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REVIEW

Moving toward earlier treatment of multiple sclerosis: Findings from a decade of clinical trials and implications for clinical practice ☆

Mark S. Freedman[a,*], Giancarlo Comi[b], Nicola De Stefano[c], Frederik Barkhof[d], Chris H. Polman[d], Bernard M.J. Uitdehaag[d], Lorenz Lehr[e,1], Bettina Stubinski[e,1], Ludwig Kappos[f]

[a]*Department of Medicine, Ottawa Hospital Research Institute, University of Ottawa, 501 Smyth Road, Ottawa, Ontario, K1H 8L6, Canada*
[b]*Department of Neurology and Institute of Experimental Neurology, Università Vita-Salute San Raffaele, Via Olgettina 60, 20132 Milan, Italy*
[c]*Department of Neurology, Neurosurgery & Behavioral Sciences, University of Siena, Viale Bracci 2, 53100 Siena, Italy*
[d]*VU University Medical Center, Postbus 7057, 1007 MB Amsterdam, The Netherlands*
[e]*Global Clinical Development Unit, Merck Serono S.A., 9 Chemin des Mines, 1202 Geneva, Switzerland*
[f]*Departments of Neurology and Biomedicine, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland*

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Abstract
The first clinical presentation of multiple sclerosis (MS) is usually a single episode of typical symptoms and signs and is designated a "first clinical demyelinating event" (FCDE) or a "clinically isolated syndrome". Patients with an FCDE who show 'silent' magnetic resonance imaging lesions are at high risk of further clinical events and therefore of meeting the criteria for the diagnosis of clinically definite MS (CDMS). Here we review five Phase III trials, in which treatment with the following disease-modifying drugs (DMDs) was initiated at this early stage: interferon beta (ETOMS, CHAMPS, BENEFIT, and REFLEX) and glatiramer acetate (PreCISe). Differences in the design of the trials and their patient inclusion criteria limit comparisons. However, the proportion of placebo-treated patients who developed CDMS within 2 years was 38–45% across studies, and this rate was significantly reduced by DMD treatment. Conversion to

Abbreviations: CDMS, clinically definite multiple sclerosis; CI, confidence interval; CNS, central nervous system; DMD, disease-modifying drug; FCDE, first clinical demyelinating event; GA, glatiramer acetate; Gd, gadolinium; HR, hazard ratio; IFNβ, interferon beta; MRI, magnetic resonance imaging; MS, multiple sclerosis; q.w., once weekly; s.c., subcutaneous(ly); t.i.w., three times weekly

*Corresponding author. Tel.: +1 613 737 8532; fax: +1 613 737 8162.
E-mail address: mfreedman@toh.on.ca (M.S. Freedman).

[1]Affiliation at the time of manuscript preparation.

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McDonald MS was reported by only two of the trials: BENEFIT (2001 criteria) and REFLEX (2005 criteria). Around 85% of placebo-treated patients developed McDonald MS by 2 years in each, and again a beneficial effect of DMD treatment was seen. Overall, these studies support early use of DMDs to treat patients with an FCDE who are at high risk of conversion to CDMS.

Contents

1. Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system (CNS) that is characterized by demyelination and axonal injury and loss. The clinical presentation of this chronic disorder is usually a single acute first clinical demyelinating event (FCDE), also known as clinically isolated syndrome. This is a neurologic episode lasting >24 h that is consistent with demyelination within the CNS, and typically involves the optic nerve, brainstem, subcortical white matter, or spinal cord (Miller et al., 2005). Many patients who experience an FCDE often have further attacks separated by periods of clinical stability, a pattern characterizing the relapsing-remitting form of MS. If clinically 'silent' brain or spinal cord lesions are seen on a magnetic resonance imaging (MRI) scan performed at the time of the FCDE, the patient is at particularly high risk of further attacks. About 5–10% of patients go on to experience steady progression of disease without further attacks, also known as primary progressive MS.

In the early stages of MS, inflammatory activity leads to demyelination, which is thought to contribute to the axonal damage and neuronal loss that usually manifests later in the disease course (Bruck, 2005). Typically, demyelination and axonal loss are seen mostly within MS plaques, but axonal damage can also be found in normal appearing white matter (Bjartmar and Trapp, 2003). Less frequently in early MS, lesions may also be seen in gray matter, and diffuse structural changes have been described in normal appearing gray matter (Hulst and Geurts, 2011). Demyelination and subsequent axonal loss are associated with clinical relapses and cumulative functional disability, respectively (Bruck, 2005; De Stefano et al., 2001).

