THERAPEUTICS INITIATIVE Independent Healthcare Evidence

Drug Assessment Working Group (DAWG)

Multiple Sclerosis Therapeutic Review Project

PRIORITY 3 Report

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TABLE OF CONTENTS

MS Therapeutic Review Project - PRIORITY 3

1. Priority 3 questions from Pharmaceutical Services Division:

Question 1: Should treatment with various MS drug therapies be continued in patients 60 years or older with relapsing remitting MS (RRMS)?

Question 2: Should treatment with various MS drug therapies be continued in patients with relapsing remitting MS (RRMS) with an Expanded Disability Status Scale (EDSS) score greater than 5.5?

2. Discontinuation of MS therapy in patients over 60 years

In older patients with MS, should providers consider discontinuing MS therapy?

a. In patients with stable disease with minimal or mild disability, if the benefits of continued immune modulation with MS therapy have not been shown.
b. In progressive patients who have reached significant disability (i.e. loss of independent ambulation EDSS score more than 5.5), where MS therapies are of marginal additional benefit.

Overall Summary of evidence

1. No RCT was identified that examined the role of continuing or stopping MS treatment(s) based on age less than 60 years as compared to 60 years and older.
2. No RCT was identified that examined the role of continuing drug or stopping MS treatment(s) in adult patients with RRMS based on their EDSS score ranging from 0 to 5.5 as compared to those with EDSS score greater than 5.5.

3. Supporting evidence on discontinuation from observational studies in patients aged over 55 years

Two recent observational studies address these questions:

a. **A retrospective, observational study by Hua 2019** included 600 patients from the United States with confirmed diagnosis of MS, who were aged over 60 years, and were on disease modifying therapy (DMT) > 2 years. 156 (26%) patients had RRMS. (1, 2) 90.5% of patients were treated using interferon (INF) therapies at some point during their disease. Glatiramer acetate (GA) was also commonly prescribed (42.2%) and over 1/5th of patients were treated with unapproved therapies (i.e. azothiaprine, methotrexate, rituximab, mycophenolate mofetil, cyclophosphamide, or investigational products) reflecting treatment exposure prior to MS therapy availability or clinical decision (N = 132; 22.0%).

   Methods used: Cause-specific Cox proportional hazards regression modeled time to discontinuation and time to re-initiation of therapy. Pre- and post-discontinuation comparisons of Performance Scales (PS), Timed 25-Foot Walk, and Patient Health Questionnaire-9 (PHQ9) were analyzed using linear mixed models.

   Results: 178 (29.7%) patients discontinued treatment, of which 97 (54.5%) discontinuers were diagnosed with RRMS. Providers initiated discontinuation more than patients (68.0%). The reasons for discontinuation most often cited were side effects (49.4%), stable disease (28.1%), age (22.5%), lack of benefit (21.3%), secondary progressive disease (20.2%), comorbidities (15.2%), and cost (10.1%). 42.1% of patients discontinuing were able to ambulate independently.

   - Discontinuers were 2.2 years older and had 3.2 years longer disease duration than continuers.
   - Discontinuers had 1.6 years less treatment exposure than continuers.
   - Only one clinical relapse occurred in discontinuers.
   - 10.7% of patients reinitiated MS therapy.

- Patients with discontinuation initiated by their provider were significantly less likely to reinitiate MS therapy compared with those that requested discontinuation (hazard ratio (HR): 0.34; 95% confidence interval (CI): 0.12-0.97; *p* = 0.044).
- GA use was a significant predictor of discontinuation compared to INF (HR: 1.46; 95% CI: 1.02–2.09, *p* = 0.039).
- A larger number of DMT starts in RRMS patients led to an increased risk of discontinuation compared to the same in PPMS patients (HR: 1.99; 95% CI: 1.04-3.79; *p* = 0.037).
- In discontinuers, RRMS patients had lower PS on average than PPMS. The average RRMS patient had a PS score 2.51 less than PPMS (95% CI: 0.54-4.57; p = 0.013).
    - Provider-initiated discontinuation was associated with lower PS than patient-initiated discontinuation, with an average difference of 2.01 between the two groups (95% CI: 0.63-3.38; *p* = 0.005).
- Timed 25-Foot Walk patients who could independently ambulate, on average, walked 0.40 feet per second faster than those who could not (95% CI: 0.08-0.73; *p* = 0.016).
- PHQ9 scores appeared higher in those stopping intravenous (IV) therapies (natalizumab and mitoxantrone) than INFs, indicating worse outcomes (4.55; 95% CI: 1.20-7.90; p = 0.008).

Limitations of Hua 2019 study: A retrospective study design; potential selection bias in patients referred to specialty clinics; missing data limit more detailed analysis (e.g. outcome models contained a minority of patients (~50%) of the total number of discontinuers); rate of progression after MS therapy discontinuation and cognitive measures were unavailable; and 33% of patients included in this study were diagnosed long before MS therapies became available and thus were exposed to unapproved immune-suppressive therapies. Also discontinuation models did not account for MS therapy changes over time.

Hua 2019 authors concluded that "most patients over age 60, who discontinued DMT, remained off DMT. Re-initiation rates were low at approximately 10% and were primarily due to patient preference. Only one relapse occurred in the discontinuers, and very few had MRI changes or clinical progression that led to a decision to reinitiate treatment. DMT discontinuation is more successful when age is considered, compared to disease stability alone, as this can help serve as a surrogate for "burnt out" inflammatory processes and aging immune systems".

b. **Schwehr 2020** study's objective was to project the outcomes of MS therapy discontinuation (IFN beta, fingolimod, or natalizumab) among older adults (age 55 or 70 years) with RRMS who were relapse-free for 5 or more years and had not reached an EDSS score of 6. Outcomes included in the study were the percentage of people who had at least one relapse or reached EDSS 6, and quality-adjusted life-years (QALYs), which incorporated both relapses and disability. (3)

Method used: Simulation modeling.

Schwehr 2020 found lower projected benefits for MS therapy continuation at 70 years of age than at 55 years of age. Compared with discontinuation, the projected benefit of MS therapy continuation ranged from 0.007 to 0.017 QALYs at 55 years of age and dropped to 0.002-0.006 at 70 years of age. The annual projected benefits of MS therapy continuation (0.1-3.0 QALYs) were very low compared with typical patient preferences regarding treatment burden.

