ANSWERING REVIEWERS

August 25, 2012

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 9462 revised.doc).

Title: Is non-biological treatment of Rheumatoid arthritis as good as biologicals?
Author: Parida JR, Misra DP, Wakhlu A, Agarwal V

Name of Journal: *World Journal of Orthopedics*

ESPS Manuscript NO: 9462

The manuscript has been improved according to the suggestions of reviewers:

1. Reviewer's comment:

"TITLE: The title seems to be too strong. DMARDs and other therapy are often effective in the clinical outcome of RA but I should be more prudent ! As you declare in the text radiographic progression of the disease seem to be differently reduced"

Authors' response:

The title of the article has been changed and toned down as per the suggestion of the reviewer.

2. Reviewer's comment:

"Risk of serious infections and malignancy. We probably do not know what the real risk with biologic drugs is. As you said, ten more years of use are necessary to discover the real dimension of these risks.

But is clear that glucocorticoids are the most important causes of serious infections, up to 4-fold in a dose-dependent manner (Listing, Rheumatology, 2013). Anyway we can't forget that low-dose glucocorticoids in association with DMARDs are effective (Da Silva, 2005 and 2006)."

Authors' response:

We agree that with limited experience with biologics, the complete risk profile is yet to be revealed, and the same has been reiterated in our manuscript. With respect to glucocorticoids, we concur that they are an important predisposing factor for infection. With regards to the effectiveness of low dose glucocorticoids with DMARDs in RA, it is a well-established fact; however, the same deviates from the focus of our review which is to compare effectiveness of conventional DMARDs versus biologic DMARDs in RA.

3. Reviewer's comment:

"I do not agree when you say ("Treat to target " approach) that before the era of biologics remission in RA was a distant dream. In my opinion the history of RA changed with methotrexate. MTX is the first drug able to reach the remission in the majority of RA patients. The problem is : when and how to use it."

Authors' response:

We agree with the reviewer that methotrexate usage has changed the outcome in RA. We have already mentioned in our manuscript that initial methotrexate monotherapy is a reasonable option and responses achieved are comparable to those with Etanercept alone (reference 14), with almost half the patients achieving ACR 50 response in early RA.

We have changed the sentence 'Before the era of biologics, remission in RA was a distant dream' to 'Before the era of biologics, remission in majority of RA was not achievable due to fear of toxicity and

restricted the use of combination of cDMARDs.'

4. Reviewer's comment:

"In my opinion one of the most important causes of inefficacy of MTX therapy is the excess of folic acid association. The trial you cited have a correct approach to the folic acid supplementation: therefore results are evident."

Authors' response:

In our humble opinion, our experience does not suggest that excessive folic acid administration significantly alters responsiveness to methotrexate in the real life setting.

5. Reviewer's comment:

"Finally, if possible, it should be interesting to show the most important characteristics of the cited trials in a Table (f. i. acid folic, glucocorticoids dose, early arthritis ecc)."

Authors' response:

We agree that such information would be really interesting, but feel that it deviates from the message we want to convey through our paper, viz. combination of conventional DMARDs is almost as effective as biologic DMARDs and is a cheaper and cost-effective option; hence we have decided to not include the data.

Thank you again for publishing our manuscript in the *World Journal of Orthopedics*.

Sincerely yours,

9/4/14

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