According to the diagnostic criteria first developed in 1983 by Poser et al. (1983), a diagnosis of clinically definite MS (CDMS) requires a patient to experience an FCDE, followed by a second clinical attack, at least a month later (showing dissemination of disease activity in time) and involving different areas of the CNS (showing dissemination in space). However, new diagnostic criteria were developed in 2001 by McDonald et al. (2001), which acknowledge the utility of MRI techniques in demonstrating dissemination in time and space using subclinical disease activity. The McDonald criteria integrate clinical and paraclinical diagnostic methods, in particular MRI findings, to allow an earlier diagnosis of MS than the Poser criteria that only use clinical parameters. In 2005, the McDonald criteria were updated to allow dissemination in time to be demonstrated by the appearance of a new T2 lesion on a scan, compared to a baseline or reference scan performed at least 30 days before (Polman et al., 2005). In 2010, the McDonald criteria were revised again, and now dissemination in time could be demonstrated by the presence of a new T2 and/or gadolinium (Gd)-enhancing lesion on follow-up MRI performed at any time following the reference scan, or by the simultaneous presence of asymptomatic Gd-enhancing and non-enhancing lesions in the first scan (Polman et al., 2011). This revision to the McDonald criteria enables MS to be diagnosed even earlier in the disease course than does the previous 2005 version, as long as the criteria for dissemination in space are also fulfilled. The 2010 criteria are still being validated but initial reports support their utility (Gomez-Moreno et al., 2012; Sedani et al., 2012).

Multiple sclerosis can be treated with disease-modifying drugs (DMDs), such as interferon beta (IFNβ) and glatiramer acetate (GA), which aim to reduce the frequency and severity of clinical attacks and delay the progression of disability. The effects of DMDs on clinical disease activity are usually paralleled by reductions in counts of active MRI lesions and in lesion burden (Comi et al., 2001b; Jacobs et al., 1996; Paty and Li, 1993; PRISMS Study Group, 1998). MS pathology is known to start before the clinical signs of the disease appear, and evidence suggests that the anti-inflammatory effects of DMDs are most effective during the early, inflammatory stages of the disease, and less effective in the progressive stages (Kieseier, 2011; Wolinsky et al., 2007). Therefore, treating at

Table 1 Summary of study designs.

Study	Randomization groups	Entry requirements				Time of primary analysis	Primary endpoint	Definition of CDMS
		Time from FCDE to study start	Presentation	MRI	Age (years)			
CHAMPS (Jacobs et al., 2000)	IFNβ-1a, 30 μg i.m. q.w. ($n=193$) Placebo ($n=190$)	≤27 days	Monofocal[a]	≥2 clinically 'silent' T2 lesions ≥3 mm diameter; ≥1 periventricular, or ovoid	18-50	Stopped after 18-month interim analysis	Cumulative probability of CDMS	Second clinical neurologic event (lasting >48 h that could be attributed to a different part of the central nervous system to that underlying the initial event); or an increase of ≥1.5 EDSS score from Month 1
ETOMS (Comi et al., 2001a)	IFNβ-1a, 22 μg s.c. q.w. ($n=154$) Placebo ($n=155$)	≤3 months	Monosymptomatic/ polysymptomatic	≥4 white-matter lesions on T2-weighted scans; ≥3 white-matter lesions, if ≥1 infratentorial or Gd+	18-40	2 years	Proportion of patients reaching CDMS	Second exacerbation (appearance of a new symptom or worsening of a present symptom shown by change in EDSS or functional system score, lasting ≥24 h, preceded by ≥30 days' clinical stability)
BENEFIT (Kappos et al., 2006a)	IFNβ-1b 250 μg s.c. e.o.d. ($n=292$) Placebo ($n=176$)	≤60 days	Monofocal/ multifocal	≥2 clinically 'silent' T2 lesions ≥3 mm diameter; ≥1 periventricular, ovoid or infratentorial	18-45	2 years	Proportion of patients reaching CDMS/ McDonald MS (2001 criteria)	Second exacerbation (appearance of a new symptom or worsening of a present symptom lasting ≥24 h, preceded by ≥30 days' clinical stability)
PreCISe (Comi et al., 2009)	GA, 20 mg s.c. daily ($n=243$) Placebo ($n=238$)	≤90 days	Monofocal	≥2 T2 lesions ≥6 mm diameter	18-45	3 years	Time to CDMS	Second exacerbation (appearance of a new symptom or worsening of a present symptom, with increase in EDSS score or functional system score, lasting ≥48 h, preceded by ≥30 days' clinical stability)
REFLEX (Comi et al., 2012)	IFNβ-1a, 44 μg s.c. t.i.w. ($n=171$)	≤60 days	Monofocal/ multifocal	≥2 clinically 'silent' T2 lesions ≥3 mm diameter; ≥1	18-50	2 years	Time to McDonald MS	Second event affecting a different functional system from the first event and lasting ≥24 h, preceded by ≥30 days' clinical stability or

