

Drug Class Review on Disease-modifying drugs for Multiple Sclerosis

Update #1: Preliminary Scan Report #2

July 2009

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, Director
Marian S. McDonagh, PharmD, Principal
Investigator
Drug Effectiveness Review Project

Update Scan conducted by Susan Carson, MPH



Copyright © 2009 by Oregon Health & Science University
Portland, Oregon 97239. All rights reserved.

OBJECTIVE

The purpose of this preliminary updated literature scan process is to provide the Participating Organizations with a preview of the volume and nature of new research that has emerged subsequent to the previous full review process. Provision of the new research presented in this report is meant only to assist with Participating Organizations' consideration of allocating resources toward a full update of this topic. Comprehensive review, quality assessment and synthesis of evidence from the full publications of the new research presented in this report would follow only under the condition that the Participating Organizations ruled in favor of a full update. The literature search for this report focuses only on new randomized controlled trials, and actions taken by the FDA or Health Canada since the last report. Other important studies could exist.

Date of Last Update

The Original Final Report was completed in July 2007 (searches through September 2006).

Date of Last Preliminary Update Scan

June 2008

Scope and Key Questions

Key Questions

1. What is the comparative effectiveness of disease-modifying treatments for multiple sclerosis, including use of differing routes and schedules of administration?
2. What is the comparative tolerability and safety of disease-modifying treatments for multiple sclerosis?
3. What is the effectiveness of disease-modifying treatments for patients with a clinically isolated syndrome?
4. Are there subgroups of patients based on demographics (age, racial or ethnic groups, and gender), other medications, or co-morbidities for which one disease-modifying treatment is more effective or associated with fewer adverse events?

Study inclusion criteria

Population(s)

Adult outpatients with Multiple Sclerosis

- Relapsing Remitting MS (RRMS)
- Secondary Progressive MS (SPMS)
- Primary Progressive MS (PPMS)
- Progressive Relapsing MS (PRMS)

Adult outpatients with a clinically isolated syndrome (also known as 'first demyelinating event', first clinical attack suggestive of MS, or monosymptomatic presentation)

Interventions (all formulations)

- Glatiramer acetate (Copaxone[®])
- Interferon β 1a (Avonex[®], Rebif[®])
- Interferon β 1b (Betaseron[®])
- Mitoxantrone (Novantrone[®])
- Natalizumab (Tysabri[®])
-

Effectiveness outcomes

Multiple Sclerosis

- Disability
- Clinical exacerbation/relapse
- Quality of life
- Functional outcomes (e.g. wheel-chair use, time lost from work)
- Persistence (discontinuation rates)

Clinically isolated syndrome

- Disability
- Clinical exacerbation/relapse
- Quality of life
- Functional outcomes (e.g. wheel-chair use, time lost from work)
- Persistence (discontinuation rates)
- Progression to MS diagnosis

Note: MRI findings are not included, as they are intermediate or surrogate outcomes.

Safety outcomes

- Overall rate of adverse effects
- Withdrawals due to adverse effects
- Serious adverse events
- Specific adverse events (cardiovascular, hepatotoxicity, progressive multifocal leukoencephalopathy (PML), secondary cancers, etc.)
-

Other outcomes

- Interferon β neutralizing antibodies
 - Rates of occurrence
 - Persistence with continued use
 - Impact on clinical outcomes (above)

Study designs

- For effectiveness, controlled clinical trials and good-quality systematic reviews. Observational studies with two concurrent arms of at least 100 patients each and duration ≥ 1 year will be included (e.g. cohort, case-control).
- For safety, in addition to controlled clinical trials, observational studies will be included.

METHODS**Literature Search**

To identify relevant citations, we searched MEDLINE starting from the date of the last preliminary update scan (June 2008 through July 28, 2009). We used terms for included drugs and limits for humans, English and controlled clinical trials. We also searched FDA (<http://www.fda.gov/medwatch/safety.htm>) and Health Canada ([MS Drugs
Update #1](http://www.hc-sc.gc.ca/dhp-</p>
</div>
<div data-bbox=)

mps/medeff/advisories-avis/prof/index-eng.php) websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0[®]) and duplicate citations were removed.

