, Teva Neuroscience, Bayer, Sanofi/Genzyme, and Questcor and as a speaker for Novartis and Sanofi/Genzyme. He has received research support from Novartis, Biogen Idec, Teva Neuroscience, Immune Tolerance Network, Acorda Therapeutics, Actelion, Genzyme, Roche/Genentech, Bayer, and GlaxoSmithKline. X. Meng, P. Chin, and R. Hashmonay are employees of Novartis Pharmaceuticals Corporation. A. Grinspan was an employee of Novartis Pharmaceuticals Corporation at the time of the analysis and is currently an employee of Acorda Therapeutics.

References

- Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. *Brain* 2003;**126**:770–782.
- Scafari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. *Brain* 2010;**133**:1914–1929.
- Tremlett H, Yousefi M, Devonshire V, Rieckmann P, Zhao Y, U. B. C. Neurologists. Impact of multiple sclerosis relapses on progression diminishes with time. *Neurology* 2009;**73**:1616–1623.
- Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. 2. predictive value of the early clinical course. *Brain* 1989;**112**:1419–1428.
- Lublin FD, Baier M, Cutter G. Effect of relapses on development of residual deficit in multiple sclerosis. *Neurology* 2003;**61**:1528–1532.
- Prosperini L, Gianni C, Barletta V, et al. Predictors of freedom from disease activity in natalizumab treated-patients with multiple sclerosis. *J Neurol Sci* 2012;**323**:104–112.
- Rio J, Rovira A, Tintore M, et al. Relationship between MRI lesion activity and response to IFN-beta in relapsing-remitting multiple sclerosis patients. *Mult Scler* 2008;**14**:479–484.
- Rio J, Castillo J, Rovira A, et al. Measures in the first year of therapy predict the response to interferon beta in MS. *Mult Scler* 2009;**15**:848–853.
- Rudick RA, Lee JC, Cutter GR, et al. Disability progression in a clinical trial of relapsing-remitting multiple sclerosis: eight-year follow-up. *Arch Neurol* 2010;**67**:1329–1335.
- Sormani MP, Bonzano L, Roccatagliata L, Cutter GR, Mancardi GL, Bruzzi P. Magnetic resonance imaging as a potential surrogate for relapses in multiple sclerosis: a meta-analytic approach. *Ann Neurol* 2009;**65**:268–275.
- Sormani MP, Bonzano L, Roccatagliata L, Mancardi GL, Uccelli A, Bruzzi P. Surrogate endpoints for EDSS worsening in multiple sclerosis. A meta-analytic approach. *Neurology* 2010;**75**:302–309.
- Sormani MP, Li DK, Bruzzi P, et al. Combined MRI lesions and relapses as a surrogate for disability in multiple sclerosis. *Neurology* 2011;**77**:1684–1690.

13. Trojano M, Pellegrini F, Paolicelli D, et al. Real-life impact of early interferon beta therapy in relapsing multiple sclerosis. *Ann Neurol* 2009;**66**: 513–520.
14. Kappos L, Freedman MS, Polman CH, et al. Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study. *Lancet* 2007;**370**:389–397.
15. Compston A, Coles A. Multiple sclerosis. *Lancet* 2008;**372**:1502–1517.
16. Davies S, Nicholson T, Laura M, Giovannoni G, Altmann DM. Spread of T lymphocyte immune responses to myelin epitopes with duration of multiple sclerosis. *J Neuropathol Exp Neurol* 2005;**64**: 371–377.
17. Goebels N, Hofstetter H, Schmidt S, Brunner C, Wekerle H, Hohlfeld R. Repertoire dynamics of autoreactive T cells in multiple sclerosis patients and healthy subjects: epitope spreading versus clonal persistence. *Brain* 2000;**123**(Pt 3):508–518.
18. Tremlett H, Zhao Y, Joseph J, Devonshire V; UBCMS Clinic Neurologists. Relapses in multiple sclerosis are age- and time-dependent. *J Neurol Neurosurg Psychiatry* 2008;**79**:1368–1374.
19. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010;**362**:402–415.
20. Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med* 2010;**362**:387–401.
21. Coles AJ, Fox E, Vladic A, et al. Alemtuzumab more effective than interferon beta-1a at 5-year follow-up of CAMMS223 clinical trial. *Neurology* 2012;**78**:1069–1078.
22. Vanderlugt CL, Miller SD. Epitope spreading in immune-mediated diseases: implications for immunotherapy. *Nat Rev Immunol* 2002;**2**:85–95.
23. Miller SD, Eagar TN. Functional role of epitope spreading in the chronic pathogenesis of autoimmune and virus-induced demyelinating diseases. *Adv Exp Med Biol* 2001;**490**:99–107.