Table 1 (*continued*)

Study	Randomization groups	Entry requirements				Time of primary analysis	Primary endpoint	Definition of CDMS
		Time from FCDE to study start	Presentation	MRI	Age (years)			
	IFNβ-1a, 44 μg s.c. q.w. (n=175) Placebo (n=171)			periventricular, ovoid or infratentorial				a sustained ≥1.5 point increase in EDSS score

CDMS, clinically definite multiple sclerosis; EDSS, Expanded Disability Status Scale; e.o.d., every other day; FCDE, first clinical demyelinating event; GA, glatiramer acetate; Gd+, gadolinium-enhancing; IFNβ, interferon beta; i.m., intramuscularly; MRI, magnetic resonance imaging; MS, multiple sclerosis; q.w., once weekly; s.c., subcutaneously; t.i.w., three times weekly.

[a] *Post hoc* analysis found that some patients were multifocal.

the earliest possible opportunity—the FCDE—may be the most effective strategy to manage disease progression.

The currently available preparations of IFNβ and GA have been investigated in clinical trials assessing whether treatment initiation at the FCDE delays the diagnosis of MS. This review paper aims to explore the results from the randomized phases of these studies and to discuss the implications of these findings for future clinical practice.

2. Methods

The source material was obtained from the primary publications from all manufacturer-sponsored trials comparing IFNβ or GA with placebo in patients with an FCDE who had not received prior treatment with immunosuppressant or immunomodulatory agents. Secondary publications were only considered if they provided clarification or correction of information in the primary papers.

The MEDLINE and EMBASE databases were searched from 1995 to 1 June 2012. Searches were limited to studies in humans and papers published in English. A total of 799 articles were identified, within which there were five primary publications describing five manufacturer-sponsored trials of IFNβ or GA in patients with an FCDE.

- **CHAMPS** (**C**ontrolled **H**igh-risk **A**vonex **M**ulti**p**le **S**clerosis; IFNβ-1a, 30 μg intramuscularly once weekly [q.w.]); patients enrolled 1996–1998 (Jacobs et al., 2000)
- **ETOMS** (**E**arly **T**reatment **O**f **MS**; IFNβ-1a, 22 μg subcutaneously [s.c.] q.w.); patients enrolled 1995–1997 (Comi et al., 2001a)
- **BENEFIT** (**Be**taferon/Betaseron in **N**ewly **E**merging multiple sclerosis **F**or **I**nitial **T**reatment; IFNβ-1b, 250 μg s.c. every other day); patients enrolled 2002–2003 (Kappos et al., 2006a)
- **PreCISe** (early glatiramer acetate treatment in delaying conversion to clinically definite MS in subjects **Pre**senting with a **C**linically **I**solated **S**yndrom**e**; GA, 20 mg s.c. daily); patients enrolled 2004–2006 (Comi et al., 2009)
- **REFLEX** (**RE**bif **FLEX**ible dosing in early MS; IFNβ-1a, 44 μg s.c. three times weekly [t.i.w.] or q.w.), study conducted 2006–2010 (Comi et al., 2012).

3. Results

3.1. Study designs

While all five studies examined the effects of DMD treatment in patients who had experienced an FCDE, there were differences in the study designs, which are summarized in Table 1.

Inclusion and exclusion criteria were broadly similar across studies, although the PreCISe study design specified that patients had to have monofocal presentation only, that is, symptoms and signs that could be explained by one brain lesion. In contrast, BENEFIT and REFLEX permitted monofocal or multifocal presentation. The CHAMPS study design specified that only patients with monosymptomatic

Table 2 Summary of baseline patient characteristics.