Study Selection

One reviewer assessed abstracts of citations identified from literature searches for inclusion, using the criteria described above.

RESULTS

Overview

We identified 103 new citations in this scan. Of those, there are 8 new potentially relevant trials (Appendix A). Six of these are new trials and 2 are secondary analyses of already-included trials; 2 are head-to-head trials (Mikol 2008 and Minagara 2008). Table 1 provides details of the populations and treatment comparisons addressed in the publications.

Table 1. Studies identified in the current Preliminary Update Scan

Author Year Trial Name	Population	Notes
<i>New Trials</i>		
Camms Trial Investigators 2008 CAMMS	Early RRMS	Alemtuzumab vs interferon beta-1a; Alemtuzumab arm discontinued early for adverse events
Goodman 2009 GLANCE	RRMS	Natalizumab added to glatiramer vs glatiramer alone; Primary outcome MRI, has safety results
Hurwitz 2008	RRMS	Interferon beta-1b 250 mcg vs 500 mcg Dose-ranging pilot study
Mikol 2008 REGARD	RRMS	Interferon beta-1a vs glatiramer acetate; Head-to-head trial
Minagara 2008 PROOF	RRMS	IM interferon beta-1a (Avonex) vs SC interferon beta-1b (Rebif); Head-to-head trial
Vollmer 2008	RRMS	Glatiramer after mitoxantrone induction therapy vs glatiramer alone; Primary outcome was incidence of adverse events
<i>Secondary Publications of Existing Trials</i>		
Havrdova 2009 AFFIRM	RRMS	Post hoc analysis of AFFIRM: proportion free of disease activity over 2 years
Polman 2008 BENEFIT	CIS	Subgroup analysis of BENEFIT: Treatment effects in subgroups based on demographics, clinical and laboratory findings

Table 2 shows the studies identified in the previous preliminary update scan.

Table 2. Studies identified in Preliminary Update Scan #1 (June 2008)

Author Year	Population	Notes
<i>New Trials</i>		
Pakdaman 2007	CIS	Avonex vs placebo
Bonavita 2006	Unclear	Avonex vs Betaseron vs Rebif
Phillips 2006	Unclear	Natalizumab-related hypersensitivity reactions: Eligibility pending confirmation of study design, duration and sample size – unclear if this is a trial.
<i>Secondary Publications of Existing Trials</i>		
Kappos 2007	CIS	BENEFIT (Betaseron vs placebo): Secondary analyses of early vs delayed treatment from 3-year follow-up phase
Balcer 2007	RRMS	Pooled analysis of visual acuity outcome data from previously included AFFIRM and SENTINEL: natalizumab vs placebo
Rudick 2007	RRMS	Pooled analysis of QOL data from previously included AFFIRM and SENTINEL: natalizumab vs placebo
Schwid 2007	RRMS	Full results from EVIDENCE: Rebif vs Avonex

New Drugs

No new disease-modifying drugs for multiple sclerosis were identified.

New Indications

Glatiramer acetate (Copaxone[®]): Approved for reduction of the frequency of relapses in patients with Relapsing-Remitting Multiple Sclerosis, including patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis [February 2009].

New Safety Alerts

Natalizumab (Tysabri[®]): FDA informed healthcare professionals of two new cases of progressive multifocal leukoencephalopathy (PML) in European patients receiving Tysabri monotherapy for multiple sclerosis for more than one year. PML, which is usually fatal, is a known risk of Tysabri treatment, but previous cases in patients with multiple sclerosis were seen in combination with other immunomodulatory therapies. Approximately 39,000 patients have received treatment with Tysabri worldwide, with approximately 12,000 patients receiving treatment for a least one year. No new cases have been seen in the US, where about 7,500 patients have received the drug for greater than one year and approximately 3,300 patients have received the drug for at least one and one-half years. In the U.S., Tysabri is available only to patients with relapsing multiple sclerosis or Crohn's disease who are enrolled in the risk minimization plan called the TOUCH Prescribing Program. Under this program, every Tysabri-treated patient is closely monitored and followed for the occurrence of PML and other serious opportunistic infections. While the two patients who developed PML were on monotherapy, the

