Author's response to reviews

Title: Inflammation and corticosteroid responsiveness in ex-, current- and never-smoking asthmatics

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Author's response to reviews: see over
To: Tonilynn Manibo  
Editorial offices  
BioMed Central  

Groningen, 20 July 2013,  

Dear Dr. Manibo,  

We are thankful for the comments of the reviewers. They have been of great help to improve our manuscript entitled “Inflammation and corticosteroid responsiveness in ex-, current- and never-smoking asthmatics” (MS ID: 1964287129960689).  

Please find a point-by-point response to the reviewers comments below. In the revised version, deletions have been highlighted with strikethrough and red color. New insertions have been highlighted with underline and blue color.  

We hope that you will now find our manuscript suitable for publication in *BMC Pulmonary Medicine*.  

With the best regards,  

Also on behalf of all authors,  

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Point by point response to the comments of the reviewers

Reviewer 1:

Major comments

1. It is very important finding that after 1-year treatment, significant improvement in ex-smoker was observed, which was not significant after 2-wks treatment. But, the trend of ΔFEV1 (%pred) after 2-week treatment (8.1, 4.1, 2.4 (table 3), never-, ex-, and current-smoker, respectively) and 1-year treatment (10.2, 5.1, 3.1 (table 4)) seems to be fundamentally the same (Never- > Ex- > Current-). It seems not to be a firm conclusion that “Although ex- and current-smokers have a reduced short-term CS treatment response, their long term response appears to be comparable to that of never-smokers (Conclusion in Abstract)” because the patient population analyzed for 2-week and 1-year treatment response is different as shown in Figure 1. This point seems to be limitation of this study and it is better to be stated in Discussion.

The reviewer correctly points out that the short- and long-term corticosteroid response was not investigated in the same groups due to the design of our study. We now discuss this issue in the revised version of our manuscript. (pages 17-18, lines 23- 7)

Our study was originally a three-arm study (figure 1). However, in the 2-week treatment analyses we included only patients treated with ICS, and in the 1-year treatment analyses we excluded one group of patients who were treated according to a program with step-down and eventually complete discontinuation of corticosteroids, which is not in agreement with the current guidelines. Due to this study design, the short- and long-term corticosteroid response was not investigated in the same groups. In this context, it is important to mention that the randomization of the study was performed with minimization for smoking status, age, previous dose of ICS, FEV1 %predicted, reversibility after 200 µg of salbutamol, PC20 methacholine, and serum IgE. This minimization ensures comparable treatment arms with minimal baseline differences, resulting in similar distribution of ex-, current- and never-smokers across the treatment arms.
2. Table 4: The number of treatment group in 1-year study seems to be different between Ex-, Current-, and Never- smokers (11/10, 6/11, 20/17, FP500/self management). Final dose of ICS in each group should be stated.

The reviewer is correct: in both long-term treatment groups, i.e. the fixed dose and self-management group, there were more never-smokers than ex- or current-smokers with asthma. The number of ex-, current- and never-smokers did not significantly differ between the two treatment groups (chi-square p=0.42).

In the self-management group, the median daily dose of fluticasone over the 50-week period was 275 µg/day (range 200-1375 µg/day), which was significantly lower than the 500 µg/day in the fixed-dose group. We have now added this data to the manuscript (page 12 lines 9-11)

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**Minor Essential Revisions**

1. Were Baseline characteristics in Table 1 drawn from the data at V2 (Figure 1)?

Yes, the baseline characteristics are taken from V2. We have now made this clearer by adding the following text in the results section (page 10 line 4):

   Their baseline characteristics, after tapering of ICS (visit 2), are presented in table 1.

2. Were Bronchodilators not consistently used during throughout the study?

   Although it seems to be noted in Online supplementary file (l. 2), it is better to be stated in Method section.