Trial	Monofocal (%)	Steroid treatment (%)	T1 Gd+ lesions[a]	T2 lesions[b]	Male (%)	Age (years)	Time from event to treatment (days)
CHAMPS (Jacobs et al., 2000)	100[c]	100[d]	0[e]	50% with >4; 29% with >7	25	33[f]	19[e]
ETOMS (Comi et al., 2001a)	61	70	59% with ≥1[g]	91% with >8[g]	36[g]	28[e,g]; 28.4[f,g]	84[g,h]; 78.6[g,i]
BENEFIT (Kappos et al., 2006a)	53	71	0[e]	18[e]	29	30[e]	Unknown
PreCISE (Comi et al., 2009)	100	64	1.5[f]; 0[e]	32[f]; 22[e]	33	31.2[f]	74[e]
REFLEX (Comi et al., 2012)	53.6	70.6	1.3[f]; 0[e]	22.3[f]; 17[e]; 72.9% with ≥9	35.8	30.7[f]	57.6[f]

Gd+, gadolinium-enhancing; MRI, magnetic resonance imaging.
[a]Gd+ lesions indicate the number of active MRI lesions with ongoing inflammatory processes.
[b]T2 lesions indicate the total number of MRI lesions (active and inactive).
[c]Following re-analysis by O'Connor et al. (2009), 30% were found to be multifocal with monofocal presentation, 100% were classified as monofocal on original inclusion criteria.
[d]Some patients received >1 course of steroid treatment.
[e]Median.
[f]Mean.
[g]Data supplied on request (Merck Serono S.A. — Switzerland).
[h]Median to randomization.
[i]Mean to randomization.

presentation were eligible, although a *post hoc* analysis discovered evidence that 30% of patients had multifocal findings at baseline (O'Connor et al., 2009). ETOMS grouped patients as being monosymptomatic or polysymptomatic, but these terms cannot be equated to monofocal or multifocal presentation.

All the trials examined the drug regimens licensed in patients with relapsing forms of MS, except ETOMS, which used a lower dose and frequency of IFNβ-1a (22 μg s.c. q.w.) than is currently licensed. In addition to the licensed regimen for IFNβ-1a (44 μg s.c. t.i.w.), REFLEX also investigated a 44 μg q.w. regimen.

"Clinically definite" multiple sclerosis was the primary endpoint in all of the studies, except REFLEX, in which it was the main secondary endpoint; the primary endpoint in REFLEX was McDonald MS (2005 criteria) (Comi et al., 2012). The BENEFIT study had the co-primary endpoint of McDonald MS (2001 criteria) (McDonald et al., 2001). The definition of CDMS differed among studies, but all required a second clinical event or deterioration of present symptoms or disability for a diagnosis of CDMS (Table 1).

The primary analyses of BENEFIT and ETOMS took place after 2 years, as did the event-driven analysis of REFLEX. The primary analysis was planned after 3 years in both CHAMPS and PreCISe; however, CHAMPS was stopped after an 18-month interim analysis showed a benefit of active treatment compared with placebo. For the same reason, the double-blind, placebo-controlled phase of PreCISe was stopped and the data analyzed when patients had a mean treatment exposure of 2.3 years.

In BENEFIT, REFLEX, and PreCISe, all patients who experienced a second attack and converted to CDMS were switched to open-label active treatment. In contrast, in ETOMS, further treatment was at the discretion of the treating physician; only 22/155 (14%) of the patients randomized to placebo switched to open-label s.c. IFNβ-1a treatment upon conversion to CDMS. In addition, the design of CHAMPS was such that patients who converted to CDMS left the study, rather than switched to open-label active treatment.

The five studies varied in the patient baseline characteristics they reported (Table 2). As with time from the FCDE to study entry, the median time between the FCDE and starting treatment differed among studies and was shortest in CHAMPS and longest in ETOMS. The time from the FCDE to initiation of treatment was not reported in BENEFIT. All the studies included patients who had received prior steroid treatment. In CHAMPS, all patients received steroid treatment at baseline; in fact some patients may have received ≥1 steroid treatment if it was felt that any pre-study steroid therapy was suboptimal. In comparison, 70% to 71% of patients in ETOMS, BENEFIT, and REFLEX and 64% of patients in PreCISe had received prior steroid treatment. The ratio of male to female patients and their mean age were similar among studies.

