## PEER REVIEW HISTORY



## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Real World Validation of the Minimal Disease Activity Index in Psoriatic Arthritis: An Analysis from a Prospective, Observational, Biological Treatment Registry |
| **AUTHORS** | Rahman, Proton; Zummer, Michel; Bessette, Louis; Baer, Philip; Haraoui, Boulos; Chow, Andrew; Kelsall, John; Kapur, Suneil; Rampakakis, Emmanouil; Psaradellis, Eliofotisti; Lehman, Allen; Nantel, Francois; Osborne, Brendan; Tkaczyk, Cathy |

## VERSION 1 - REVIEW

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| **REVIEWER** | Lars Erik Kristensen<br>The Parker Institute, Copenhagen University, DK<br><br>Speaker and consulting fees recieved from Pfizer, AbbVie, Amgen, Biogen, UCB, Celegene, BMS, MSD, Novartis, Eli Lilly, and Janssen pharmaceuticals. |
| **REVIEW RETURNED** | 23-Dec-2016 |

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| **GENERAL COMMENTS** | I read the manuscript: ” Real World Validation of the Minimal Disease Activity Index in Psoriatic Arthritis: An Analysis from a Prospective, Observational, Biological Treatment Registry” with great interest. I do have some comments:<br><br>In abstract it is stated that you also look at ” ustekinumab”; however, I cannot find any data on this.<br>The wording predictors is used in manuscript rather use prognostic factors which is more appropriate with regard to the study design.<br>Why is the study period 2005-2010? – this should be justified and discussed.<br>ITT population is used but you require at least 1 MDA recording at follow-up. This introduces an attrition bias. So its actually more a per protocol/or as observed study rather than an ITT. Please revise wording used in manuscript, and discuss the implications of this.<br>If sample size allows, please add as a sensitivity analysis patients with sustained MDA – i.e. at both 6 and 12 months. Patients with flare up (MDA at 6 but not 12 months) and patients with dropout between 6 and 12 months. Do these patients differ in background characteristics?<br>Please describe how the multivariate regression model was constructedz |

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| **REVIEWER** | Siba P Raychaudhuri<br>University of California Davis, School of Medicine |
| **REVIEW RETURNED** | 05-Jan-2017 |

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| **GENERAL COMMENTS** | Over all this is a well written paper. I agree with the hypothesis, methodology and results of this study.<br>A minor comment both the result section and the discussion section can be reduced; together the text of the manuscript can be reduced by 10-15% from its current status. |

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| **REVIEWER** | Philip Helliwell<br>University of Leeds, UK<br><br>I am an originator of the MDA |
| **REVIEW RETURNED** | 23-Jan-2017 |

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| **GENERAL COMMENTS** | Real World Validation of the Minimal Disease Activity Index in Psoriatic Arthritis: An Analysis from a Prospective, Observational, Biological Treatment Registry<br><br>This is a nice report of 'real life' outcomes of patients in a restricted Canadian biologic registry. The authors are constrained by the available data and a glaring hole in this data is the lack of a 66/68 swollen and tender joint count. As the main outcome of interest is based on just such a count then, unfortunately, this comparison and analysis becomes invalid. |

## VERSION 1 – AUTHOR RESPONSE

**Reviewer #1:**
Reviewer Name: Lars Erik Kristensen
Institution and Country: The Parker Institute, Copenhagen University, DK Competing Interests: Speaker and consulting fees recieved from Pfizer, AbbVie, Amgen, Biogen, UCB, Celegene, BMS, MSD, Novartis, Eli Lilly, and Janssen pharmaceuticals.

I read the manuscript: " Real World Validation of the Minimal Disease Activity Index in Psoriatic Arthritis: An Analysis from a Prospective, Observational, Biological Treatment Registry" with great interest. I do have some comments:

1. In abstract it is stated that you also look at "ustekinumab"; however, I cannot find any data on this.
2. The wording predictors is used in manuscript rather use prognostic factors which is more appropriate with regard to the study design.
3. Why is the study period 2005-2010? – this should be justified and discussed.
4. ITT population is used but you require at least 1 MDA recording at follow-up. This introduces an attrition bias. So its actually more a per protocol/or as observed study rather than an ITT. Please revise wording used in manuscript, and discuss the implications of this.
5. If sample size allows, please add as a sensitivity analysis patients with sustained MDA – i.e. at both 6 and 12 months. Patients with flare up (MDA at 6 but not 12 months) and patients with dropout between 6 and 12 months. Do these patients differ in background characteristics?
6. Please describe how the multivariate regression model was constructed.