Schwehr 2020 authors concluded "that the benefits of DMDs may not be substantial among older adults with relapsing-onset MS. However, direct clinical evidence remains limited and the decision of whether to discontinue a DMD should also take into account patient preferences. It is important to gain a better understanding of how age-related changes in the trajectory of relapsing-onset MS affect treatment effectiveness among older adults".

4. Baseline characteristics across comparative RCTs included in the larger systematic review of comparative efficacy and safety of MS drugs

Due to a lack of RCT evidence of continuing or discontinuing MS therapies in older adults, we extracted the following information from all the active comparison RCTs included in the larger systematic review.
[The criteria used to diagnose patients with RRMS; patient's age range and mean age at baseline; the range of EDSS score and the mean EDSS score at baseline; mean duration of MS since diagnosis; mean relapse rate in the previous year prior to study entry; mean follow-up duration of the study; the proportion of female patients as well as percentage of Caucasians in each study].

Table 1: Comparison of baseline characteristics across comparative trials with specific drug comparisons

Comparison **Total # studies** **N = total randomized**	**Diagnostic criteria for RRMS**	**Age range (years)**	**Mean age (years)**	**EDSS range**	**Mean or median EDSS (SD)**	**Duration of MS since diagnosis Mean (SD)**	**Mean relapse rate (SD)**	**Follow up (weeks or years)**	**Caucasians C (%)** **Female F (%)**
Alemtuzumab vs INF beta 1a; 3 RCTs; All Single blind; N = 1755	McDonald 2001/2005 criteria	18 to 60	32 to 35	0 to 5.0	2.0 to 2.7	2 years	1.2 to 1.8	2 to 3 years	C: 90 to 95% F: 64 to 67%
Natalizumab vs INF beta 1a, GA, fingolimod; 2 RCTs; both open label; terminated early; N= 183	McDonald 2005/2010 criteria	18 to 64	37	0 to 5.5	NR	NR	NR	1 to 2 years	C: NR F: 79%
Ocrelizumab vs INF beta 1a; 2 RCTs; both double blind; N = 1656	McDonald 2010 criteria	18 to 55	37	0 to 5.5	2.5	3.8 to 4.2 years	1.31 to 1.34	96 weeks	C: 90% F: 65%
Teriflunomide vs INF beta 1a; 1 RCT; single blind; N = 324	McDonald 2005 criteria	18 years or older	35 to 37	0 to 5.5	2.0 to 2.3	7.0 years	1.3	64 weeks	C: 100% F: 68%
Dimethyl fumarate (DMF) vs Glatiramer acetate (GA); 1 RCT; double blind; N = 709	McDonald 2005 criteria	18 to 55	37	0 to 5.0	2.6	4.6 years	1.4	2 years	C: 84% F: 70%
Fingolimod vs other DMTs; 7 RCTs; 4 open label ; 1 triple blind; 1 double blind and 1 single blind; N = 3488	McDonald 2005/2010 criteria	18 to 65	36 to 46	0 to 6.0	2.2 to 2.4	4.3 to 6.2 years	1.4 to 1.5	0.5 to 1.5 years	C: 74% F: 66 to 77%
GA vs INF beta 1a; 4 RCTs; 2 open label; 1 single blind; and 1 double blind; N = 1453	Poser or McDonald 2001/2005 criteria	18 to 60	36 to 38	0 to 5.5	2.0 to 2.3	1 to 6 years	1.2 to 1.7	1.9 to 3 years	C: 88 to 94% F: 70 to 79%
GA vs INF beta 1b; 2 RCTs; 1 open label and 1 double blind; N = 2345	McDonald 2001 criteria	18 to 55	36	0 to 5.5	2.3	1 to 5 years	1.6 to 1.9	2 years	C: 52 to 92% F: 69%
INF beta 1a vs 1b; 5 RCTs; 3 open label; 1 single blind; and 1 double blind; N = 1382	Poser or McDonald 2005 criteria	15 to 65	28 to 41	0 to 6.0	2.0	1.5 to 6.3 years	1.3 to 2.2	12 weeks to 2 years	C: 88 to 91% F: 65 to 76%
INF beta 1a (Avonex) **vs INF beta 1a** (Rebif); **4 RCTs; 2 open label; 1 single blind; and 1 double blind; N = 876**	Poser or McDonald 2005 criteria	18 to 65	29 to 38 years	0 to 6.0	2.0 to 2.3	3.2 to 6.6 years	1.2 to 2.6	1 to 2 years	C: 91 to 92% F: 65 to 76%
OVERALL **11 comparisons**	Poser or McDonald 2001/2005/ 2010 criteria	18 to 65 years	29 to 46 years	0 to 6.0	2.0 to 2.7	1 to 7 years	1.2 to 2.6	12 weeks to 3 years	C: 74 to 94% F: 65 to 95%

Note: APPENDIX 1 and 2 provides detailed information for each study included in Table 1.

Overall summary of baseline characteristics

In the comparative RCTs identified the age ranged from 18 to 65 years (mean age ranging from 29 to 46), and the EDSS score ranged from 0 to 6.0 (mean EDSS score ranging from 2.2 to 2.7). Therefore no RCT studied patients beyond an age of 65 years and an EDSS score beyond 5.5 or 6.0. For patients included in the trials data were not presented by age category.

RCTs in MS enrolled relatively young, mildly impaired patients with a history of recent relapses or new magnetic resonance imaging (MRI) lesions. In these patients, MS therapies decreased rates of relapses and, in some instances, short-term disability progression.