FDA still believes that Tysabri monotherapy may confer a lower risk of PML than when Tysabri is used together with other immunomodulatory medications. Prescribing information for Tysabri will be revised to include information informing prescribers and patients that cases of PML have occurred in patients taking Tysabri as monotherapy. Healthcare professionals should continue to monitor patients for sign and symptoms of PML. Additionally, Tysabri should not be infused if PML is suspected. [Posted 08/25/2008]

APPENDIX A. Abstracts of potentially relevant trials (N=8)

Camms Trial Investigators, A. J. Coles, et al. (2008). "Alemtuzumab vs. interferon beta-1a in early multiple sclerosis.[see comment]." New England Journal of Medicine **359**(17): 1786-801.

BACKGROUND: Alemtuzumab, a humanized monoclonal antibody that targets CD52 on lymphocytes and monocytes, may be an effective treatment for early multiple sclerosis. **METHODS:** In this phase 2, randomized, blinded trial involving previously untreated, early, relapsing-remitting multiple sclerosis, we assigned 334 patients with scores of 3.0 or less on the Expanded Disability Status Scale and a disease duration of 3 years or less to receive either subcutaneous interferon beta-1a (at a dose of 44 microg) three times per week or annual intravenous cycles of alemtuzumab (at a dose of either 12 mg or 24 mg per day) for 36 months. In September 2005, alemtuzumab therapy was suspended after immune thrombocytopenic purpura developed in three patients, one of whom died. Treatment with interferon beta-1a continued throughout the study.

RESULTS: Alemtuzumab significantly reduced the rate of sustained accumulation of disability, as compared with interferon beta-1a (9.0% vs. 26.2%; hazard ratio, 0.29; 95% confidence interval [CI], 0.16 to 0.54; $P < 0.001$) and the annualized rate of relapse (0.10 vs. 0.36; hazard ratio, 0.26; 95% CI, 0.16 to 0.41; $P < 0.001$). The mean disability score on a 10-point scale improved by 0.39 point in the alemtuzumab group and worsened by 0.38 point in the interferon beta-1a group ($P < 0.001$). In the alemtuzumab group, the lesion burden (as seen on T(2)-weighted magnetic resonance imaging) was reduced, as compared with that in the interferon beta-1a group ($P = 0.005$). From month 12 to month 36, brain volume (as seen on T(1)-weighted magnetic resonance imaging) increased in the alemtuzumab group but decreased in the interferon beta-1a group ($P = 0.02$). Adverse events in the alemtuzumab group, as compared with the interferon beta-1a group, included autoimmunity (thyroid disorders [23% vs. 3%] and immune thrombocytopenic purpura [3% vs. 1%]) and infections (66% vs. 47%). There were no significant differences in outcomes between the 12-mg dose and the 24-mg dose of alemtuzumab.

CONCLUSIONS: In patients with early, relapsing-remitting multiple sclerosis, alemtuzumab was more effective than interferon beta-1a but was associated with autoimmunity, most seriously manifesting as immune thrombocytopenic purpura. The study was not powered to identify uncommon adverse events. (ClinicalTrials.gov number, NCT00050778.) 2008 Massachusetts Medical Society

Goodman, A. D., H. Rossman, et al. (2009). "GLANCE: results of a phase 2, randomized, double-blind, placebo-controlled study." Neurology **72**(9): 806-12.