**Author Response:**

1. Patients in the BioTRAC registry can be treated with infliximab (IFX), golimumab (GLM) or ustekinumab (UST) as mentioned in the Design section of the abstract. In Participants

section, however, it is clearly stated that participants included PsA patients receiving IFX or GLM. Therefore, no data on patients receiving UST are presented in this paper (the reason being the low number of patients with sufficient follow-up at this point).

2. Wording of predictors will be changed to prognostic factors.
3. The study period is not 2005-2010 but rather patients were enrolled in the registry since 2005 for IFX and since 2010 for GLM which is indicative of when these treatments were approved in Canada. In order to avoid confusion to the readership, the wording in the abstract will be adjusted to read '*223 PsA patients treated with IFX (enrolled since 2005) or GLM (enrolled since 2010), with …*'.
4. We agree with the reviewer that this is a modified ITT population. As per the Reviewer's suggestion, we will replace 'ITT' with 'As Observed'.
5. Sustained MDA was reported in our manuscript, though the sample size did not allow for statistical comparisons in background characteristics or identification of prognostic factors, we therefore simply described what proportion of patients had sustained MDA.
6. Information on the multivariate model is already included in the footnote under Table 3B ('*Multivariate analysis was assessed with backward conditional logistic regression, covariates entered were: province, gender, age, baseline biologic agent, MDGA, PtGA, Pain, HAQ, SJC28, TJC28, and enthesitis count with probability for stepwise entry and removal at the 0.05 and 0.10 level, respectively*'). We will make sure to include this information in the Statistical Analysis section of the Methods.

**Reviewer #2:**

Reviewer Name: Siba P Raychaudhuri
Institution and Country: University of California Davis, School of Medicine, USA Competing Interests: No

Over all this is a well written paper. I agree with the hypothesis, methodology and results of this study. A minor comment both the result section and the discussion section can be reduced; together the text of the manuscript can be reduced by 10-15% from its current status.

**Author Response:** We are glad to hear that the Reviewer is satisfied with our manuscript. In the revised version we will also reduce the discussion sections by 10-15% as suggested by the reviewer.

**Reviewer #3:**

Reviewer Name: Philip Helliwell
Institution and Country: University of Leeds, UK Competing Interests: I am an originator of the MDA

This is a nice report of 'real life' outcomes of patients in a restricted Canadian biologic registry. The authors are constrained by the available data and a glaring hole in this data is the lack of a 66/68 swollen and tender joint count. As the main outcome of interest is based on just such a count then, unfortunately, this comparison and analysis becomes invalid.

**Author Response:**

We understand the reviewer's point, however unfortunately this is a limitation of the way that the data are collected within our registry. Given that: (i) prior studies (e.g. Englbrecht M et al. Arthritis Care Res (Hoboken). 2010 Jul;62(7):977-83) have shown that simplified joint counts are sufficiently sensitive to measure clinical response in PsA patients, and (ii) we already clearly acknowledge in the Discussion section the limitation of using 28-joint counts rather than 66/68 counts, and in consideration that this one of the first studies validating MDA in real-world we believe that our study will be of great interest to the readership of BMJ Open and merits publication.