5. Age related decrease in relapse rates in patients with RRMS

Studies have documented a continuous decline in inflammatory activity with age, and the need for anti-inflammatory therapy declines accordingly. (4) Disease activity decreases with age, and a threshold level of disease activity may be necessary for the benefit of MS therapies to outweigh the treatment burden for older people with RRMS.

a. **Tremlett 2016** examined the relative relapse-rate patterns over time in a RRMS cohort (N = 2477) to investigate potential predictors of relapse rates and periods of low-relapse activity. (5) Annualised relapse rates (ARR) were examined according to sex, age at onset, the patient's current age and disease duration. The relationship between relapse rates and baseline characteristics (sex, onset age and onset symptoms) were examined using Poisson regression. Time to the first 5 years relapse-free was examined using Kaplan-Meier survival analysis. The author reported that the mean follow-up time (from onset of MS symptoms) in this cohort was 20.6 years, during which time 11,722 post-onset relapses were recorded. The relapse rate decreased by 17% every 5 years (between years 5 to 30 post-onset), but this decline increased in magnitude with increasing onset age. Women and those with onset sensory symptoms exhibited a higher relapse rate ($p < or = 0.001$). Over 75% of patients (1692/2189) experienced a 5-year relapse-free period during the RR phase. Tremlett 2016 study concluded that relapse rates were age and time-dependent. The clinical implications of the observations in this study were: 1) any drug able to modify relapse rates has the greatest potential for a population impact in patients < 40 years old and within the first few demi-decades of disease; 2) continuation of drug beyond these times may be of limited value; 3) long-term follow-up studies must consider that relapse rates probably decline at different rates over time according to the patient's onset age; and 4) a relapse-quiescent period in MS is not uncommon.

b. **Schwehr 2019** examined age-related decrease in relapse rate among patients with RRMS. (6) They used a simulation modeling approach to examine a range of assumptions about changes in ARR due to age versus disability status. Model parameters were developed through analysis of MS patients in British Columbia, Canada, and literature review. They found a substantial age-specific decrease in ARR in all simulated scenarios, independent of disability worsening. Under a range of clinically plausible assumptions, 88-97% of the decrease was attributed to age and 3-13% to disability. The age-specific decrease ranged from 22% to 37% per 5 years for a wide range of initial ARR (0.33-1.0). Schwehr 2019 study concluded that decreases in ARR were due mostly to age rather than disability status.

6. Continuation or discontinuation of MS therapy after prolonged relapse free period

Kister 2016 studied discontinuation of MS therapies in patients after a prolonged relapse free period using MSBase registry. (7) This registry is an ongoing, longitudinal, strictly observational registry that tracks outcomes of routine clinical practice for patients with MS.

Based on this registry, 426 drug therapy stoppers and 852 drug therapy stayers were matched with propensity scores. Inclusion criteria for 'DMT stoppers' were: diagnosis of MS by Poser or McDonald criteria; aged ≥18 years at DMT discontinuation ('baseline'); no relapses for ≥5 years prior to baseline; continuous treatment with injectable DMT (INF beta or GA) for ≥3 years prior to baseline; ≥3 years of follow-up after baseline; no restart of a DMT for ≥3 months after baseline (these early re-starters were excluded because they were considered 'treatment switchers' rather than

'treatment stoppers'). The discontinued therapy among stoppers was INF beta in 88.3% and GA in 11.7%. The main reason for drug discontinuation was recorded for 40% of stoppers as medication intolerance (26.2%); lack of improvement (23.8%); adverse event (13%) and disease progression (11%). Drug therapy was restarted by 198 (46%) of stoppers after a mean of 0.93 (1.6) years. Patients with MS who stayed on medications were eligible for matching were required to have had no relapses for ≥5 years prior to baseline, and to have been continuously treated with an injectable drugs (INF beta or GA) for ≥3 years prior to baseline and ≥3 years afterwards. Among stayers, the continued therapy was INF beta in 80.7% and GA in 19.3%. Mean post-baseline follow-up for stayers was 5.02 (3.81, 6.96) years.

A logistic regression model was used in which stopping MS therapy was the outcome variable, and the baseline and pre-baseline characteristics (sex, age, disease duration, baseline EDSS, pre-baseline MS drug exposure and country) formed the explanatory variables in order to calculate the propensity score for stoppers.

The primary end points were time to first relapse and time to first 3-month confirmed disability progression. Confirmed disability progression events were defined as a minimum one-point increase in EDSS score above a baseline EDSS of 1 to 5.5, confirmed at a repeat assessment at least 3 months later. Baseline EDSS scores of zero required a confirmed 1.5 point increase, and baseline EDSS scores ≥6 required a 0.5 increase above baseline confirmed at least 3 months later. EDSS scores recorded within 30 days of a relapse were excluded.

Relapse rate comparisons between stoppers and stayers

- Of the 426 stoppers, 155 (36.4%) reported a relapse during follow-up as compared to 322 (37.8%) stayers during a median 5 year follow up. The mean ARR: 0.27 (± 0.57) for stoppers and 0.25 (± 0.51) for stayers, p = 0.503. Thus, stopping therapy after a prolonged relapse-free period was not associated with an increased risk of relapse.
- The median inter quartile range (IQR) time to first relapse among stoppers was 1.81 years (0.67, 2.92) compared to stayers 2.01 years (0.88, 3.42). Survival time to first relapse among stoppers and stayers was nearly identical (adjusted HR = 1.07, 95% CI: 0.84-1.37; p = 0.584).
- Significant predictors of relapse risk among stoppers were younger age (25% reduction in relapse risk ratio for every 10 years older at baseline, adjusted HR = 0.75, 95% CI: 0.62-0.92; p = 0.005) and lower baseline disability (13% decreased risk of relapse for every 1-point increase in EDSS, adjusted HR = 0.87, 95% CI: 0.80-0.95; p = 0.001).
- The risk of relapses among stoppers was higher in younger and less disabled patients, consistent with natural history studies that document an inverse relationship between age and risk of relapse.

Disability progression rate comparisons between stoppers and stayers

- Confirmed 3-month disability progression during follow-up was recorded for 131/391 (33.5%) stoppers for whom sufficient data were available. Survival time to confirmed disability progression, was significantly shorter among stoppers than stayers (adjusted HR = 1.47, 95% CI: 1.18-1.84; p = 0.001).
    - Among patients who were progression-free prior to baseline, that is, with no change in EDSS for 5 years or more, the stoppers had a higher hazard of progression compared to stayers (adjusted HR = 1.58, 95% CI: 1.19-2.08; p = 0.001).
    - Among patients with pre-baseline disability progression, hazard of post-baseline progression was similar in stoppers and stayers (adjusted HR = 1.32, 95% CI: 0.91-1.91; p = 0.151).
    - Variables significantly associated with increased hazard of confirmed progression in the multivariable model were older age (32% increase in hazard of confirmed disability progression for every 10 years older at baseline, adjusted HR = 1.32, 95% CI: 1.08-1.62; p = 0.008) and prior INF beta 1b-use (adjusted HR = 2.10 (1.19 to 3.72), p = 0.011).
    - Sex, disease duration, baseline disability, disability progression prior to baseline, number of pre-baseline MS drug starts and proportion of disease duration on treatment were not associated with post-discontinuation disability progression among stoppers.
    - Risk of disability progression increased with age among stoppers, in agreement with the well-known observation that older patients are more likely to have progressive disease.