OBJECTIVE: To evaluate the safety and tolerability of natalizumab when added to glatiramer acetate (GA) in patients with relapsing multiple sclerosis. The primary outcome assessed whether this combination would increase the rate of development of new active lesions on cranial MRI scans vs GA alone. **METHODS:** This phase 2, randomized, double-blind, placebo-controlled study included patients aged 19 to 55 years who were treated with GA for at least 1 year before randomization and experienced at least one relapse during the previous year. Patients received IV natalizumab 300 mg ($n = 55$) or placebo ($n = 55$) once every 4 weeks plus GA 20 mg subcutaneously once daily for $< \text{or} = 20$ weeks. **RESULTS:** The mean rate of development of new active lesions was 0.03 with combination therapy vs 0.11 with GA alone ($p = 0.031$). Combination therapy resulted in lower mean numbers of new gadolinium-enhancing lesions (0.6 vs 2.3 for GA

alone, $p = 0.020$) and new/newly enlarging T2-hyperintense lesions (0.5 vs 1.3, $p = 0.029$). The incidence of infection and infusion reactions was similar in both groups; no hypersensitivity reactions were observed. One serious adverse event occurred with combination therapy (elective hip surgery). With the exception of an increase in anti-natalizumab antibodies with combination therapy, laboratory data were consistent with previous clinical studies of natalizumab alone. **CONCLUSION:** The combination of natalizumab and glatiramer acetate seemed safe and well tolerated during 6 months of therapy.

Havrdova, E., S. Galetta, et al. (2009). "Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study.[see comment]." Lancet Neurology **8**(3): 254-60.

BACKGROUND: The efficacy of natalizumab on clinical and radiological measures in the phase III Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study has prompted the investigation of whether natalizumab can increase the proportion of patients with relapsing-remitting multiple sclerosis who do not have disease activity. **METHODS:** Post-hoc analyses of data from the AFFIRM study were done to determine the effects of natalizumab compared with placebo on the proportion of patients who were free of disease activity over 2 years. Absence of disease activity was defined as no activity on clinical measures (no relapses and no sustained disability progression), radiological measures (no gadolinium-enhancing lesions and no new or enlarging T2-hyperintense lesions on cranial MRI), or a composite of the two. **FINDINGS:** 383 (64%) of 596 patients taking natalizumab and 117 (39%) of 301 taking placebo were free of clinical disease activity (absolute difference 25.4%, 95% CI 18.7-32.1%, $p < 0.0001$); 342 (58%) of 593 and 42 (14%) of 296 were free of radiological disease activity (43.5%, 37.9-49.1%, $p < 0.0001$); and 220 (37%) of 600 and 22 (7%) of 304 were free of combined activity (29.5%, 24.7-34.3%, $p < 0.0001$) over 2 years. The effect of natalizumab versus placebo was consistent across subgroups of patients with highly active or non-highly active disease at baseline. **INTERPRETATION:** Disease remission might become an increasingly attainable goal in multiple sclerosis treatment with the use of newer, more effective therapies.

Hurwitz, B. J., D. Jeffery, et al. (2008). "Tolerability and safety profile of 12- to 28-week treatment with interferon beta-1b 250 and 500 microg QOD in patients with relapsing-remitting multiple sclerosis: a multicenter, randomized, double-blind, parallel-group pilot study." Clinical Therapeutics **30**(6): 1102-12.

BACKGROUND: It is not known whether the currently available treatment regimen of interferon beta-1b (IFNbeta-1b) 250 microg provides the maximum benefit possible in the treatment of relapsing-remitting multiple sclerosis (RRMS), or whether higher doses of IFNbeta-1b will prove to be more beneficial. **OBJECTIVE:** The objective of the present study was to evaluate the tolerability and safety profile of IFNbeta-1b 500 microg compared with the currently approved 250-microg dose. **METHODS:** A multicenter, randomized, double-blind, parallel-group pilot study was carried out to compare IFNbeta-1b 250 microg with IFNbeta-1b 500 microg, both self-administered SC QOD for ≥ 12 weeks in patients with RRMS. Patients in both groups started with 25% (0.25 mL) of their final dose and were scheduled to increase the dose by 0.25 mL every 2 weeks, so

