

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Effect of adherence to the first-generation injectable immunomodulatory drugs on disability accumulation in multiple sclerosis: a longitudinal cohort study
AUTHORS	Zhang, Tingting; Kingwell, Elaine; Zhu, Feng; Petkau, John; Kastrukoff, Lorne; Marrie, Ruth; Tremlett, Helen; Evans, Charity

VERSION 1 – REVIEW

REVIEWER	Ron Milo Department of Neurology Barzilai Medical Center Ashkelon Israel
REVIEW RETURNED	29-Jul-2017

GENERAL COMMENTS	<p>This article examines the impact of short-term adherence to first-line injectable DMTs on disability accumulation in MS. The authors used administrative health data to assess adherence in their cohort, and longitudinal EDSS data from clinical records. No association was found between optimal adherence and disability accumulation, or time to sustained EDSS=6.0 as a secondary outcome.</p> <p>The article is well-written, and the authors used appropriate methods that are comprehensively and clearly described. The results justify the interpretation and conclusions. The discussion focuses mainly on the key question of the article (albeit not on other minor positive results, such as the impact of sex, time or baseline EDSS on disability accumulation).</p> <p>I believe that this article will make a nice contribution to the field of MS and recommend publication without revision.</p>
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REVIEWER	Bardia Nourbakhsh Johns Hopkins University, Baltimore, Maryland, USA
REVIEW RETURNED	04-Aug-2017

GENERAL COMMENTS	<p>Using linked clinical and administrative data in a Canadian province, authors in this manuscript studied the proportion of patient with good adherence to first line injectable MS medications and assess its association with disability accumulation.</p> <ul style="list-style-type: none"> - Abstract results: “nor with time to sustained EDSS 6 (adjOR 0.91) should probably be adjHR – Hazard ratio- as the authors mentioned in the methods that they used Cox model. - “Adherence was estimated using the proportion of days covered (PDC) measure, calculated as the total number of days of drug dispensed during the one-year period divided by 365 days”. This method of estimating adherence clearly does not capture non-adherence in patients who received the medication from pharmacies but did not do the injections as they were instructed to. The authors mentioned this point in the discussion section. - Why the adherence (PDC) was not used as a continuous variable in the models? The authors mentioned that PDC>80% was used because it has been associated with other health-related outcomes in the past and for the sake of consistency. But by arbitrarily categorizing the variable, authors might have lost a chance to find an association between adherence and disability progression. I would run this model at least as a sensitivity analysis. - Can the authors show the distribution of adherence among their patients? - Although the authors mentioned their rationale regarding using adherence only in the first year of starting medications as the predictor and reported that it has been shown that adherence in the first year is associated with adherence over long term; it is not uncommon in the clinical practice to see “needle fatigue”, patients who get tired of doing injections after few years.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Ron Milo

Institution and Country: Department of Neurology, Barzilai Medical Center, Ashkelon, Israel

Competing Interests: None declared

This article examines the impact of short-term adherence to first-line injectable DMTs on disability accumulation in MS. The authors used administrative health data to assess adherence in their cohort, and longitudinal EDSS data from clinical records. No association was found between optimal adherence and disability accumulation, or time to sustained EDSS=6.0 as a secondary outcome.

The article is well-written, and the authors used appropriate methods that are comprehensively and clearly described. The results justify the interpretation and conclusions. The discussion focuses mainly on the key question of the article (albeit not on other minor positive results, such as the impact of sex, time or baseline EDSS on disability accumulation).

I believe that this article will make a nice contribution to the field of MS and recommend publication without revision.

Response:

--We thank the reviewer for these supportive comments.

Reviewer: 2

Reviewer Name: Bardia Nourbakhsh

Institution and Country: Johns Hopkins University, Baltimore, Maryland, USA Competing Interests: None declared.

Using linked clinical and administrative data in a Canadian province, authors in this manuscript studied the proportion of patient with good adherence to first line injectable MS medications and assess its association with disability accumulation.

Abstract results: “nor with time to sustained EDSS 6 (adjOR 0.91) should probably be adjHR – Hazard ratio- as the authors mentioned in the methods that they used Cox model.

Response:

--We thank the reviewer for catching this error. We have made the correction.

“Adherence was estimated using the proportion of days covered (PDC) measure, calculated as the total number of days of drug dispensed during the one-year period divided by 365 days”. This method of estimating adherence clearly does not capture non-adherence in patients who received the medication from pharmacies but did not do the injections as they were instructed to. The authors mentioned this point in the discussion section.

Response:

--We agree with the reviewer that we have discussed this limitation in the manuscript. Therefore, we have not made any revisions related to this comment.

Why the adherence (PDC) was not used as a continuous variable in the models? The authors mentioned that PDC>80% was used because it has been associated with other health-related outcomes in the past and for the sake of consistency. But by arbitrarily categorizing the variable, authors might have lost a chance to find an association between adherence and disability progression. I would run this model at least as a sensitivity analysis.

Response:

--We did examine adherence (PDC) as a continuous variable, but did not include it in the main model as continuous because the distribution was skewed. We also ran the models with the PDC categorized into quartiles and using a cut-off of 90%. There was no evidence of an association between adherence and subsequent disability accumulation with these alternative methods of categorizing adherence. We have now included the details about these sensitivity analyses in the methods, results and discussion sections.

Can the authors show the distribution of adherence among their patients?

Response:

--In the results section, we report that 74.7% of subjects had optimal adherence, and we have now added a histogram showing the entire adherence distribution as Figure 1.

Although the authors mentioned their rationale regarding using adherence only in the first year of starting medications as the predictor and reported that it has been shown that adherence in the first year is associated with adherence over long term; it is not uncommon in the clinical practice to see “needle fatigue”, patients who get tired of doing injections after few years.

Response:

--We thank the reviewer for this suggestion. We have added a comment (and reference) about this in the discussion. It now reads: "Although it is not known how long a person should be on an IMD before gaining benefit, assessment of adherence over the first year may be insufficient, and may miss non-adherence that occurs after the first year, due to needle fatigue for example."

VERSION 2 – REVIEW

REVIEWER	Bardia Nourbakhsh Johns Hopkins University, Baltimore, MD, USA
REVIEW RETURNED	23-Aug-2017
GENERAL COMMENTS	The authors have adequately addressed the comments.