The **limitations of this study** relate to the biases attendant to observational studies, including selection bias, confounding by unmeasured variables (i.e., lesion burden on MRI at baseline) and lack of data completeness for some variables. MRI data were of insufficient density to be included in the final models. This study focused exclusively on 'first-line' injectable therapies, since the required 3 (or more) years of post-discontinuation follow-up was only available for these older therapies. The data on the post-injectable disease course may not be generalizable to the newer agents. The conclusions of this study need not (and probably do not) apply to younger patients with frequent relapses in whom MS therapy discontinuation is generally not advisable.

Kister 2016 authors concluded that stopping immunomodulatory therapy in patients who were relapse-free and progression-free for an extended period of time did not adversely affect relapse outcomes, but was associated with a 50% increase in risk of disability progression. It remains to be determined whether therapy can be safely discontinued in subsets of relapse-free patients, such as older patients who already entered the progressive phase, without increasing risk of disability progression. To definitively answer the question about safety of drug discontinuation in this patient subset, an RCT is required.

People who discontinue medication when they are older are less likely to relapse compared with younger people but few studies of discontinuation focused on older adults have been completed. A current prospective RCT (NCT03073603) on discontinuation of therapies in MS is ongoing.

7. Ongoing RCT on discontinuation of MS therapy

NCT03073603 is a prospective RCT on discontinuation of disease modifying therapies in MS in those over the age of 55 years with stable disease. (8) The primary outcome is the number of patients with new disease activity upon discontinuation of therapy vs. those continuing therapy. Secondary outcomes are: Patient's quality of life using the MSIS-29 Scale; total number of new T2 lesions on MRI; and evaluation of change in physical disability, using the EDSS. Another outcome evaluated is patient's disability using patient-determined disease steps. Hopefully this study will provide more definitive guidance.

8. References

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8a. References of included RCTs in the main review

Alemtuzumab vs INF beta 1a

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- **CARE MS I.** Cohen JA, Coles AJ, Arnold DL, Confavreux C, Fox EJ, Hartung HP, et al. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet* 2012; 380(9856):1819–28.
- **CARE MS II.** Coles AJ, Twyman CL, Arnold DL, Cohen JA, Confavreux C, Fox EJ, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet* 2012; 380 (9856):1829–39.

Natalizumab vs INF beta 1a, GA, or Fingolimod

- **NCT02342704.** A multicenter, randomized, open-label study to assess the impact of natalizumab versus fingolimod on central nervous system Tissue damage and recovery in active relapsing-remitting multiple sclerosis subjects.
- **NCT01058005. SURPASS.** A multicenter, randomized, open-label, parallel-group, active-controlled study to evaluate the benefits of switching therapy (Glatiramer acetate or Interferon beta-1a) to natalizumab in subjects with relapsing remitting multiple sclerosis.

Ocrelizumab vs INF beta 1a

- **OPERA I.** Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, Lublin F, Montalban X, Rammohan KW, Selmaj K, Traboulsee A, Wolinsky JS, Arnold DL, Klingelschmitt G, Masterman D, Fontoura P, Belachew S, Chin P, Mairon N, Garren H, Kappos L; OPERA I and OPERA II Clinical Investigators. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med. 2017 Jan 19; 376(3):221-234. doi: 10.1056/NEJMoa1601277. Epub 2016 Dec 21.
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Teriflunomide vs INF beta 1a

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Dimethyl fumarate (DMF) vs Glatiramer acetate (GA)

- **CONFIRM**. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. New England Journal of Medicine 2012; 367(12):1087–97.

Fingolimod vs other injectable DMTs

- Cree BAC, Arnold DL, Cascione M, et al. Phase IV study of retention on fingolimod versus injectable multiple sclerosis therapies: a randomized clinical trial. Ther Adv Neurol Disord. 2018; 11:1-15.
- **NCT01633112.** A 12-month, Randomized, Rater- and Dose-blinded Study to Compare the Efficacy and Safety of Fingolimod 0.25 mg and 0.5 mg Administered Orally Once Daily With Glatiramer Acetate 20 mg (Copaxone)Administered Subcutaneously Once Daily in Patients With Relapsing-remitting Multiple Sclerosis
- **NCT01317004.** To evaluate the change in patient-reported treatment satisfaction after six months of treatment with fingolimod 0.5mg/day vs. DMT standard of care using the global satisfaction subscale of the Treatment Satisfaction Questionnaire for Medication (TSQM-9).

- **NCT01534182.** A 6-month, randomized, active comparator, open-label, multi-center study to evaluate patient outcomes, safety and tolerability of (Fingolimod) 0.5 mg/Day in patients with relapsing remitting multiple sclerosis who are candidates for multiple sclerosis (MS) therapy change from previous disease modifying therapy (DMT).
- **NCT01216072.** A 6-month, randomized, open-label, patient outcomes, safety and tolerability study of fingolimod (FTY720) 0.5 mg/day vs. Comparator in patients with relapsing forms of multiple sclerosis (**EPOC**).

- **NCT01333501.** An 18-month, open-label, Rater-blinded, randomized, multi-center, active-controlled, parallel-group pilot study to assess efficacy and safety of fingolimod in comparison to interferon beta 1b in treating the cognitive symptoms associated with relapsing-remitting multiple sclerosis and to assess possible relationship of these effects to regional brain atrophy.
- **TRANSFORM**. Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. New England Journal of Medicine 2010; 362(5):402–15.

GA vs INF beta 1a or INF beta 1b

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- **NCT01058005. SURPASS.** A multicenter, randomized, open-label, parallel-group, active-controlled study to evaluate the benefits of switching therapy (Glatiramer acetate or Interferon beta-1a) to natalizumab in subjects with relapsing remitting multiple sclerosis.