that the full dose (1.0 mL, 250 microg or 500 microg) would be reached by week 7. The primary outcome measure was the percentage of patients experiencing each of the following adverse events (AEs): influenza-like symptoms (general term used to code the presence of >1 symptom typical of influenza), fever, myalgia, asthenia, headache, injection-site reactions, injection-site pain, or liver or hematologic abnormalities. All patients underwent a priori magnetic resonance imaging (MRI) with 0.1 mmol/kg gadolinium (Gd)-diethylenetriaminepentaacetic acid as contrast medium at screening and at week 12. MRI evaluation was included as a safety measure to monitor for excessive new disease not visible through clinical symptoms. RESULTS: Seventy-seven patients were assessed for inclusion in the study. Of these, 6 patients were screening failures and the remaining 71 were randomized to treatment (38-250 and 33-500 microg IFNbeta-1b). The uneven numbers in the groups were a consequence of the randomization process. Two patients in the 250-microg group (withdrawal of consent) and 1 in the 500-microg group (not completing follow-up visit) prematurely discontinued medication. The demographic characteristics were not significantly different between the 250-microg (n=38; mean [SD] age, 37.9 [8.3] years; weight, 83.5 [19.0] kg; height, 168.4 [9.3] cm) and 500-microg (n=33; mean [SD] age, 37.8 [7.7] years; weight, 82.3 [19.5] kg; height, 169.9 [10.5] cm) treatment groups. The patients in both groups were mostly white (87% and 73%, respectively). Baseline Expanded Disability Status Scale scores also were not significantly different between the 2 groups (mean [SD] score, 2.8 [1.4] vs 2.0 [1.4], respectively). In the IFN(2)-1b 250-microg group, 97% of the patients titrated to the full dose at some point during the course of the study, compared with 91% of the 500-microg group (P=NS). A dose-response effect was observed in some of the more frequent AEs (no. [%]) that included influenza-like syndrome (250-microg group, 13 [34] vs 500-microg group, 16 [48]), asthenia (13 [34] vs 16 [48], respectively), headache (12 [32] vs 12 [36]), myalgia (10 [26] vs 13 [39]), hypesthesia (10 [26] vs 11 [33]), nausea (6 [16] vs 8 [24]), paresthesia (6 [16] vs 8 [24]), myasthenia (4 [11] vs 8 [24]), chills (3 [8] vs 6 [18]), depression (3 [8] vs 5 [15]), back pain (2 [5] vs 5 [15]), increased liver enzymes (4 [11] vs 6 [18]), lymphopenia (4 [11] vs 3 [9]), fever (2 [5] vs 4 [12]), and pain in extremities (1 [3] vs 4 [12]). The between-group incidence of injection-site reactions was not significantly different. No new or unexpected AEs were recorded. Changes in MRI parameters between screening and 12 weeks were not significantly different between dose groups; these included median T2 lesion volume, median Gd-enhanced lesion volume, median Gd-enhanced lesion number, and mean number of newly active lesions. CONCLUSIONS: IFNbeta-1b 500 microg administered SC QOD was generally well tolerated in these patients with RRMS. Large, randomized controlled studies are needed to determine if there are significant differences in MRI end points between the 250- and 500-microg doses.

Mikol, D. D., F. Barkhof, et al. (2008). "Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial.[see comment]." *Lancet Neurology* 7(10): 903-14.

BACKGROUND: Interferon beta-1a and glatiramer acetate are commonly prescribed for relapsing-remitting multiple sclerosis (RRMS), but no published randomised trials have directly compared these two drugs. Our aim in the REGARD (REbif vs Glatiramer Acetate in Relapsing MS Disease) study was to compare interferon beta-1a with

