Author's response to reviews

Title: Retrospective US Database Analysis of Persistence with Glatiramer Acetate vs. Available Disease-Modifying Therapies for Multiple Sclerosis: 2001-2010

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Author's response to reviews: see over
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Robert Zivadinov, MD
Section Editor
BMC Neurology

Dear Dr. Zivadinov:

On behalf of my co-authors, I thank you for the opportunity to submit responses to reviewers’ comments on our manuscript entitled, *Retrospective US Database Analysis of Persistence with Glatiramer Acetate vs. Other Disease-Modifying Therapies for Multiple Sclerosis*. Below are the point-by-point responses:

**Reviewer #1: Philip Buck**

**Major Compulsory Revisions:**

1. Primary concern that GA cohort is a subset of the full DMT-treated cohort.

**Authors’ Response:** We understand the reviewer’s concern that the GA cohort is a subset of the full DMT-treated cohort, and, short of reanalyzing the data which is not feasible, we have revised the descriptions of the cohorts being compared to clearly state that the GA cohort is being compared to a cohort of all patients being treated with DMT available in the time frame of 2001 to 2010.

Considering that the GA cohort represents about one-third of the full DMT-treated cohort included in these analyses but has a mean persistence rate that is consistently higher than the full DMT-treated cohort, it would seem to follow that the GA-treated cohort is raising the mean persistence for the full DMT-treated cohort and making less of a distinction between the groups. In other words, including GA in the full DMT-treated cohort is not biasing the comparisons in favor of the GA cohort.

**Minor Essential Revisions:**

1. Patient Identification, paragraph 1--Rationale for including Tysabri

**Author’s Response:** As was true for users of GA and the beta interferons, Tysabri users had a diagnostic code for MS and at least one prescription claim for the therapy in the time frame of 2001 to 2008. Users of all therapies also had at least 24 months of eligibility for insurance coverage following the first DMT prescription claim extending the analysis to December 2010. Very few Tysabri users were captured between the initial product launch in late 2004 and market removal in February 2005. Nearly all Tysabri were captured between the re-launch in 2006 and the end of the study window in 2010. Given that Tysabri users met the inclusion criteria for the study, we could find no justification for excluding them from the analyses. No new rationale for including Tysabri has been added here.
2. Patient Identification, paragraph 1 and Subject cohorts, paragraph 1--Discrepancy between length of eligibility and length of follow-up

Authors’ Response: The minimum 24 months of insurance eligibility, as stated under Patient Identification, was one of the inclusion criteria for the analyses. The 12 months of follow-up was a defining variable for one of the three cohort comparisons made in the study. Patients with at least 12 months of follow-up were still required to have at least 24 months of eligibility for insurance coverage but only their first 12 months of follow-up were used for the 12-month cohort comparison. No change to the text was made since a distinction had been made between insurance eligibility and patient follow-up.

3. Discussion, paragraph 1 -- Representativeness of sample not equated by size alone.

Authors’ Response: The reviewer makes an excellent point. We have compared the characteristics of the patient sample from the Reynolds’ paper with our sample. We find the age distribution and proportion of female gender very similar. Additionally, both samples have the largest representation from the Midwest and the least representation from the West. We have modified the final sentence of this paragraph to remove reference to our sample being more representative. It now says: “The characteristics of the patient samples in terms of age, gender and geographic distribution were very similar.”

Discretionary Revisions:

1. Background, paragraph 1 –add overall incidence of MS in the US

Authors’ Response: The reviewer raises an interesting point. We cited an incidence figure for MS among Caucasians in the US based on a study from the Mayo Clinic. We had looked for an MS incidence rate that would be inclusive of the whole US population but found that published incidence figures are extremely variable. To quote the National MS Society website section, “Epidemiology of MS:”

“With the challenges inherent in promptly and correctly identifying people with MS, arriving at an accurate incidence figure has been virtually impossible. Most epidemiologists have chosen instead to focus on the prevalence of MS — the number of people with MS at a particular point in time.”

We have elected to leave the incidence and prevalence figures for Caucasians in this paragraph since they represent nearly 90% of the MS cases in the US. However, we recognize that MS occurs in most ethnic groups including African Americans, Asians, and Hispanic/Latinos but their prevalence is much lower.

2. Limitations, paragraph 1 – mention that the new generation of oral agents was not included in the current analyses

Authors’ Response: This has been added to the Limitations section, paragraph 2.

Reviewer #2: Roberto Cappellani
No revisions requested.

Reviewer #3: Steven L. Hass

Major Compulsory Revisions:

1. GA included in the DMT-treated cohort

Authors’ Response: We understand the reviewer’s concern that the GA cohort is a subset of the full DMT-treated cohort, and, short of reanalyzing the data which is not feasible, we have revised the descriptions of the cohorts being compared to clearly state that the GA cohort is being compared to a cohort of all patients being treated with DMT available in the time frame of 2001 to 2010.

Considering that the GA cohort represents about one-third of the full DMT-treated cohort included in these analyses but has a mean persistence rate that is consistently higher than the full DMT-treated cohort, it would seem to follow that the GA-treated cohort is raising the mean persistence for the full DMT-treated cohort and making less of a distinction between the groups. In other words, including GA in the full DMT-treated cohort is not biasing the comparisons in favor of the GA cohort.