INF beta 1a (rebif) vs INF beta 1a (Avonex) vs INF beta 1b (Betaseron)

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9. APPENDIX 1

Comparing baseline characteristics in RCTs of RRMS patients treated with biologics (alemtuzumab, natalizumab and ocrelizumab)

TABLE A: Biologic MS drugs comparisons (See Appendix 2 for details relating to each individual study)

Comparison Total # studies N = total randomized	Diagnostic criteria for RRMS	Age range (years)	Mean age (years)	EDSS range	Mean or median EDSS (SD)	Mean (SD) duration of MS since diagnosis (years)	Mean relapse rate (SD)	Follow up (weeks or years)	Caucasians (C)% Female (F) %
Alemtuzumab vs INF beta 1a; 3 RCTs; All single blind; N = 1755	McDonald 2001/2005 criteria	18 to 60	32 to 35	0 to 5.0	2.0 to 2.7	2 years	1.2 to 1.8	2 to 3 years	C: 90 to 95% F: 64 to 67%
Natalizumab vs INF beta 1a or fingolimod or GA; 2 RCTs; both open label; terminated early; N = 183	McDonald 2005/2010 criteria	18 to 64	37	0 to 5.5	NR	NR	NR	1 to 2 years	C: NR F: 79%
Ocrelizumab vs INF beta 1a; 2 RCTs; both double blind; N = 1656	McDonald 2010 criteria	18 to 55	37	0 to 5.5	2.5	3.8 to 4.2 years	1.31 to 1.34	96 weeks	C: 90% F: 65%
OVERALL	McDonald 2001/2005/2010 criteria	18 to 64 years	32 to 37 years	0 to 5.5	2.0 to 2.5	2 to 4.2 years	1.2 to 1.8	1 to 3 years	C: 90 to 95% F: 64 to 79%

Alemtuzumab has only been compared to one injectable drug, IFN beta 1a, in 3 single blind studies in 1,755 RRMS patients with a follow up of 2 to 3 years. Mean age across these studies was 32 to 35 years; mean EDSS score 2.0 to 2.7. Evidence in terms of grading of evidence was of low certainty for alemtuzumab.

Ocrelizumab has only been compared to one injectable drug, IFN beta 1a, in 2 double blind studies in 1,656 RRMS patients with a follow up of 96 weeks. Mean age across these studies was 37 years; mean EDSS score 2.5. Evidence in terms of grading of evidence was of moderate certainty for ocrelizumab.

Natalizumab has been compared to two injectable drugs, IFN beta 1a and GA, in one open label study and to one oral drug, fingolimod, in 1 open label study in 183 adult RRMS patients with a follow up of 1 to 2 years. Mean age across these studies was 37 years; mean EDSS score was not reported. No data available to evaluate comparative evidence for natalizumab.

No RCT was identified comparing rituximab to any other MS therapy.

Since both studies comparing natalizumab to other MS treatments were terminated early and clinical outcome data was not reported, and with no study identified for rituximab, we have reported on the differences in the baseline characteristics and quality of evidence of alemtuzumab vs ocrelizumab.

Differences between RCTs:

a. Total number of patients randomized was greater in alemtuzumab vs INF beta 1a (N = 1755) compared to ocrelizumab trials vs INF beta 1a (N = 1656).
b. The diagnostic criteria used were McDonald 2001 and 2005 in alemtuzumab studies as compared to McDonald 2010 criteria in ocrelizumab studies.
c. Although the age range for inclusion was similar ranging from 18 to 60 years, patients in the ocrelizumab studies had a greater mean age of 37 years as compared to mean age ranging from 32 to 35 years in the alemtuzumab studies.
d. The mean duration of the disease was greater in ocrelizumab studies (3.8 to 4 years) compared to 2 years in alemtuzumab group.

e. The EDSS score range from 0 to 5.5 was similar but the mean/median EDSS score at baseline was lower in two studies in alemtuzumab group (2.0 in treatment naïve patients) as compared to mean EDSS score of 2.7 in RRMS patients failing a previous drug treatment in alemtuzumab group in CARE MS II study and 2.5 in the ocrelizumab group (OPERA I and OPERA II studies).
f. The mean relapse rate was greater in ocrelizumab studies (1.31 to 1.34) and also in one alemtuzumab study CARE MS II (1.8) as compared to 1.2 in the other two alemtuzumab studies in group (CAMMS223 and CARE I).
g. The mean duration of follow up was greater in alemtuzumab studies (2 to 3 years) as compared to less than 2 years (96 weeks) in ocrelizumab studies.
h. The high risk of bias assessment in alemtuzumab studies (unclear risk of selection bias; high risk of performance and detection bias [single blind studies]; attrition bias; selective reporting bias; and conflict of interest bias) as compared to ocrelizumab studies (low risk of selection bias; unclear risk of performance and detection bias [although both studies were double blind differences in adverse effects may have compromised blinding]; high risk of attrition bias and conflict of interest bias) led us to grade overall evidence as moderate certainty for ocrelizumab as compared to low certainty for alemtuzumab.

Comparing baseline characteristics in RCTs of RRMS patients treated with oral MS drugs (Dimethyl fumarate, fingolimod and teriflunomide)

TABLE B: Oral MS drugs comparisons (See Appendix 2 for details relating to each individual study)

Comparison
Total # studies
N = total randomized
	Diagnostic criteria for RRMS	Age range (years)	Mean age (years)	EDSS range	Mean or median EDSS (SD)	Mean (SD) duration of MS since diagnosis (years)	Mean relapse rate (SD)	Follow up (weeks or years)	Caucasians (C)%
									Female (F)%

Dimethyl fumarate (DMF) vs Glatiramer acetate (GA); 1 RCT: double blind; N = 709	McDonald 2005 criteria	18 to 55	37	0 to 5.0	2.6	4.6	1.4	2 years	C: 84% F: 70%
Fingolimod vs other DMTs; 7 RCTs; 4 open label; 1 triple blind; 1 double blind and 1 single blind; N = 3488	McDonald 2005/2010 criteria	18 to 65	36 to 46	0 to 6.0	2.2 to 2.4	4.3 to 6.2	1.4 to 1.5	1 to 1.5 years	C: 74% F: 66 to 77%
Fingolimod vs Natalizumab NCT02342704; 1 open label RCT in patients previously Rx with INF beta or GA; Study terminated; N = 108	McDonald 2010 criteria	18 to 64	36.5	0 to 5.5	NR	NR	NR	1 year	C: NR F: 69%
Teriflunomide vs INF beta 1a; 1 RCT; single blind; N = 324	McDonald 2005 criteria	18 years or older	35 to 37	0 to 5.5	2.0 to 2.3	7.0	1.3	66 weeks	C: 100% F: 67.6%
OVERALL	McDonald 2005/2010 criteria	18 to 65 years	35 to 46 years	0 to 5.5	2.0 to 2.6	4.3 to 7.0 years	1.3 to 1.5	1 to 1.5 years	C: 74 to 100% F: 66 to 77%

