**Reviewer's report**

**Title:** Relapse rates after elective discontinuation of anti-TNF therapy in rheumatoid arthritis: A Meta-analysis and Review of Literature

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**Reviewer:** T Kuijper

**Reviewer's report:**

With interest I read the manuscript by Mangoni et al. The authors present a meta-analysis on relapse rates after elective discontinuation of anti-TNF therapy in rheumatoid arthritis. The topic is relevant and several new studies were included that have not yet been included in previous meta-analyses on this topic. The used methodology appears to be sound and in addition to the main analysis several sensitivity analyses were performed as well. However some concerns remain that need to be addressed first before the manuscript can be considered for publication.

**Major concerns**

**Introduction**

"Though elective TNF-alpha inhibitor discontinuation is justified in several RA patients, there is lack of sufficient data to guide the decision. Further, the course of action post-withdrawal also remains to be understood, although a decision based on sustained remission has been proposed [5]. Nonetheless, a consensus about patient selection and the timing of withdrawal remains to be reached.

The objective of the study is to address this issue by investigating the pooled relapse rates after elective withdrawal of TNF-alpha inhibitor therapy in RA patients through meta-analysis of eligible studies.

There appears to be a mismatch between the study questions proposed in the introduction and in the main objective. In the last part of the introduction, three questions are proposed that are of clinical interest, i.e:

1. Which patients can be selected to withdraw TNF-alpha inhibitor therapy
2. At what moment should the therapy be withdrawn and
3. How should RA be managed after withdrawal of therapy.

Although relevant, the main objective of the study does not directly answer any of these questions. I would suggest to add something like: "As a first step to answering these questions, we investigated whether TNF-alpha therapy can be withdrawn in general. To this end, we performed a meta-analysis..." In order to make the introduction connect well with the main aim.

Methods

* Bullet 3 inclusion criteria: "considering that biologic disease-modifying antirheumatic drugs (DMARDs) are the major class of drugs that interfere with the entire RA process [8]"

The reasoning is not clear to me. Other outcomes of interest than relapse rate could have been of interest (i.e. radiographic progression, time to flare). Also, other DMARDs could have been of interest, as all DMARDs by definition, have an impact on disease activity. To do a meta-analysis one should make a focus, which is fine. Argumentation for this should be made in the introduction. I think the quoted part here is redundant and can best be removed.

* Data extraction and methodological quality assessment: "If most [ do we have a cut-off point or % of positives (...) is considered of limited quality] (...)"

The quoted part between square brackets [] should be removed.

Based on the "majority of items on CASP positive" criterion all studies are high quality now. What would be the impact if another definition were chosen, i.e. high quality if number of items positive > median number of positive CASP items of included non-randomized studies?

Results

* A short and general discussion of highlighted aspects of included studies is currently missing. This should be added, with reference to table 2.

* "Four RCTs were of high quality, whereas Moghadam et al., 2016 scored a 2 and was considered a low-quality study (Table 3)."
This is true according to the definition authors used to define low- and high-quality studies. Being the only low-quality study among 16 studies, this makes the study look rather bad when presented in this way. However, looking at Table 3, all "good-quality" studies only scored 3 points out of 5 as well. Hence, the difference in quality may not be as large as is (implicitly) suggested. Perhaps it would be fair to also mention the number of points of the other studies, so that it is clear that it is not a large difference. Also, it may be of interest to the reader to explicitly mention the criterion that Moghadam failed to fulfill compared to the other studies, so that the reader can make his or her own judgement on the quality and potential impact on the results.

* "The shape of the funnel plot reveals visual evidence of asymmetry. Publication bias was detected in the included set of studies as more studies were plotted on the left side of the graph (Figure 5)"

Looking at figure 5, I count 9 points on the left side and 7 points on the right side. I wonder if this is sufficient to make the claim that the plot indicates publication bias. Although subjective, the plot looks quite symmetric to me and in agreement with what one would expect to find under the null-hypothesis of no publication bias.