glatiramer acetate in patients with RRMS. **METHODS:** In this multicentre, randomised, comparative, parallel-group, open-label study, patients with RRMS diagnosed with the McDonald criteria who had had at least one relapse within the previous 12 months were randomised to receive 44 mug subcutaneous interferon beta-1a three times per week or 20 mg subcutaneous glatiramer acetate once per day for 96 weeks to assess the time to first relapse. A subpopulation of 460 patients (230 from each group) also had serial MRI scans to assess T2-weighted and gadolinium-enhancing lesion number and volume. Treatments were assigned by a computer-generated randomisation list that was stratified by centre. Analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT00078338. **FINDINGS:** Between February and December, 2004, 764 patients were randomly assigned: 386 to interferon beta-1a and 378 to glatiramer acetate. After 96 weeks, there was no significant difference between groups in time to first relapse (hazard ratio 0.94, 95% CI 0.74 to 1.21; $p=0.64$). Relapse rates were lower than expected: 258 patients (126 in the interferon beta-1a group and 132 in the glatiramer acetate group) had one or more relapses (the expected number was 460). For secondary outcomes, there were no significant differences for the number and change in volume of T2 active lesions or for the change in the volume of gadolinium-enhancing lesions, although patients treated with interferon beta-1a had significantly fewer gadolinium-enhancing lesions (0.24 vs 0.41 lesions per patient per scan, 95% CI -0.4 to 0.1; $p=0.0002$). Safety and tolerability profiles were consistent with the known profiles for both compounds. The overall number and severity of adverse events were similar between the treatments and were not an important cause for discontinuation of the trial during the 96 weeks. **INTERPRETATION:** There was no significant difference between interferon beta-1a and glatiramer acetate in the primary outcome. The ability to predict clinical superiority on the basis of results from previous studies might be limited by a trial population with low disease activity, which is an important consideration for ongoing and future trials in patients with RRMS.

Minagara, A., T. J. Murray, et al. (2008). "Efficacy and tolerability of intramuscular interferon beta-1a compared with subcutaneous interferon beta-1a in relapsing MS: results from PROOF." Current Medical Research & Opinion **24**(4): 1049-55.

OBJECTIVE: Benefits from interferon beta (IFNbeta) treatment in patients with multiple sclerosis are affected by many factors, including sustained clinical efficacy, acceptable tolerability, adherence to therapy, and the development of neutralizing antibodies (NAbs). The Prospective and Retrospective Long-Term Observational Study of Avonex and Rebif (PROOF) was designed to compare the relative efficacy and tolerability of the two IFNbeta-1a products for up to 5 years. **METHODS:** PROOF compared the relative efficacy and tolerability of intramuscular (IM) IFNbeta-1a (Avonex) 30 microg once weekly ($n = 69$) and subcutaneous (SC) IFNbeta-1a (Rebif) 44 microg three times per week ($n = 67$). The duration of the retrospective portion of the study was 12-24 months. Due to slow enrollment, PROOF ended earlier than planned and the final duration of the prospective portion of the study was 6 months. Therefore, between 18 and 30 months of efficacy and tolerability data were available for analysis. **RESULTS:** After controlling for baseline disability level, Expanded Disability Status Scale (EDSS) scores revealed no statistically significant differences between the treatment groups during the prospective portion of the study, with sustained disability progression similar in both groups (25.8% IM IFNbeta-1a 30 mug once weekly vs. 26.7% SC IFNbeta-1a 44 mug three times per

week). Relapse rates were similar in the groups, as were MRI endpoints of brain parenchymal fraction, T1 lesion volume, T2 lesion volume, number of new/enlarging T2 lesions, and gadolinium-enhancing (Gd+) lesion volume and count. Treatment groups differed in frequency of NABs, with 19% of patients treated with SC IFNbeta-1a 44 microg three times per week NAb+ compared with none treated with IM IFNbeta-1a 30 microg once weekly. More NAb+ patients compared with NAb- patients had disability progression (40.0% vs. 27.8%, $p = \text{NS}$), new or enlarging T2 lesions at the end of treatment (63.6% vs. 40.7%, $p = 0.003$), and Gd+ lesions after 12-24 months of treatment (36.4% vs. 15%, $p = 0.001$). The IFNbeta-1a products had comparable tolerability. However, fewer patients treated with IM IFNbeta-1a 30 microg once weekly had injection-site reactions (2.9% vs. 6.0%). Limitations of this study include its design and sample size, both of which hinder detection of differences in efficacy between IFNbeta-1a treatments. **CONCLUSIONS:** The results of the present study show that the two IFNbeta-1a products have comparable efficacy and differing immunogenicity.