Since clinical outcome data was not reported for NCT02342704 (an RCT with 108 patients with RRMS comparing fingolimod vs natalizumab) we summarized baseline characteristics of oral drugs (fingolimod, DMF and teriflunomide) versus injectable drugs.

a. Total number of patients randomized in fingolimod vs other injectable MS drugs (N = 3488) was much higher compared to DMF vs GA (N = 709) and teriflunomide vs INF beta 1a (N =324).
b. The diagnostic criteria used were McDonald 2005 for all studies; however McDonald 2010 criteria were also used in 2 studies (NCT01633112 and Cree 2008).
c. The age range for inclusion was similar across studies ranging from 18 to 65 years, and so was the mean age (35 to 37 years) in most studies except for NCT01216072 study with mean age of 46 years comparing fingolimod to other injectable MS drugs.
d. The mean duration of the disease was ranging from (4 to 6 years) for most studies comparing fingolimod or DMF to injectable MS drugs as compared to 7 years for 1 study (TENERE 2014) comparing teriflunomide to other injectable MS drugs.
e. The EDSS score range from 0 to 5 was similar across studies but the mean/median EDSS score at baseline was lower in fingolimod and teriflunomide studies (2.0 to 2.4) as compared to mean EDSS score of 2.6 in DMF vs GA study (TENERE 2014).
f. The mean relapse rate was similar across all studies (1.3 to 1.5).

g. The mean duration of follow up was lower in fingolimod and teriflunomide studies ranging from 1 to 1.5 years as compared to 2 years in DMF vs GA study (CONFIRM 2012).

Comparing baseline characteristics in RCTs of RRMS patients treated with injectable drugs (INF beta 1a, INF beta 1b, GA)

TABLE C: Injectable MS drugs comparisons (See Appendix 2 for details relating to each individual study)

Comparison Total # studies N total randomized	Diagnostic criteria for RRMS	Age range (years)	Mean age (years)	EDSS range	Mean or median EDSS (SD)	Mean (SD) duration of MS since diagnosis (years)	Mean relapse rate (SD)	Follow up (weeks or years)	Caucasians (C) Female (F)%
GA vs INF beta 1a 4 RCTs; 2 open label; 1 single blind; and 1 double blind N =1453	Poser criteria McDonald 2001/2005 criteria	18 to 60	36 to 38	0 to 5.5	2.0 to 2.3	1 to 6	1.2 to 1.7	1.9 to 3 years	C: 88 to 94% F: 70 to 79%
GA vs INF beta 1b 2 RCTs; 1 open label; and 1 double blind; N = 2345	McDonald 2001 criteria	18 to 55	36	0 to 5.5	2.33	1 to 5	1.6 to 1.9	2 years	C: 52 to 92% F: 69%
INF beta 1a vs INF beta 1b; 5 RCTs; 3 open label; 1 single blind; and 1 double blind; N = 1382	Poser criteria McDonald 2005 criteria	15 to 65	28 to 41	0 to 6.0	2.0 to 3.0	1.5 to 7.8	1.3 to 3.2	12 weeks to 2 years	C: 66% to 91% F: 65 to 76%
INF beta 1a (Avonex) **vs INF beta 1a** (Rebif) **4 RCTs; 2 open label; 1 single blind and 1 double blind; N = 876**	Poser criteria McDonald 2005 criteria	18 to 65	29 to 38	0 to 6.0	2.0 to 2.3	3.2 to 6.6	1.2 to 2.6	1 to 2 years	C: 91 to 92% F: 65 to 76%
OVERALL	Poser criteria McDonald 2001/2005 criteria	18 to 65 years	28 to 41 years	0 to 6.0	2.0 to 3.0	1 to 7.8 years	1.2 to 3.2	12 weeks to 3 years	C: 52 to 94% F: 65 to 79%

a. Out of 15 studies using injectable MS drugs, the total number of patients randomized was greater in GA vs INF beta 1b (2 studies; N = 2345) compared to GA vs INF beta 1a (4 studies; N = 1453) and INF beta 1a vs INF beta 1b (5 studies; N = 1382) and INF beta 1a (Avonex) vs INF beta 1a (Rebif) (4 studies; N = 876).
b. The diagnostic criteria used were Poser criteria and McDonald 2005 criteria for most studies; McDonald 2001 criteria were used in four studies comparing GA vs INF beta 1b or INF beta 1a (REGARD 2008 and CombiRx 2013; BECOME 2009 and BEYOND 2009).
c. The age range for inclusion was similar across studies ranging from 15 to 65 years; however the mean age differed significantly across studies ranging from 28 to 41 years.
d. The mean duration of the disease also differed significantly between studies ranging from 1 to 7.8 years.
e. The EDSS score ranged from 0 to 5.5 or 6.0 and were similar across the 15 studies; the mean/median EDSS score was also similar across studies (2.0 to 2.3).
f. The mean relapse rate differed across the 15 studies ranging from 1.2 to 2.6.
g. The mean duration of follow up ranged from 12 weeks (1 study); to 3 years across the 15 studies.

10. APPENDIX 2

Details of the baseline characteristics in each included RCT in Appendix 1.

