Author’s response to reviews

Title: Tight controlled dose-reduction of biologics in psoriasis patients with low disease activity: a randomized pragmatic non-inferiority trial

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Author’s response to reviews:

Dear Editor,

Thank you for the useful comments made by the reviewers. We are grateful that you have given us the opportunity to resubmit our manuscript entitled ‘Tight controlled dose-reductions of biologics in psoriasis patients with low disease activity: a randomized pragmatic non-inferiority trial’.

Please see below a point-by-point reply to the comments made by the reviewers. In our revised manuscript, the changes are shown in green bold letters.
Comments of the first reviewer:

1. Investigators from Netherlands are planning to conduct a clinical trial to compare the dose-reduction of biologics in psoriasis patients with low disease activity (PASI ≤5) in comparison with control group who will be in the stable dose according to label of the biologic drug. They chose adalimumab, etanercept and ustekinumab. This is a very interesting idea because indeed some patients in the real clinical practice may be treated with lower dose but still not enough data are available to support this hypothesis. The design of the study is well prepared.

I have only one question to the authors: We know that some patients can stay in remission several months after stopping the biologic therapy. Maybe the interval you are planning to follow the patients (1 year) in the reduced dose is short? I can imagine that most of the patients during the 1 year follow up in a lower dose will do OK, but the question is for how long? Do you plan to continue the trial?

Reply: We fully agree with this comment. We have planned to do an extension study.

See discussion, page 13-14 line 338-340.

Comments of the second reviewer:

2. This clinical trial design would be informative in order to describe beneficial effects induced by a biologic therapy used in a dose tapering regimen. How cost-effectiveness will be calculated? Shall a comparison with the labeled regimen be performed?

Reply: The cost-effectiveness analyses will be performed with intention to treat analyses. A comparison will be made with the control arm where regular regime will be performed. We acknowledge that we gave minimal information about the analyses of the cost-effectiveness in the original manuscript. Therefore we revised this part in the following way:

Page 12-13, lines 310-320: “Thereafter, cost effectiveness analyses will be calculated based on the questionnaires medical consumption, productivity costs and generic health related quality of life measured with the SF-36. Because we anticipate non-inferiority we will primarily analyze cost-savings: direct medical cost as well as total costs (medical and non-medical costs) will be
compared between dose tapering strategy and usual care. A possible small but acceptable loss of effect can be incorporated in the analyses by determining a decremental cost-effectiveness ratio (DCER) by dividing the difference in costs by the difference in Quality Adjusted Life Years (QALYs) between the groups. The DCER expresses with how much money a loss of 1 QALY is compensated. If this amount is high the decision makers are willing to accept a loss of effect. Furthermore, the Net Monetary Benefit (NMB) per patient will be calculated for different levels of willingness to pay (WTP) in dollars per QALY, using the formula: WTP * effect (difference in QALY) - costs. This results in the net amount of money saved, when the possible loss of QALY is corrected for, using different WTP levels per QALY.”

3. How beneficial effects will be detailed if no arms with labeled regimen be performed?

Reply: I think that there is a misunderstanding. Patients will be randomized into 1:1 (1) dose-tapering strategy or (2) drug continuation strategy of the standard dose of adalimumab, etanercept or ustekinumab.

See also randomization, blinding, treatment allocation section, page 8, lines 186-188.

4. What is the evidence supporting the identification of DLQI and PASI of 5 as minimal disease activity? This should be supported somehow because it could represent a non-successful outcome if baseline PASI score was around 11/12, and not a minimal disease activity.

Reply: This is indeed a good point. DLQI ≤5 means mild influence on quality of life and is part of the published treatment goals (1-2-3). Zweegers et al. showed that the mean PASI of patients that remain on a biologic is ≤5 (4). Moreover, PASI≤5 is associated with low DLQI scores (5). Therefore we think that PASI ≤5 is a good threshold for minimal disease activity in general. In the exceptional case were PASI 5 still represents relatively active disease, DLQI score is expected to be high and patients will still be classified as having a flare.

See also: revised text definition of (persistent) disease flare, page 10, lines 250-255.


In your reply to our original submission you stated that it was possible to resubmit our manuscript. We would like to use this opportunity and hereby resubmit our revised manuscript for review in the ‘BioMed Central Dermatology’.

Yours faithfully,

S. Atalay, MD

On behalf of all co-authors