## VERSION 2 – REVIEW

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| **REVIEWER** | Lars Erik Kristensen<br>The Parker Institute, DK<br><br>Member of GRAPPA, and active within PsA-research including outcome measures |
| **REVIEW RETURNED** | 22-Mar-2017 |

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| **GENERAL COMMENTS** | I read the study "Real World Validation of the Minimal Disease Activity Index in Psoriatic Arthritis: An Analysis from a Prospective, Observational, Biological Treatment Registry" with great interest. The study is informative well written and interesting, but could be improved considerably by adding additional analysis, by also using DAPSA remission, CPDAI/PASDAS if the data allows for this.<br><br>Moreover, it would be interesting if modified MDA by having Skin & swollen joints as mandatory criterias out of the 5/7!<br><br>Data and statistics on agreement and predictabilities on these measures would be of great interes to the community.<br><br>Moreover, did a protocol exist and where can it be accessed.<br><br>Finally I would like a drop-out analysis to see how different the proportion of patients with missing data were – in order to illustrate degree of selection bias |

## VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Lars Erik Kristensen
Institution and Country: The Parker Institute, DK
Competing Interests: Member of GRAPPA, and active within PsA-research including outcome measures

1. I read the study "Real World Validation of the Minimal Disease Activity Index in Psoriatic Arthritis: An Analysis from a Prospective, Observational, Biological Treatment Registry" with great interest. The study is informative well written and interesting, but could be improved considerably by adding additional analysis, by also using DAPSA remission, CPDAI/PASDAS if the data allows for this.

Author's Response: Additional analyses have been conducted to evaluate DAPSA remission. Results have now been included in the manuscript to illustrate these findings. Unfortunately, Dermatology Life Quality Index (DLQI) and SF-36 are not collected in the BioTRAC registry. As such, the CPDAI and PASDAI could not be assessed in this analysis.

2. Moreover, it would be interesting if modified MDA by having Skin & swollen joints as mandatory criterias out of the 5/7!

Author's Response: Modified MDA as per the reviewer's suggestion (skin and swollen joints as mandatory criteria) has been calculated and added to the manuscript.
A manuscript addressing this question is also under preparation.

3. Data and statistics on agreement and predictabilities on these measures would be of great interest

to the community.

Author's Response: Supplementary analyses assessing agreement and predictabilities have been conducted to address this comment. These results have now been included in the manuscript.

4. Moreover, did a protocol exist and where can it be accessed.

Author's Response: The registry's study protocol has been appended to the submission. Furthermore, BioTRAC is registered at ClinicalTrials.gov (Identifier: NCT00741793).

5. Finally, I would like a drop-out analysis to see how different the proportion of patients with missing data were – in order to illustrate degree of selection bias.

Author's Response: Descriptive baseline statistics have been produced comparing patients with available MDA data and those with missing MDA data due to any reason at 6 months. Overall, patients were comparable. These results are shown below.

| Parameter | Available MDA 6-Month Data (N=138) | Missing MDA 6-Month Data (N=85) | p-value |
|---|---|---|---|
| Socio-demographics | | | |
| Gender, n (%) a | | | |
| Male | 65 (52.4) | 36 (46.2) | 0.470 |
| Female | 59 (47.6) | 42 (53.8) | |
| Age (years), mean (SD) | 48.5 (11.6) | 52.2 (9.8) | 0.069 |
| Disease Parameters, mean (SD) | | | |
| Disease duration (years) | 5.5 (6.0) | 5.4 (7.1) | 0.455 |
| DAS28 | 4.2 (1.6) | 4.5 (1.5) | 0.117 |
| TJC28 | 6.4 (6.0) | 8.0 (7.6) | 0.296 |
| SJC28 | 4.5 (4.4) | 5.2 (4.6) | 0.196 |
| MDGA (VAS cm) | 5.3 (2.4) | 5.1 (1.9) | 0.607 |
| PtGA (VAS mm) | 49.2 (26.6) | 52.6 (25.2) | 0.370 |
| AM stiffness b (min) | 44.6 (44.5) | 45.6 (45.9) | 0.843 |
| HAQ | 1.0 (0.7) | 1.1 (0.7) | 0.373 |
| Pain (VAS mm) | 46.1 (25.7) | 49.8 (24.9) | 0.284 |
| PASI | 2.4 (4.5) | 3.1 (4.3) | 0.124 |
| Enthesitis count c | 4.5 (3.2) | 5.4 (3.8) | 0.322 |
| ESR (mm/h) | 19.8 (20.9) | 22.1 (20.4) | 0.406 |
| CRP (mg/L) | 13.2 (23.9) | 17.1 (35.9) | 0.599 |
| Previous biologic use, n (%) | 16 (13.7) | 9 (11.4) | 0.670 |

aPercentages based on available data
bCapped at 120 minutes.
cAmong patients with enthesitis.
DAS28, Disease Activity Score; HAQ, Health assessment questionnaire; MDGA, Physician Global Assessment of Disease Activity; PASI, Psoriasis Area and Severity Index; PtGA, Patient Global Assessment of Disease Activity; SJC, Swollen joint count; TJC, Tender joint count;