Table A1: Alemtuzumab vs INF beta 1a

Study detail	Diagnostic criteria for RRMS	Age range years	Mean age years	EDSS range	Mean or median EDSS (SD)	Mean (SD) duration of MS since diagnosis	Mean relapse rate (SD)	Follow up	Race % Female %
CAMMS223 2008 SBRCT; Rx naïve; N = 334	McDonald 2001 criteria	18 to 60	32.1 (8.4)	0 to 3.0	2.0 (0.74)	NR	1.2 (0.7)	3 years	White 90.1% Female 64%
CARE MS I; SBRCT; Rx naïve; N = 581	McDonald 2005 criteria	18 to 50	33.2 (8.5)	0 to 3.0	2.0 (0.8)	2.0 (1.4) years	1.8 (0.8)	2 years	White 95% Female 65%
CARE MS II; SBRCT; Pts failed on INF beta or GA after 6 months; N = 840	McDonald 2005 criteria	18 to 55	35.1 (8.5)	0 to 5.0	2.7 (1.17)	2.0 (1.3) years	1.7 (0.9)	2 years	White 90% Female 67%
Overall 3 studies; N = 1755	McDonald 2001/2005 criteria	18 to 60 years	32 to 35 years	0 to 5.0	2.0 to 2.7	2 years	1.2 to 1.8	2 to 3 years	White 90 to 95% Female 64 to 67%

Table A2: Natalizumab vs INF beta 1a or GA or fingolimod

Study detail	Diagnostic criteria for RRMS	Age range (years)	Mean age (years)	EDSS range	Mean or median EDSS (SD)	Mean (SD) duration of MS since diagnosis	Mean relapse rate (SD)	Follow up (weeks or years)	Race % Female %
NCT02342704; REVEAL Natalizumab vs fingolimod; Open label RCT; Rx previously with INF beta or GA; Study terminated; N = 108	McDonald 2010 criteria	18 to 64	36.5	0 to 5.5	NR	NR	NR	52 weeks	White NR Female 69%
SURPASS; NCT01058005 Natalizumab vs INF beta or GA; Open label RCT; previously Rx with INF beta or GA; Naïve to Natalizumab; N = 75	McDonald 2005 criteria	18 to 60	37.1	0 to 5.5	NR	NR	NR	108 weeks	White NR Female 79%
Overall 2 studies; N = 183	McDonald 2005/2010 criteria	18 to 64 years	37 years	0 to 5.5	NR	NR	NR	52 to 108 weeks	White NR Female 79%

Table A3: Ocrelizumab vs INF beta 1a (Rebif)

Study detail	Diagnostic criteria for RRMS	Age range years	Mean age years	EDSS range	Mean or median EDSS	Mean (SD) duration of MS since diagnosis	Mean relapse rate (SD)	Follow up Weeks or years	Race % Female %
OPERA I 2017; DBRCT; 73% patients were Rx naïve; N = 821	McDonald 2010 criteria	18 to55	37	0 to 5.5	2.5	3.8 years	1.31 (0.65)	96 weeks	White 90 Female 65%
OPERA II 2017; DBRCT; 73% patients were Rx naïve; N = 835	McDonald 2010 criteria	18 to 55	37	0 to 5.5	2.5	4.1 to 4.2 years	1.34 (0.73)	96 weeks	White 90 Female 65%
OVERALL 2 studies; N = 1656	McDonald 2010 criteria	18 to 55 years	37 years	0 to 5.5	2.5	3.8 to 4.2 years	1.31 to 1.34	96 weeks	White 90% Female 65%

Table A4: Teriflunomide vs INF beta 1a

Study detail	Diagnostic criteria for RRMS	Age range years	Mean age years	EDSS range	Mean or median EDSS (SD)	Mean (SD) duration of MS since diagnosis	Mean (SD) relapse rate	Follow up	Race % Female %
TENERE 2014 SBRCT; N = 324	McDonald 2005 criteria	18 years or older	35 to 37 (10.6)	0 to 5.5	2.0 to 2.3 (1.4)	7.0 (6.9) years	1.3 (0.8)	63.6 weeks	White 100% Female 67.6%
OVERALL 1 study; N = 324	McDonald 2005 criteria	18 years or older	35 to 37 years	0 to 5.5	2.0 to 2.3	7.0 years	1.3	63.6 weeks	White 100% Female 68%

Table A5: Dimethyl fumarate (DMF) vs Glatiramer acetate (GA)

Study detail	Diagnostic criteria for RRMS	Age range years	Mean age years	EDSS range	Mean or median EDSS (SD)	Mean (SD) duration of MS since diagnosis	Mean relapse rate	Follow up years	Race % Female %
CONFIRM 2012 DBRCT; N = 709	McDonald 2005 criteria	18 to 55	36.8	0 to 5.0	2.6	4.6 years	1.4	2 years	White 84% Female70%
OVERALL 1 study; N = 709	McDonald 2005 criteria	18 to 55 years	37 years	0 to 5.0	2.6	4.6 years	1.4	2 years	White 84% Female 70%

Table A6: Fingolimod vs other DMTs

Study detail	Diagnostic criteria for RRMS	Age range (years)	Mean (SD) age (years)	EDSS range	Mean or median EDSS (SD)	Mean (SD) duration of MS since diagnosis (years)	Mean relapse rate (SD)	Follow up (weeks or years)	Race % Female %
Cree BAC 2018; NCT01623596; Open label RCT Rx naïve or Rx with only 1 class of MS drug INF or GA; N = 861	McDonald 2010 criteria	18 to 65	42 (10.6)	0 to 6.0	2.4 (1.5)	4.3(6.3)	1.4	48 weeks	White 81% Female 73%
NCT01633112; ASSESS; DBRCT; N = 1064	McDonald 2010 criteria	18 to 65	40 (11.0)	0 to 6.0	NR	NR	NR	1 year	White 74% Female 74%
NCT01317004; EPOC; Open label RCT; Patients treated with a single drug previously but naïve to fingolimod; N = 61	McDonald 2005 criteria	18 to 65	37 (8.7)	0 to 5.5	NR	NR	NR	24 weeks	White NR Female 66%
NCT01534182; Open label RCT; patients Rx with a single drug previously but naïve to fingolimod; N = 298	McDonald 2005 criteria	18 to 70	36 (9.8)	0 to 6.0	NR	NR	NR	24 weeks	White NR Female 71%
NCT01333501; SB (rater blinded) RCT; N = 151	McDonald 2005 criteria	18 to 50	39 (9.3)	0 to 5.0	NR	NR	NR	1.5 years	White NR Female 65%
NCT01216072; Fox 2014; Open label RCT; Patients Rx with DMT but naïve to fingolimod; N = 1053	McDonald 2005 criteria	18 to 65	46 (9.8)	0 to 5.5	NR	NR	NR	24 weeks	White NR Female 77%
TRANSFORM; Cohen 2010; NCT003408334; Triple blind RCT; N = 861	Revised McDonald criteria	18 years or older	37 (8.8)	0 to 5.5	2.2(1.3)	6.2	1.5(1.2)	1 year	White 94% Female 68%
OVERALL 7 studies; N = 3488	McDonald 2005/2010 criteria	18 to 65 years	36 to 46 years	0 to 6.0	2.2 to 2.4	4.3 to 6.2 years	1.4 to 1.5	0.5 to 1 year	White 74% Female 66 to 77%