Polman, C., L. Kappos, et al. (2008). "Subgroups of the BENEFIT study: risk of developing MS and treatment effect of interferon beta-1b." *Journal of Neurology* **255**(4): 480-7.

BACKGROUND : The BENEFIT study examined interferon beta (IFNB)-1b treatment in patients with clinically isolated syndrome (CIS) and ≥ 2 clinically silent brain MRI lesions. **METHODS :** Subgroups of 468 patients (IFNB-1b: $n = 292$; placebo: $n = 176$) were created for demographics, clinical, laboratory, and MRI findings at onset. The 'natural' risk of clinically definite MS (CDMS) over 2 years was estimated by Kaplan Meier statistics in placebo-treated patients; the IFNB-1b treatment effect was analysed by Cox proportional hazards regression. **RESULTS :** The risk of CDMS was increased in placebo-treated patients (overall 45 %) if they were younger (< 30 years: 60%), were cerebrospinal fluid (CSF)-positive (49 %), or had received steroid treatment (48 %). MRI parameters implied a higher risk in placebo-treated patients with ≥ 9 T2-lesions (48%) or ≥ 1 gadolinium (Gd)-enhancing lesions (52 %). The CDMS risk was highest (75 %) in placebo-treated patients with monofocal disease onset displaying MRI disease activity (≥ 1 Gd-lesion) and dissemination (≥ 9 T2-lesions). Treatment effects were significant across almost all subgroups including patients with less disease dissemination/activity at onset (monofocal: 55%; < 9 T2-lesions: 60%; no Gd-lesions: 57%) and patients without steroid treatment for the CIS (62 %). Monofocal patients had greater treatment effects if they had ≥ 9 T2-lesions (61 %), Gd-lesions (58 %), or both (65 %). **CONCLUSIONS :** This study confirms the impact of age of onset, CSF and MRI findings on risk of conversion from CIS to CDMS. IFNB-1b treatment effect was robust across the study population including patients without MRI disease activity and less clinical or MRI disease dissemination at onset and patients not receiving steroids for the CIS.

Vollmer, T., H. Panitch, et al. (2008). "Glatiramer acetate after induction therapy with mitoxantrone in relapsing multiple sclerosis." *Multiple Sclerosis* **14**(5): 663-70.

Forty relapsing multiple sclerosis patients with 1-15 gadolinium (Gd)-enhancing lesions on screening brain magnetic resonance imaging (MRI) and Expanded Disability Status Scale (EDSS) scores 0-6.5 were randomized to receive short-term induction therapy with mitoxantrone (three monthly 12 mg/m²) infusions) followed by 12 months of daily

glatiramer acetate (GA) therapy 20 mg/day subcutaneously for a total of 15 months (M-GA, n = 21) or daily GA 20 mg/day for 15 months (GA, n = 19). MRI scans were performed at months 6, 9, 12 and 15. The primary measure of outcome was the incidence of adverse events; secondary measures included number of Gd-enhanced lesions, confirmed relapses and EDSS changes. Except age, baseline demographic characteristics were well matched in both treatment arms. Both treatments were safe and well tolerated. M-GA induction produced an 89% greater reduction (relative risk (RR) = 0.11, 95% confidence interval (CI): 0.04-0.36, p = 0.0001) in the number of Gd-enhancing lesions at months 6 and 9 and a 70% reduction (RR = 0.30, 95% CI: 0.11-0.86, p = 0.0147) at months 12 and 15 versus GA alone. Mean relapse rates were 0.16 and 0.32 in the M-GA and GA groups, respectively. Short-term immunosuppression with mitoxantrone followed by daily GA for up to 15 months was found to be safe and effective, with an early and sustained decrease in MRI disease activity.