In summary, while the study designs and patient populations were broadly similar, there were also important differences that preclude direct comparison of trial results.

3.2. CDMS

The proportions of placebo-treated patients who converted to CDMS over 2 years ranged from 38% to 45% (Table 3). Each of the studies reported a significantly lower risk of developing CDMS in the active treatment arms at either 2 years (ETOMS, BENEFIT, PreCISe, REFLEX) or 3 years (CHAMPS) (Table 4). The risk reductions for CDMS were similar in

BENEFIT, PreCISe, and REFLEX, as demonstrated by the hazard ratios (HRs) that ranged from 0.48 to 0.55. In REFLEX there was no significant difference in treatment effect between the s.c. IFNβ-1a t.i.w. and q.w. treatment regimens.

Median time to CDMS was not reported in any of the studies because fewer than 50% of patients in each study had reached CDMS within the 2-year follow-up period. ETOMS reported the time taken for 30% of patients to develop CDMS (569 days in patients receiving IFNβ-1a 22 μg s.c. q.w. and 252 days in those receiving placebo). PreCISe reported the time taken for 25% of patients to reach CDMS as 722 days with GA, compared with 366 days with placebo.

Overall, all of the trials reported similar rates of conversion to CDMS in patients who received placebo, and this rate of conversion was reduced by DMD treatment in all five trials. BENEFIT, REFLEX, and PreCISe all reported treatment effects of a similar size, with the caveat of the differences in study design discussed above.

3.3. McDonald MS

When ETOMS and CHAMPS were initiated, the McDonald diagnostic criteria had not yet been developed. BENEFIT and REFLEX were the only studies to report conversion to McDonald MS. The proportion of placebo-treated patients who went on to develop McDonald MS was high and similar between the two studies: 85% in BENEFIT and 86% in REFLEX after 2 years.

Both BENEFIT and REFLEX reported a reduction in the proportion of patients developing McDonald MS in the treatment arms compared with placebo. In BENEFIT, 69% of patients receiving s.c. IFNβ-1b reached McDonald MS (2001 criteria) over 2 years (HR: 0.54; 95% confidence interval [CI]: 0.43–0.67; $p<0.001$). In REFLEX, the proportions of patients with McDonald MS (2005 criteria) at 2 years were 62% and 76% for the t.i.w. and q.w. treatment groups, respectively. Risk reductions were, for t.i.w. vs. placebo, adjusted HR: 0.49 (95% CI: 0.38–0.64; $p<0.001$); for q.w. vs. placebo, adjusted HR: 0.69 (95% CI: 0.54–0.87; $p=0.008$); and for t.i.w. vs. q.w., adjusted HR: 0.71 (95% CI: 0.54–0.91; $p=0.009$). Furthermore, both dosing frequencies of s.c. IFNβ-1a delayed McDonald 2005 MS. The median time from initiation of treatment to McDonald MS (2005 criteria) was 97 days for placebo, 182 days for s.c. IFNβ-1a q.w., and 310 days for s.c. IFNβ-1a t.i.w.

3.4. MRI

The advent of the McDonald criteria placed further importance on assessment of MRI parameters for assessing potential MS disease activity in patients with an FCDE. However, each of the five studies assessed different MRI measures, which precludes comparison among the studies. Nonetheless, all of the studies demonstrated significant reductions in some measures of MRI disease activity when treatment was compared with placebo. All studies allowed patients in the placebo arm to switch to active treatment if they developed CDMS within 2 years, which means that the MRI data are biased, either by the inclusion of partially treated placebo groups (if all 2-year scans are included), or by censoring data when patients converted to CDMS.

4. Discussion

Five Phase III clinical trials, all with broadly similar patient populations, have investigated the effects of DMD treatment in patients with an FCDE. While there were differences in study designs that preclude direct efficacy comparisons between the studies, all five showed that treatment with IFNβ or GA significantly delayed the onset of MS, whether defined as CDMS or McDonald MS. The rates of conversion to CDMS in the placebo arms were similar among all the studies, as was the rate of conversion to McDonald MS in BENEFIT and REFLEX. Taken together, the results of these studies show that, if untreated, 38% to 45% of patients with an FCDE and ≥2 T2 lesions convert to CDMS, and approximately 85% reach McDonald MS, within 2 years of the first event. In the REFLEX trial, although both t.i.w. and q.w. treatment delayed the occurrence of clinical relapses, the t.i.w. regimen had a more pronounced effect on the subclinical MRI activity that leads to the diagnosis of McDonald MS in patients who had not yet developed CDMS (Comi et al., 2012).