Table A7: Glatiramer Acetate (Copaxone) vs INF beta 1a (Avonex or Rebif)

Study detail	Diagnostic criteria for RRMS Poser or McDonald	Age range years	Mean age years	EDSS range	Mean or median EDSS (SD)	Mean (SD) duration of MS since diagnosis years	Mean relapse rate (SD)	Follow up Weeks or years	Race % Female %
Calaberse 2012; Open label RCT; Only MRI outcomes assessor was blinded; N = 141	Poser or McDonald criteria	18 to 55	36.5	0 to 5.0	2.1 (1.1)	5.6 (2.4) years	1.2 (0.7)	2 years	White 92% Female 70%
CombiRx 2013 DBRCT; N = 509	Poser or McDonald 2001 criteria	18 to 60	38.3	0 to 5.5	2.0	1.2 years	1.7	3 years	White 88% Female 70%
REGARD 2008 SB,RCT in Rx naïve patients; N = 764	McDonald 2001 criteria	18 to 60	36.8	0 to 5.5	2.34	6.2 years	NR	1.9 years	White 94% Female 71%
SURPASS; Open label RCT; Patients Rx with INF beta/GA but naïve to natalizumab; N = 39	McDonald 2005 criteria	18 to 60	37.1	0 to 5.5	NR	NR	NR	2.1 years	White NR Female 78.7%
OVERALL 4 studies; N = 1453	Poser or McDonald 2001/2005 criteria	18 to 60	36 to 38	0 to 5.5	2.0 to 2.3	1 to 6 years	1.2 to 1.7	1.9 to 3 years	White 88 to 94% Female 70 to 79%

Table A8: INF beta 1a vs INF beta 1b

Study detail	Diagnostic criteria for RRMS Poser or McDonald	Age range (years)	Mean age (SD) (years)	EDSS range	Mean (SD) or median EDSS	Mean duration of MS (SD) since diagnosis	Mean relapse rate (SD)	Follow up weeks or years	Race % Female %
Etemadifar 2006; SBRCT; N = 60	Poser criteria	15 to 50	28.5	0 to 5.0	2.0	3.2 years	2.2	2 years	Race – NR Female 76%
INCOMIN 2002; Open Label RCT; N = 188	Poser criteria	18 to 50	36.9	1 to 3.5	1.97	6.3 years	1.45	2 years	White 91% Female 75%
Koch-Henriksen 2006; Open label RCT; N = 301	Poser criteria	18 to 55	38	0 to 5.5	2.98	7.8	3.2	2 years	White 91% Female 66%
Mokhber 2012; DBRCT; N =69	McDonald 2005 criteria	18 to 65	29(7.95)	0 to 6.0	2.02	NR	NR	1 year	White NR Female 64.6%
REFORMS 2012; NCT00428584; Open label RCT; Patients Rx naïve to INF beta; N=764	Poser or McDonald 2005 criteria	18 to 60	40.5 (9.7) years	Not an entry criteria	NR	1.47 (3.3)	1.3 (0.5)	12 weeks	White 87.6% Female 70%
OVERALL 5 studies; N = 1382	Poser or McDonald 2005 criteria	15 to 65 years	28 to 41 years	0 to 6.0	2.0	1.5 to 6.3 years	1.3 to 2.2	12 weeks to 2 years	White 88 to 91% Female 65 to 76%

Table A9: INF beta 1a (Avonex) vs INF beta 1a (Rebif)

Study detail	Diagnostic criteria for RRMS Poser or McDonald	Age range years	Mean age years	EDSS range	Mean or median EDSS (SD)	Mean duration of MS since diagnosis (SD)	Mean relapse rate (SD)	Follow up weeks or years	Race % Female %
Calaberse 2012; Open label RCT; MRI assessors blinded; N = 93	Poser or McDonald criteria	18 to 55	36.5	0 to 5.0	2.1 (1.1)	5.6 (2.4) years	1.2 (0.7)	2 years	White 92% Female 70.2%
Etemadifar 2006; SBRCT; N = 60	Poser criteria	15 to 50	28.5	0 to 5.0	2.0	3.2 years	2.2	2 years	Race – NR Female 76%
EVIDENCE; Panitch 2002 SBRCT; Rx naïve patients; N = 677	Poser criteria	18 to 55	37.5	0 to 5.5	2.3	6.6 years	2.6	64 weeks	White 91% Female 75%
Mokhber 2012; DBRCT N = 46	McDonald 2005 criteria	18 to 65	29 (7.95)	0 to 6.0	2.02	NR	NR	1 year	White NR Female 64.6%
OVERALL 4 studies; N = 876	Poser and McDonald 2005 criteria	18 to 65 years	29 to 38 years	0 to 6.0	2.0 to 2.3	3.2 to 6.6 years	1.2 to 2.6	1 to 2 years	White 91 to 92% Female 65 to 76%

Table 10: GA vs INF beta 1b

Study detail	Diagnostic criteria for RRMS Poser or McDonald	Age range (years)	Mean age (year)	EDSS range	Mean or median EDSS	Mean (SD) duration of MS since diagnosis (years)	Mean relapse rate (SD)	Follow up (years)	Race % Female %
BECOME 2009; Open label RCT; MRI outcome assessors blinded; Rx naïve patients; N = 75	McDonald 2001 criteria (19% pts with Clinically isolated syndrome	18 to 55	36	0 to 5.5	2.0	0.9 to 1.2	1.8 to 1.9	2 years	White 52% Female 69%
BEYOND 2009 DBRCT; N = 2270	McDonald`s criteria 2001	18 to 55	35.6	0 to 5.0	2.33	5.2 years	1.6	2 years	White 92% Female 69%
OVERALL 2 studies; N = 2345	McDonald 2001 criteria	18 to 55 years	36 years	0 to 5.5	2.33	1 to 5 years	1.6 to 1.9	2 years	White 52 to 92% Female 69%