## VERSION 3 – REVIEW

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| **REVIEWER** | Lars Erik Kristensen<br>The Parker Institute, DK |
| **REVIEW RETURNED** | 27-Apr-2017 |

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| **GENERAL COMMENTS** | I read the paper with interest, I do have some comments:<br>In table 1 it seems there is a mismatch in n=total and the number of subjects reported under gender; Please state number of missing subjects for each of the variables presented in the table, and make it more transparant were the patients went?<br>Please discuss the risk for selection bias since so many patients are missing MDA at follow-up - please do a drop out analysis so see if these differ?<br>Please discuss selection bias as a potential limitation<br>Is there a risk for confounding by indication in this study? |

## VERSION 3 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Lars Erik Kristensen
Institution and Country: The Parker Institute, DK Competing Interests: Member of GRAPPA

1. I read the paper with interest, I do have some comments:
In table 1 it seems there is a mismatch in n=total and the number of subjects reported under gender; Please state number of missing subjects for each of the variables presented in the table, and make it more transparent were the patients went?

Author's Response: Table 1 of the manuscript has been revised and the missing category for gender is now included. Furthermore, for certain parameters encompassing the "Medications" in Table 1, the proportions have also been revised.

2. Please discuss the risk for selection bias since so many patients are missing MDA at follow-up - please do a drop out analysis so see if these differ?

Author's Response: Kindly note this comment had been mentioned in the previous round of revisions and that point was addressed by providing the results from table below in our last response. The table describes the descriptive baseline statistics comparing patients with available MDA data with missing MDA data due to any reason at 6 months. Also, please note that we have now adjusted the limitations section in the discussion addressing this point on pages 16-17 of the manuscript . Thank you.

Parameter Available MDA 6-Month Data (N=138) Missing MDA 6-Month Data (N=85) p-value
Socio-demographics
Gender, n (%) a
Male 65 (52.4) 36 (46.2) 0.470
Female 59 (47.6) 42 (53.8)
Age (years), mean (SD) 48.5 (11.6) 52.2 (9.8) 0.069
Disease Parameters, mean (SD)
Disease duration (years) 5.5 (6.0) 5.4 (7.1) 0.455
DAS28 4.2 (1.6) 4.5 (1.5) 0.117
TJC28 6.4 (6.0) 8.0 (7.6) 0.296
SJC28 4.5 (4.4) 5.2 (4.6) 0.196

MDGA (VAS cm) 5.3 (2.4) 5.1 (1.9) 0.607
PtGA (VAS mm) 49.2 (26.6) 52.6 (25.2) 0.370
AM stiffnessb (min) 44.6 (44.5) 45.6 (45.9) 0.843
HAQ 1.0 (0.7) 1.1 (0.7) 0.373
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PASI 2.4 (4.5) 3.1 (4.3) 0.124
Enthesitis countc 4.5 (3.2) 5.4 (3.8) 0.322
ESR (mm/h) 19.8 (20.9) 22.1 (20.4) 0.406
CRP (mg/L) 13.2 (23.9) 17.1 (35.9) 0.599
Previous biologic use, n (%) 16 (13.7) 9 (11.4) 0.670
aPercentages based on available data
bCapped at 120 minutes.
cAmong patients with enthesitis.
DAS28, Disease Activity Score; HAQ, Health assessment questionnaire; MDGA, Physician Global Assessment of Disease Activity; PASI, Psoriasis Area and Severity Index; PtGA, Patient Global Assessment of Disease Activity; SJC, Swollen joint count; TJC, Tender joint count;

3. Please discuss selection bias as a potential limitation Is there a risk for confounding by indication in this study?

Author's Response: Thank you for your comment. We have addressed this point in the limitation section of the discussion on page 17 of the manuscript.