

Drug Class Review on Disease-modifying drugs for Multiple Sclerosis

Update #1: Preliminary Scan Report #1

June 2008

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 Kim Peterson, MS



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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 of 2007. This is the first preliminary scan for consideration of a full update.

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[®])
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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.)
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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 (September 2006 to June 2008). We used terms for included drugs and limits for humans, English and controlled clinical trials. We searched FDA and Health Canada websites for identification of new drugs, indications, and safety alerts. All citations were imported into an electronic database (EndNote 9.0).

Study Selection

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

RESULTS

Overview

We identified 111 new citations in this scan. Of those, there are 7 new potentially relevant publications (Appendix A). The table below provides details of the populations and treatment comparisons addressed in the publications. Four publications report further analyses of previously included trials. None evaluated head-to-head comparisons involving glatiramer, mitoxantrone or natalizumab.

Author Year	Population	Notes
New Trials		
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.
Secondary Publications of Existing Trials		
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 identified. Corticotropin injectable (H.P. Acthar gel[®]) is approved for treating acute exacerbations, as are injectable corticosteroids.

New Indications

In January 2008, natalizumab was granted FDA approval for use in “inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn’s Disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF- α .” The supplemental report issued regarding this approval can be accessed at:

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist

New Safety Alerts

Also described in the supplemental report from January 2008 are the following safety-related changes to the natalizumab product label:

Warnings and Precautions:

1. Additional information added about 3 cases of Progressive Multifocal Leukoencephalopathy (PML) that led to addition of boxed warning and initiation of special distribution program in June 2006.
2. Information about increased risks for infections (section 5.4) and hepatotoxicity (section 5.5)

Adverse Reactions:

1. Information about rare, but serious adverse events reported in the pivotal trials of patients with Crohn's Disease (intestinal obstruction or stenosis, acute hypersensitivity reactions, abdominal adhesions, and cholelithiasis)
2. Information about more common adverse events reported in the pivotal trials of patients with Crohn's Disease, which are generally similar to those reported in trials of patients with MS.

APPENDIX A

Balcer, L. J., S. L. Galetta, et al. (2007). "Natalizumab reduces visual loss in patients with relapsing multiple sclerosis." *Neurology* **68**(16): 1299-304.

OBJECTIVE: To examine the effects of natalizumab on low-contrast letter acuity as a prespecified tertiary endpoint in two randomized clinical trials and to evaluate the usefulness of low-contrast letter acuity testing as a candidate test of visual function in multiple sclerosis (MS). **METHODS:** AFFIRM and SENTINEL were randomized, double-blind, placebo-controlled, multicenter, phase 3 clinical trials of natalizumab in relapsing MS. Natalizumab was evaluated as monotherapy in AFFIRM and as add-on to interferon beta-1a in SENTINEL. Vision testing was performed at 100% contrast (visual acuity) and low-contrast (2.5% and 1.25%). **RESULTS:** The risk of clinically significant visual loss (predefined as a two-line worsening of acuity sustained over 12 weeks) at the lowest contrast level (1.25%) was reduced in the natalizumab treatment arms by 35% in AFFIRM (hazard ratio = 0.65; 95% CI: 0.47 to 0.90; p = 0.008) and by 28% in SENTINEL (hazard ratio = 0.72; 95% CI: 0.54 to 0.98; p = 0.038, Cox proportional hazards models). Mean changes in vision scores from baseline were also significantly different, reflecting worsening in non-natalizumab groups. **CONCLUSIONS:** Natalizumab reduces visual loss in patients with relapsing multiple sclerosis. Low-contrast acuity testing has the capacity to demonstrate treatment effects and is a strong candidate for assessment of visual outcomes in future multiple sclerosis trials.

Bonavita, S., D. Dinacci, et al. (2006). "Treatment of multiple sclerosis with interferon beta in clinical practice: 2-year follow-up data from the South Italy Mobile MRI Project." *Neurological Sciences* **27 Suppl 5**: S365-8.

This follow-up study assessed the 2-year clinical and magnetic resonance imaging (MRI) outcomes of patients with multiple sclerosis (MS) originally enrolled in an MRI study conducted at eight centres in south Italy (the South Italy Mobile MRI Project). Of the 597 MS patients recruited at baseline, 391 returned for the follow-up study. Of these, 363 provided 2-year clinical and MRI follow-up data, and 215 were still undergoing treatment with one of four interferon beta regimens: Avonex, 30 mcg intramuscularly once weekly; Betaferon, 250 mcg subcutaneously (sc) every other day; Rebif 22 mcg sc three times weekly (tiw; Rebif 22); or Rebif 44 mcg sc tiw (Rebif 44). Over the 2-year follow-up period, patients receiving the higher dose of Rebif were more likely to remain **free from relapses** [odds ratio (OR) = 2.23] and from developing both new T2 (OR = 0.15) and new T1 black hole lesions (OR = 0.22), when compared with patients in the Avonex group. Despite some limitations in the trial design, the results from this follow-up study provide helpful clinical and MRI data on the efficacy of interferon beta regimens in MS patients treated in the clinical setting.

