Author's response to reviews

Title: Prevention of exacerbations in patients with COPD and vitamin D deficiency through vitamin D supplementation (PRECOVID): a study protocol

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Author's response to reviews: see over
Amsterdam, 6 September 2015

Dear Editor,

Hereby we would like to submit our revised manuscript entitled ‘Prevention of exacerbations in patients with COPD and vitamin D deficiency through vitamin D supplementation (PRECOVID): a study protocol’.

We would like to thank the reviewers for their time invested in reviewing our manuscript and their constructive comments. We will answer the issues raised by the reviewers point-by-point. Changes in the manuscript are indicated by an underlined text in red colour.

Reviewer 1
I would like to see a power calculation showing that the study is powered for the primary outcome.

The primary outcome for our study is exacerbation rate. In the section ‘sample size calculation’ (line 274-282), a power calculation is given for this outcome. The study is designed to demonstrate a minimum difference of one exacerbation per patient-year between the vitamin D and the placebo group. Our assumptions are based on post-hoc analyses of the RCT by Lehouck et al. which had a similar patient sample, although without selection for vitamin D deficiency. We hope this calculation is clear and are gladly willing to answer remaining questions.

Reviewer 2
1. Although weekly dosing may have some PK benefits over monthly / 2-monthly dosing, adherence is likely to be less good. What provision will be made to optimise adherence and to monitor it?

We agree with the reviewer that adherence might be less good with weekly dosing. Regular telephone contacts are planned to inquire about the study medication use and to remind participants of the medication. If deemed necessary, telephone contacts are planned more frequently. Also, participants are asked to note in their diary cards whether they took their medication every week. Finally, participants are asked to bring their medicine bottles every visit, so the remaining tablets can be counted as a measure for compliance.

2. The trial by Lehouck et al showed a benefit only in those with profound D deficiency – i.e. with baseline 25(OH)D <25 nmol/L. Are there any plans to conduct a sub-group analysis in this group?

We thank the reviewer for this good suggestion and have added this to our study protocol.

3. Adherence to completion of a study diary may be much less than 100% - is there a run-in period, and is proven ability to complete the diary an eligibility criterion? It should be.

There is no run-in period for the diary card due to logistic reasons. During the study period frequent telephone contacts are planned to maximize adherence. Ability to complete the diary card is indeed an eligibility criterion and is defined in the eligibility criteria as an exclusion criterion as ‘those who are judged by the investigator to be unsuitable for the study’.

4. Do the authors see any ethical issue in randomising patients with known vitamin D deficiency to placebo?

During the study, participants are allowed to use 400 IU vitamin D3. This is the recommended daily intake by the Dutch Health Council in the Netherlands. Because of the higher supplementation dose
needed, participants with a severe vitamin D deficiency (i.e. <15 nmol/L) are excluded from the study.

5. Multiplicity of secondary outcomes: there is a very large no. of secondary outcomes – this could lead to type 1 error. Is any adjustment for multiple analyses being made for this multiplicity? If no correction is to be applied, then the investigators may wish to add a comment to the effect that analysis of 2y outcomes is exploratory in nature. Participants are being asked to complete a large amount of paperwork, including at least 5 questionnaires - SGRQ, SF-12, CCQ, HADS, CESD. Will this heavy requirement adversely affect retention /follow-up?

We acknowledge that by including all secondary outcomes a type I error is more likely to occur. But as all the analyses for the secondary outcomes are exploratory in nature we will not apply a correction. We have added this in the manuscript.

Regarding the second part of the question, we agree that this is a large amount of paperwork. Prior to the start of the study we discussed the several study procedures with a patient panel. We have also presented them the questionnaires and asked their feedback. The participants did not experience this as a heavy requirement. Because of the added value of each questionnaire we decided to implement them all.

6. Abstract, Background: The authors write: ‘Previous studies have not demonstrated a beneficial effect of vitamin D on exacerbation rate in COPD patients. However, posthoc subgroup analyses suggested protective effects in vitamin D deficient patients’. This is not completely accurate – the ViDiCO trial (Lancet Res Med 2015) pre-specified sub-group analysis among participants with baseline D deficiency, and found a protective effect – these analyses were not post hoc.

This is indeed incorrect. We have adjusted this in the manuscript.

7. Immunological outcomes. Lines 248-256: some details of immunological outcomes are not provided. For example, ‘Pro- and anti-inflammatory cytokines will be analysed’ – which? Lines 294-5 – both the previous trials explored immunological mechanisms – this feature of the Precovid trial, while worthwhile, is not novel.

In the manuscript we have added a more elaborated explanation of the immunological outcomes (lines 254-272). While previous studies have explored immunological mechanisms, to our knowledge no study has measured inflammatory cytokines and antimicrobial peptides in nasal secretion and performed experiments with in vitro stimulation of PBMCs before.

8. Other RCTs of vitamin D supplementation have reported that genetic variation in the vitamin D pathway can modify the effects of supplementation (e.g. Martineau et al, Lancet 2011). Will participants be genotyped to detect such effects?

Blood samples of participants will be collected and frozen in order to allow future DNA isolation. In case of additional funding genotyping of all participants will be performed.

9. It is recognised that a proportion of exacerbations do not precipitate consultation with a doctor, and so remain untreated with antibiotics / steroids. Is any attempt being made to capture such ‘unreported exacerbations’?

As our primary outcome, an exacerbation is indeed defined as sustained worsening of respiratory symptoms during 48 hours requiring oral corticosteroid, antibiotic or combination treatment that was initiated by a physician.
During the study, participants are also asked to register their symptoms in their diary cards, whether or not they consulted a doctor or used medication. In this way, we hope to capture all exacerbations.

We hope the revised manuscript is suitable for publication in BMC Pulmonary Medicine.

On behalf of all authors,

Thanking you in advance,

Yours sincerely,

Rachida Rafiq, MD