The reviewer is correct that rescue medication was available during the study. We have moved the following text from the online supplement to the methods section (page 7 line 11-12):

   Rescue medication consisted of salbutamol 400 µg via Diskhaler. No other concomitant pulmonary medication was allowed.
3. Self-management plan in Online supplementary file:
According to the plan, the dose of fluticasone cannot be stepped down. Is it correct?
1. “If PEF ≤ 80 of PB, continue maintenance treatment” If PEF ≤ 80

We apologize for the confusion we may have caused. It appears that there were 2 typos in our self-management plan. At point 1 of the self-management plan where it said ≤ 80%, it should have said ≥ 80%. Additionally, in the main text it says that the patients started with a dose of 2000 mcg/day. However, this should be 200 mcg. We have corrected these mistakes in the main body and in the online supplement. Thus, if a patient then follows the self-management plan he could go up in dose according to the plan and when symptoms and PEF return to normal he could decrease the dose again (step 2-4). It is not possible to go below 200 mcg/day.

4. Online supplementary table 4 (later table) Differences in clinical and inflammatory variables between ex-, current and never-smokers at baseline#
Online supplementary table 5 Differences in clinical and inflammatory variables between ex-, current and never-smokers after 1-year ICS treatment
(Appears in Discussion section p. 16 l. 5)

As the reviewer correctly points out there were two tables named online supplementary table 4. We have now corrected the numbering of the online supplementary tables.

Discretionary Revisions
1. It is potentially interesting to see the relationship between the term from smoking cessation and the pattern of airway inflammation.

We thank the reviewer for this interesting suggesting. Accordingly, we investigated the relationship between the duration of smoking cessation on the inflammatory patterns in our study. We did not find any effect of the duration of smoking cessation on the levels of inflammation. It is possible that the inflammatory profile does not change after smoking cessation. However, due to the relatively small sample size of
our ex-smokers an alternative explanation could be a lack of power. Therefore we have decided not to use these results in our manuscript.
Point by point response to the comments of the reviewers

Reviewer 2

Major comments

1. The main message of the manuscript is not precisely clear. The abstract conclusion appears non-committal about whether 1-year steroids improve asthma equally in smokers, and the ‘Conclusion’ section concentrates on the suggestion that the steroid response is inflammation related rather than specifically smoking.

We agree with the reviewer that the main message of the manuscript could be expressed more clearly. To make the abstract more clear, we changed the last conclusion of the abstract. It now reads (page 2 line 25)

Although ex- and current-smokers have a reduced short-term corticosteroid treatment response, we did not find a difference in their long-term treatment response. Their long-term response appears to be comparable to that of never-smokers.

Furthermore, we changed the conclusion of the discussion. It now reads (page 18 line 15-18):

Although we agree with the literature that ex- and current-smokers have a blunted short-term response to ICS, we did not find a difference in their long-term treatment response. Therefore, they should not be withheld from ICS treatment. Our data suggest that they nevertheless should not be withheld from ICS treatment, since their long-term response is similar to that of never-smokers. This long-term treatment response, even in current-smokers, is not driven by neutrophilic inflammation, but by eosinophilic inflammation.

Points of clarity:
1. **Abstract:** *In the methods: put the n= number in brackets corresponding to the 2-week and 1-year components. This will help recap when the study structure is eventually understood later.*

We have now added the numbers corresponding to the 2-week and 1-year components in brackets as suggested by the reviewer. Thank you!

2. **In the last sentence of Results it should state if ‘no differences’ related to cells and/or lung function.**

We have added the following to the sentence (page 2 line 20):

   In contrast, no differences in ICS treatment response in lung function or inflammatory cells were found between the three groups after 1 year.

3. **Introductions: third paragraph, first sentence: one of the comparisons presumably was intended to mean ex-smokers.**

The studies that were referred to did not include ex-smokers, therefore there were no comparisons with ex-smokers. What we attempted to state was that the studies mentioned showed a significant improvement in FEV\textsubscript{1} in never-smokers and no improvement in FEV\textsubscript{1} in current-smokers. However, when directly comparing these 2 no significant difference was found. To make this clearer we changed the paragraph as follows (page 4 lines 15-24).