Kappos, L., M. S. Freedman, et al. (2007). "Effect of early versus delayed interferon beta-1b treatment on disability after a first clinical event suggestive of multiple sclerosis: a 3-year follow-up analysis of the BENEFIT study.[see comment]." *Lancet* **370**(9585): 389-97.

BACKGROUND: Several controlled studies provide evidence that treatment with interferon beta in patients with a first event suggestive of multiple sclerosis (MS) delays conversion to clinically definite MS (CDMS). Our aim was to determine whether early

initiation of treatment with interferon beta prevents development of confirmed disability in MS. **METHODS:** In the initial placebo-controlled phase of the double-blinded BENEFIT study, patients with a first event suggestive of MS and a minimum of two clinically silent lesions in MRI were randomised to receive either interferon beta-1b 250 microg (n=292) or placebo (n=176) subcutaneously every other day for 2 years, or until diagnosis of CDMS. Patients were then eligible to enter the follow-up phase with open-label interferon beta-1b. In the current prospectively planned analysis 3 years after randomisation, the effects of early interferon beta-1b treatment were compared with those of delayed treatment initiated after diagnosis of CDMS or after 2 years on the study. The primary outcomes of this ITT analysis were time to diagnosis of CDMS, time to confirmed expanded disability status scale (EDSS) progression, and score on a patient-reported functional assessment scale (FAMS-TOI). This trial is registered with ClinicalTrials.gov, number NCT00185211. **FINDINGS:** Of the 468 patients originally randomised, 418 (89%) entered the follow-up phase; 392 (84%) completed 3 years' post-randomisation follow-up. After 3 years, 99 (37%) patients in the early group developed CDMS compared with 85 (51%) patients in the delayed treatment group. Early treatment reduced the risk of CDMS by 41% (hazard ratio 0.59, 95% CI 0.44-0.80; p=0.0011; absolute risk reduction 14%) compared with delayed treatment. Over 3 years, 42 (16%) patients in the early group and 40 (24%) in the delayed group had confirmed EDSS progression; early treatment reduced the risk for progression of disability by 40% compared with delayed treatment (0.60, 0.39-0.92; p=0.022; absolute risk reduction 8%). The FAMS-TOI score was high and stable in both groups over the 3-year period (p=0.31). **INTERPRETATION:** Our data suggest that early initiation of treatment with interferon beta-1b prevents the development of confirmed disability, supporting its use after the first manifestation of relapsing-remitting MS.

Pakdaman, H., M. A. Sahraian, et al. (2007). "Effect of early interferon beta-1a therapy on conversion to multiple sclerosis in Iranian patients with a first demyelinating event." *Acta Neurologica Scandinavica* **115**(6): 429-31.

BACKGROUND: A new treatment approach to multiple sclerosis (MS) is the initiation of interferon therapy in the early phase of the disease when a patient presents with clinically isolated syndrome. **AIMS OF THE STUDY:** The goal of this study was to assess the effect of early treatment on the risk of conversion to clinically definite MS in Iranian patients. **METHODS:** Eligible patients had presented with a first episode of neurological dysfunction suggesting MS within the previous 3 months and had abnormal brain magnetic resonance imaging (MRI). Patients were randomly assigned to receive intramuscular interferon beta 1a 30 mug or placebo once a week for 3 years. **RESULTS:** Of the 217 patients randomized, 202 patients completed the study; 104 received Avonex and 98 received placebo. Fewer patients converted to clinically definite multiple sclerosis in the treated group than in the placebo group during the study (36.6% vs 58.2%, P < 0.003). The number of active T2-weighted MRI lesions was significantly lower in the treated group. **CONCLUSIONS:** The results of our study, which are consistent with those from western studies, show that treatment at an early stage of MS delays conversion to definite MS and has positive effects on MRI outcomes.

Phillips, J. T., P. W. O'Connor, et al. (2006). "Infusion-related hypersensitivity reactions during natalizumab treatment.[erratum appears in *Neurology*. 2007 Feb 6;68(6):473]." *Neurology* **67**(9): 1717-8.

Rudick, R. A., D. Miller, et al. (2007). "Health-related quality of life in multiple sclerosis: effects of natalizumab.[see comment]." *Annals of Neurology* **62**(4): 335-46.