The McDonald criteria were developed to both increase the accuracy of diagnosis and shorten the time it takes to diagnose MS by including evidence from MRI scans that may provide evidence of dissemination in space and time in the absence of a second clinical attack. It is of interest that a dose effect of s.c. IFNβ-1a was observed on time to McDonald 2005 MS but not on time to CDMS in the REFLEX study. This could be explained by the greater sensitivity of MRI outcomes compared with clinical outcomes, but how

Table 3 Patients with CDMS at 2 years in the 'early treatment' studies.

Study	Therapy	Patients who had CDMS at 2 years (%)		*p*-Value
		Active treatment	Placebo	
CHAMPS (Jacobs et al., 2000)	IFNβ-1a 30 μg i.m. q.w.	20	38	<0.001
ETOMS (Comi et al., 2001a)	IFNβ-1a 22 μg s.c. q.w.	34	45	0.047
BENEFIT (Kappos et al., 2006a)	IFNβ-1b 250 μg s.c. e.o.d.	28	45	<0.001
PreCISe (Comi et al., 2009)	GA 20 mg s.c. q.d.	25	43	<0.001
REFLEX (Comi et al., 2012)	IFNβ-1a 44 μg s.c. t.i.w.	21	38	<0.001
	IFNβ-1a 44 μg s.c. q.w.	22	-	0.002

CDMS, clinically definite multiple sclerosis; GA, glatiramer acetate; IFN, interferon; i.m., intramuscularly; q.d., once daily; e.o.d., every other day; q.w., once weekly; s.c., subcutaneously; t.i.w., three times weekly.

Table 4 Risk reductions for CDMS at 2 years.

Study	Therapy	Measure	Ratio	95% CI	*p*-Value
CHAMPS (Jacobs et al., 2000)	IFNβ-1a 30 μg i.m. q.w.	Rate ratio	0.56	0.38-0.81	0.002
		Adjusted rate ratio	0.49	0.33-0.73	<0.001
ETOMS (Comi et al., 2001a)	IFNβ-1a 22 μg s.c. q.w.	Odds ratio	0.61	0.37-0.99	0.045
BENEFIT (Kappos et al., 2006a)	IFNβ-1b 250 μg s.c. e.o.d.	Adjusted HR	0.50	0.36-0.70	<0.0001
PreCISe (Comi et al., 2009)	GA 20 mg s.c. q.d.	HR	0.55	0.40-0.77	0.0005
REFLEX (Comi et al., 2012)	IFNβ-1a 44 μg s.c. t.i.w. vs. placebo	Adjusted HR	0.48	0.31-0.73	<0.001
	IFNβ-1a 44 μg s.c. q.w. vs. placebo	Adjusted HR	0.53	0.35-0.79	0.002
	IFNβ-1a 44 μg s.c. t.i.w. vs. q.w.	Adjusted HR	0.90	0.56-1.43	0.774

CDMS, clinically definite multiple sclerosis; CI, confidence interval; e.o.d., every other day; GA, glatiramer acetate; HR, hazard ratio; IFNβ, interferon beta; i.m., intramuscularly; q.d., once daily; q.w., once weekly; s.c., subcutaneously; t.i.w., three times weekly.

this translates to clinical outcomes in the longer term remains unclear.

The McDonald diagnostic criteria were revised in 2010 (Polman et al., 2011): proof of dissemination in space changed from requiring ≥9 T2 lesions to ≥1 T2 lesion in ≥2 of the 4 locations characteristic for MS (juxtacortical, periventricular, infratentorial, and spinal cord). Proof of dissemination in time can now be shown by the simultaneous presence of asymptomatic Gd-enhancing and non-enhancing lesions at any time or a new T2 and/or Gd-enhancing lesion on a follow-up MRI. The high specificity of the McDonald 2010 criteria is supported by a *post hoc* analysis of REFLEX that showed that patients retrospectively diagnosed with McDonald 2010 MS at baseline were at a higher risk of developing McDonald 2005 MS during the study (Freedman et al., 2011). The use of the 2010 criteria in future clinical practice means that the proportion of patients with an FCDE who are not diagnosed with MS is therefore likely to decrease. It will be important to determine whether this putative new 'clinically isolated syndrome' population of patients would still benefit from treatment with a DMD, although the *post hoc* analysis of the REFLEX study found robust treatment effects in patient subgroups both with and without retrospective McDonald MS 2010 diagnosis (Freedman et al., 2011), suggesting that patients in this more narrowly defined population do indeed benefit from early treatment.

