Reviewer’s report

Title: A multi-center randomized, controlled, open-label trial evaluating the effects of eosinophil-guided corticosteroid-sparing therapy in hospitalised patients with COPD exacerbations - The CORTICOsteroid reduction in COPD (CORTICO-COP) study protocol

Version: 0 Date: 23 Feb 2017

Reviewer: Magdlena Paplinska-Gorya

Reviewer's report:

COPD is a complex, heterogenous disease which can be manifested in many phenotypes. Phenotyping of COPD may be based on clinical (e.g. emphysema with/without bronchial thickening, chronic bronchitis) or biological (e.g. eosinophilic, neutrophilic) criteria. Biomarkers such as eosinophils are useful tool for the identification of the different inflammatory patterns within COPD.

The role of eosinophils in the context of COPD course and response to CS treatment has been well recognized. High blood eosinophilia is associated with some COPD exacerbations. The number of blood eosinophils was reported as an informative predictor of positive response to CS measured as reduction in exacerbation rate. The hierarchical clustering of obstructive lung disease patients performed by our team showed that the most relevant cellular component differentiating mild-to-moderate COPD sub-groups was blood eosinophil percentage.

In the context of many clinical trials (initiated by pharmaceutical companies) evaluated effectiveness of CS or ICS treatment in COPD patients, the Independent Research entitled "A randomized, GCP-controlled, multi-center trial evaluating the effects of eosinophil guided corticosteroid-sparing therapy in hospitalized patients with COPD exacerbations - The Corticosteroid reduction in COPD (CORTICO-COP)" is very needed. The study protocol by Pradeesh Sivapalan et al. will be realized with the cooperation of nine divisions from Denmark and UK. The results of this trial may evaluate and verify the rationale for CS treatment in COPD exacerbations which will be pharmaco-economic beneficial.

MAJOR COMMENTS

1. In the section Study design, randomization and intervention authors wrote (line154-155):

"If a patient is discharged during the treatment period, a treatment based on the last measured eosinophil count will be prescribed for the remaining days within the 5 day-period."

I would suggest to withdraw such participants from the study because the intervention group should be treated only on the basis of increased blood eosinophilia and evaluation based on the
last measured eosinophil count in hospital (1-5 days before) will not be done precisely and the treatment may be given even when the patient has normal blood eosinophil number.

2. Exclusion criteria should contain: Patients receiving long-term oral CS for treatment of co-existenting lung disease, or who have received CS treatment within the past three weeks prior to the start of the study.

3. A figure with the study design should be done.

MINOR COMMENTS

1. I would suggest to add more information regarding demographic and baseline characteristic of patients, such as disease symptoms duration, BMI, increased cough, number of exacerbations in the past, atopy status in measurements.

2. Although the statistical calculations of sample size are correct, I found some inconsistency in one-side/ two-side test evaluation. Firstly, the authors wrote about one-sided test "We will accept a null hypothesis if the length of hospital stay in the intervention group is similar, shorter or within 1.2 days as that observed in the SC arm 14 days after recruitment." However, later they calculated with "two-sided 5% significance level". If they had calculated the power for one-sided test, the number of participants in one group would have been 250 (total 500) or 250 for 90% power test.

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.

Yes

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

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics
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