OBJECTIVE: To report the relationship between disease activity and health-related quality of life (HRQoL) in relapsing multiple sclerosis, and the impact of natalizumab. **METHODS:** HRQoL data were available from 2,113 multiple sclerosis patients in natalizumab clinical studies. In the Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis (AFFIRM) study, patients received natalizumab 300 mg (n = 627) or placebo (n = 315); in the Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1a in Patients with Relapsing Remitting Multiple Sclerosis (SENTINEL) study, patients received interferon beta-1a (IFN-beta-1a) plus natalizumab 300 mg (n = 589), or IFN-beta-1a plus placebo (n = 582). The Short Form-36 (SF-36) and a subject global assessment visual analog scale were administered at baseline and weeks 24, 52, and 104. Prespecified analyses included changes from baseline to week 104 in SF-36 and visual analog scale scores. Odds ratios for clinically meaningful improvement or worsening on the SF-36 Physical Component Summary (PCS) and Mental Component Summary were calculated. **RESULTS:** Mean baseline SF-36 scores were significantly less than the general US population and correlated with Expanded Disability Status Scale scores, sustained disability progression, relapse number, and increased volume of brain magnetic resonance imaging lesions. Natalizumab significantly improved SF-36 PCS and Mental Component Summary scores at week 104 in AFFIRM. PCS changes were significantly improved by week 24 and at all subsequent time points. Natalizumab-treated patients in both studies were more likely to experience clinically important improvement and less likely to experience clinically important deterioration on the SF-36 PCS. The visual analog scale also showed significantly improved HRQoL with natalizumab. **INTERPRETATION:** HRQoL was impaired in relapsing multiple sclerosis patients, correlated with severity of disease as measured by neurological ratings or magnetic resonance imaging, and improved significantly with natalizumab.

Schwid, S. R. and H. S. Panitch (2007). "Full results of the Evidence of Interferon Dose-Response-European North American Comparative Efficacy (EVIDENCE) study: a multicenter, randomized, assessor-blinded comparison of low-dose weekly versus high-dose, high-frequency interferon beta-1a for relapsing multiple sclerosis." *Clinical Therapeutics* **29**(9): 2031-48.

BACKGROUND: Interferon (IFN)-beta therapy represents an important advance in the management of relapsing multiple sclerosis (MS), but information about the relative benefits and risks of available preparations is limited. **OBJECTIVE:** This report describes the full results of the Evidence of Interferon Dose-response-European North American Comparative Efficacy (EVIDENCE) study, combining analyses that were previously reported in separate publications for different phases of the study. **METHODS:** The EVIDENCE study was a multicenter, randomized, assessor-blinded comparison of 2 IFN-beta dosing regimens. In the study, patients with relapsing MS were randomly assigned to SC IFN-beta1a 44 lag TIW (Rebif, Serono Inc., Geneva, Switzerland) or IM IFN-beta1a 30 mug QW (Avonex, Biogen Idec, Cambridge, Massachusetts) for 1 to 2 years. The

primary clinical end point during the comparative phase was the proportion of patients who remained free from relapses; secondary and tertiary clinical end points included the annualized relapse rate and time to first relapse, respectively. All clinical and magnetic resonance imaging (MRI) evaluations were performed by blinded assessors. In the crossover phase of the study, patients who were originally randomized to low-dose QW treatment switched to the high-dose TIW treatment for an additional 8 months. Adverse events were determined by spontaneous reporting and monthly laboratory testing during the comparative phase. RESULTS: A total of 677 patients were enrolled in the study and evenly randomized to treatment; 605 patients completed the comparative phase and 439 completed the crossover phase. During the comparative phase, a significantly higher proportion of patients in the high-dose TIW treatment group remained free from relapses when compared with patients in the low-dose QW treatment group (adjusted odds ratio, 1.5; 95% CI, 1.1-2.0; $P = 0.023$). The high-dose TIW regimen was also associated with a significant reduction in the annualized relapse rate (-17%; $P = 0.033$) and a prolonged time to first relapse (hazard ratio, 0.70; $P = 0.002$). MRI measures of disease activity were significantly reduced in the high-dose TIW group compared with the low-dose QW treatment. During the crossover phase, a 50% reduction in mean relapse rates was observed in patients who converted from low-dose QW treatment to high-dose TIW treatment ($P < 0.001$), with significant concomitant reductions in MRI activity. Injection-site reactions were significantly more common with high-dose TIW treatment than with low-dose QW treatment (85% vs 33%; $P < 0.001$). Neutralizing antibody formation was more common with high-dose TIW treatment than with low-dose QW treatment (26% vs 3%; $P < 0.001$). CONCLUSIONS: The comparative phase of the EVIDENCE study found that treatment of MS with SC IFN-beta 1a 44 microg TIW was associated with a significant reduction in clinical and imaging measures of disease activity over 1 to 2 years, when compared with IM IFN-beta 1a 30 microg QW treatment. The crossover phase found that patients who changed from low-dose QW treatment to high-dose TIW treatment experienced enhanced benefits of treatment without a substantial increase in adverse events.