Post hoc analyses of data from the BENEFIT and ETOMS studies demonstrate that MRI findings at the time of the FCDE might predict future disease activity. In the BENEFIT study, conversion to CDMS by 3 years was significantly more frequent in patients with ≥9 T2 lesions and those with ≥1 Gd-enhancing lesion on baseline MRI (Barkhof et al., 2003). Similarly in ETOMS, the odds of developing CDMS over 2 years were significantly greater in patients with ≥9 T2 lesions at baseline. The presence of at least one Gd-enhancing lesion at baseline also appeared to be predictive of CDMS but did not reach significance (Moraal et al., 2009). Caution should be exercised when interpreting the results of such *post hoc* analyses.

Extension studies were conducted for BENEFIT, CHAMPS, and PreCISe; the REFLEX extension (REFLEXION) is ongoing. While a full review of these extension studies is outside of the scope of this paper, the reported data show long-term benefit of early treatment with DMDs. In pre-planned extensions, the beneficial effects of early IFNβ-1b and GA treatment on the risk of developing CDMS were confirmed 5 years after randomization in the BENEFIT and PreCISe studies, respectively (Kappos et al., 2009; Comi et al., 2010). An investigator-initiated, post-planned extension to CHAMPS—CHAMPIONS—also confirmed the long-term benefit of early intramuscular IFNβ-1a treatment on the risk of developing CDMS (Comi et al., 2010; Kinkel et al., 2006). In REFLEXION, the primary endpoint of time to CDMS at 36 months after randomization into REFLEX has been reported, and both dose frequencies of s.c. IFNβ-1a were found to significantly delay conversion to CDMS compared with delayed treatment (Freedman et al., 2012). The pre-planned extension to year 5 is ongoing. As with the *post hoc* analyses, the data from these extension studies should be interpreted with caution.

The results from these five studies have shown that most untreated patients rapidly convert to MS following an FCDE, and that early DMD treatment can significantly reduce the risk of developing MS. The benefit of early treatment was maintained during long-term follow-up. These findings have already led to a shift toward earlier treatment (Comi, 2009). Of note, not all patients presenting with an FCDE have a second clinical event establishing CDMS (Fisniku et al., 2008). It remains to be seen whether these short-term benefits translate into long-term improvements such as reduced disability in clinical practice. Although BENEFIT found an advantage of early treatment on disability progression at 3 years' follow-up (Kappos et al., 2007), the difference between the groups did not remain significant at 5 years' follow-up (Kappos et al., 2009). However, crossover from placebo to active treatment may have masked some treatment effects. Similarly the 5-year evaluation of the CHAMPS cohort found no benefit of treatment on disability outcomes, with the additional caveat of a low patient retention rate (Kinkel et al., 2006). REFLEXION has yet to report disability outcomes. However, long-term follow-up from trials of DMDs in patients with relapsing MS suggest that early advantages are maintained over time with continued treatment (Kappos et al., 2006b; Bermel et al., 2010; Ebers et al., 2010; Ford et al., 2010). Although the evidence from the aforementioned trials supports treating with DMDs at the time of the first FCDE as an effective strategy to manage disease progression, several other factors must be considered when making the decision to

treat early, including—but not limited to—tolerability issues, local licensing laws and treatment cost.

5. Conclusion

Early treatment with DMDs benefits patients with an FCDE who are at high risk of conversion to MS by reducing the risk of conversion to MS (defined by either the Poser or McDonald criteria) and delaying the occurrence of a second attack. Although the long-term benefits of early intervention with DMDs, particularly on overall disease progression, remain to be demonstrated, results from long-term follow-up studies in patients with relapsing MS suggest that treatment with DMDs will improve outcomes for these patients. Despite the differences between the five FCDE trials in terms of study design, endpoint definition, and recruitment environment, the findings all support initiating treatment with DMDs at the time of the FCDE.

Conflicts of interest

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