2. Patient selection—clarify how inclusion criteria were operationalized

Authors’ Response: The reviewer has raised some excellent points that require clarification. The patients studied were those with a first claim for a marketed disease-modifying therapy between 1/1/2001 and 12/31/2008 and at least 24 months of insurance eligibility. This extended the study window to 12/31/2010. While it is true that fingolimod entered the market before the end of 2010, no one using that drug would meet the inclusion criteria for the study. Changes were made to the Patient Identification section of the paper to address these issues.

3. Explain why more recent data were not included and the influence that may have on the results.

Authors’ Response: Our analyses include data from January 2001 to December 2010, which is the longest continuous period of MS drug therapy use that has been investigated to date. The first new generation of oral therapies was entering the market in late 2010 but was not expected to be present in the database to a large enough extent to look at emerging treatment patterns until late 2011. We chose to investigate the ten years of data that included the entry of Rebif and Tysabri to the market. We concluded the paper by saying that with the introduction of several oral DMT’s further investigation of long-term therapy persistence should be pursued. It may take a few years for sufficient claims data for these oral therapies to accumulate before it will be feasible to pursue such an investigation. We have not made any changes to the paper to address these issues.

4. Include as a limitation the fact that there may be bias against newer therapies because they may exhibit poorer persistence when first used.—Explain why we did not include only new therapy starts.

Authors’ Response: It is true that three of the five therapies included in the analyses
were available prior to 2001 (IFNβ-1b launched in 1993; IFNβ-1a IM launched in 1996, GA launched in 1997) and some of the patients in the analyses may have used them prior to 2001. We acknowledge in the paper that patients who are new to therapy are more vulnerable to discontinuation, and that can be seen most readily in the first six months after a new therapy is started regardless of how long the therapy has been on the market. While there may be some bias against Tysabri because of its later entry to the market, it was available in the database for at least 4.5 years after its second launch in 2006. This should have provided ample time for long-term persistence data to emerge. We have not included this as a limitation of the study since none of the therapies were truly new to the market.

The reviewer suggested that we rerun the analysis to study only those patients initiating therapy by instituting a requirement of 6 to 12 months of no treatment prior to DMT initiation at the start of available data. This is a reasonable method for analyzing claims data with the intent of capturing new therapy starts. We did not use these criteria for our analyses because we wanted to capture the longest possible DMT persistence data. People with managed health care plans routinely change insurance every one to two years. If we began with a requirement of 6 to 12 months with no treatment and then wished to follow them for therapy persistence after they start DMT, we would be limited to a very small sample of patients who stayed with the same health plan and could be followed for 1 to 2 years. Few, if any, would have 3 years of follow-up. It is not feasible to rerun the analysis, and it would not meet the objective of our study.

Minor Essential Revisions

5. Rationale for using 15 days rather than some other period or alternatively an MPR in determining persistence.

**Authors' Response:** We examined the ten years of claims data for the presence of treatment gaps before we began the analyses for this study. Fifteen days was the most common threshold for a treatment gap. Since our persistence definition specifically states that we are looking at continuous treatment regardless of gaps, we investigated those with gaps of 15 days or more to see what changes in their regimens followed. We state in the paper that for the GA cohort after the initial 15-day gap, they reinitiated GA, on average, at 54 days. MPR is a therapy compliance measure that did not fit the intent of our analyses. We have added the rationale for using 15 days in the gap definition under Regimen Changes in the Methods section of the paper.

6. Discuss other factors, such as hospitalizations for an MS flare, as potential reasons for an observed gap in therapy, particularly since some medications may be more likely to be used in patients with more highly active disease.

**Authors' Response:** We have added a sentence in the Discussion paragraph about gaps in therapy to suggest reasons why there may be lower therapy re-initiation rates for some in the full DMT-treated cohort because of more active disease.

7. Was there a maximum allowable time for a start-up or a switch?

**Authors’ Response:** No, there was no maximum allowable time for a restart of therapy or a switch. We measured the lengths of time and provided the means in the
8. Results statement: “Among patients with a minimum of 12 months of follow-up, the persistence rate with GA was 79.5%.” Discussion statement: “At 12 months was 79.5%. Was this the persistence rate at 12 months or does this reflect re-initiation or combination therapy at some point after 12 months?

Authors’ Response: We have modified the Discussion statement to match the Results statement since they are each referring to the persistence rate for the 12-month cohort. Persistence includes those who remained on the same drug for 12 months without a gap in therapy as well as those with a gap who re-initiated the same therapy within the 12 months.

9. Note that switches from Tysabri due to its market withdrawal in Feb 2005 may have been included.

Authors’ Response: Very few users of NZ appeared in this database from late 2004 to Feb 2005. Claims for new therapies coming to market tend to be slow to accrue to any single database. With the reintroduction in 2006, we saw increasingly more claims for NZ over the subsequent years, and this is when the NZ users were captured for our analyses. We don’t think that there were sufficient switches from the early launch of NZ to warrant any mention in the paper.

Thank you for your time and consideration.

Sincerely,

MerriKay Oleen-Burkey, PhD
Principal, Outcomes Scribe, LLC