Discussion

* "A meta-analysis of six trials reported that TNF-alpha inhibitor treatment continuation, in RA patients in sustained remission or low disease activity, increased the probability of low disease activity (relative risk [RR] = 0.66, 95% CI 0.51-0.84) and remission (0.57, 95% CI 0.44-0.74), and reduced radiographic progression (RR = 0.91, 95% CI 0.85-0.98) though these results were not statistically significant [21]."

None of the 95% CI's of reported relative risks include the null-hypothesis of RR=1, yet the authors claim that none of the results were statistically significant. This appears to be a discrepancy.

* "The observed pooled relapse rate (...) and follow-up in individual studies"
Several old studies from the eighties and nineties, in which conventional synthetic DMARDs were withdrawn, are mentioned here. As treatment of RA was very different then compared to nowadays, patients from these different times, in my opinion, cannot be compared as they might respond very differently to DMARD withdrawal. In this light, I think that this part is of limited importance and interest.

* Several other systematic reviews and meta-analyses on withdrawal of TNF-alpha inhibitors have been published, which are not discussed, for example:


Please mention relevant systematic reviews / meta-analyses on discontinuation of TNF-alpha inhibitors in your discussion section and whether your findings are in agreement or not.

* "All the studies included in this analysis, employing rigid criteria for measuring disease activity and monitoring remissions, used improvement in DAS28 scoring system. (…) Such patients even after declare to have remitted will be more likely to relapse."

The authors mention an important caveat of using the DAS28 remission criterion alone to define remission and initiate treatment de-escalation. It is well known that active disease may occur even when the DAS28 remission criterion is fulfilled. This has led to the development of other remission criteria (e.g. Boolean), but these are not frequently used in clinical practice and may be too conservative. The discussion on active disease being present despite a DAS28 indicating remission is certainly relevant in this context and should be part of the discussion. However I do not understand the claim the authors make: "Such patients even after declare to have remitted will be more likely to relapse". If these patients have low DAS28 despite active disease, this by itself will not lead to higher relapse rates measured if relapse itself is also defined by DAS28. What is of greater concern is that the relapse rate measured by DAS28 in the meta-analysis of 47% may in reality be even higher because of under-estimation by DAS28. I suggest to emphasize this in the discussion.

Figure 1
* Some rectangles contain numbers of included/retained studies (first and last), while others contain numbers of excluded studies (middle two rectangles). Although the text explains what is meant, it still makes the figure difficult to read. Please show in the bottom line of each rectangle the number of included/retained studies, e.g.

Records excluded (n=351): abstracts, reviews and unpublished trials without results 
(n=39)

Table 2
* It is unclear to me what is meant by the column "category" with values <1 and >1. Please clarify this.

* For the first study by Quinn et all., the event% is 70. But based on the number of events (3) and total number (10) I would expect an event% of 30 here. Please look into this and correct if necessary.

* For study number 5 by van den Broek et al., DAS44 rather than DAS28 was used. This should be changed.

General
* The included studies are not incorporated in the reference list. References to the studies included in the meta-analysis should be added to the main reference list and being referred to from the tables and figures and main text.

Minor concerns
* Introduction page 4: "(…) e.g. 5-6% in some Native American groups vs % in carribean region) [1]."

The percentage should be added and "carribean" should be written with a capital letter.
Introduction page 4: "The pharmacologic therapies for RA comprise of nonsteroidan (…)"
"of" should be removed.

Introduction page 4: "(…) increased risk of cancer and heart failure, demyelinating disorders (…)"
"and" should be replace by ","

Introduction page 4: "(…) sustained response, whether remission or even low disease activity and retarded radiographic progression in a number of published metaanyses."
This should be changed to: "(…) sustained response (whether remission or low disease activity) and retarded radiographic progression in a number of published metaanyses." And references to the metaanalyses should be added.

Introduction page 5: "favoring continuation and those with elective discontinuation after remission with almost half of the patients withdrawing biologicals maintaining low disease activity. [5,6]"
Reference 6 refers to the 1987 classification criteria for RA and seems not to be of relevance here.

Results page 8: "(…) were finally eligible for inclusion criteria."
"criteria" should be removed
Results page 8: "(…) and I²=68.92%) random-effects model was used."

should be changed to "(…) and I²=68.92%), hence a random-effects model was used"

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Unable to assess

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

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