   The few studies investigating the effects of smoking on the short-term efficacy of oral or inhaled corticosteroid treatment in asthma, demonstrate suggest that the forced expiratory volume in one second (FEV\textsubscript{1}) improves significantly in never-smokers, but not in current-smokers, less in current- than never-smokers, although none of these studies found statistically significant differences between never- and current-smokers.[7,13-15] However, none of these studies found statistically significant differences in improvement in FEV\textsubscript{1} when directly comparing never- and current-smokers. The only study that included ex-smokers, showed no improvement in FEV\textsubscript{1} or asthma control after 2-week oral corticosteroid treatment in ex- and current-smokers.[15]
4. Study design: can the ‘step-down’ aspect be removed. If these patients are not studied at the latter stage then mentioning this creates unnecessary confusion.

We have removed the step-down protocol from the study design. We now briefly mention how this arm was treated and why these patients were not included in the analyses (page 7 lines 6-9). We have additionally removed the step-down group from Figure 1. The text now reads:

The fluticasone 2000 µg/day arm followed a program with step-down and eventually complete discontinuation of corticosteroids. The latter is not in agreement with the current guidelines and therefore this arm was removed from our long-term analyses.

5. Methods section: can you briefly explain ‘b’ for Table 2. Most readers are likely to better understand r (rho) correlation coefficient.

We have now added the following sentence to the statistical methods (page 9 lines 15-17):

The reported correlation coefficient (b) signifies the change in an outcome variable (e.g. FEV₁) for every unit increase of the predictor variable (e.g. cigarettes/day).

6. For all table, it’s clearer to use a comma instead of a hyphen when describing a range thus avoiding confusion with the minus sign.

We have changed the hyphen for a comma in all Tables as suggested.

7. Table 1: could the steroid doses be additionally as beclometasone-equivalent on another line for easier comparison.

The reviewer has a good point here. However, as at baseline (after ICS tapering) only 6 patients still used ICS (2 patients in all 3 groups). We have added a line in the table with the number of patients using ICS after tapering. However, as there are only 2 patients per group using ICS we have not added a median ICS dose with
During the ICS tapering period, 16 patients returned to the hospital earlier due to symptoms compatible with an asthma exacerbation. From these 16 patients, 6 still used ICS at the start of the treatment period (2 ex-smokers, 2 current-smokers and 2 never-smokers) with a median beclomethasone equivalent dose of 450 µg/day (range 400 – 800 µg/day); the remaining 10 patients had discontinued ICS completely for a median period of 12 days (range 2 – 21 days).

8. **Table 1: Can the authors comment on the surprising finding that the FeNO at baseline was no different between the smoking groups, which is inconsistent with most literature.**

We agree with the reviewer that it is surprising that no differences in FeNO were found. However, when one looks at the numbers of the three groups there appears to be some effect of smoking on the FeNO. The current-smokers appear to have a somewhat lower FeNO than the ex- and never-smokers. Although the ANOVA test is not significant, there is a clear trend (p=0.058). For this reason, we feel these data to be consistent with the literature, i.e. lower FeNO in current-smokers.

9. **The legend for Figure 2 could provide more information in particular to explain how the magnitude of the response was calculated. The authors could comment on whether the findings by others reporting improvement only among non-smokers might be interpreted differently if the magnitude of the response was used.**

The magnitude of response per patient was calculated by subtracting the value of a variable at baseline (e.g. FEV₁) from the value after treatment (i.e. after 2-week or 1-year treatment). Tables 3 and 4 report the median of the values found. We believe it is quite important to directly compare the results between groups directly. As mentioned previously the earlier studies investigating ICS response in never- and current-smokers only found that never-smokers improved significantly and current-smokers did not improve significantly. However, when these studies compared the
response between the groups they were unable to detect a difference between current- and never-smokers.

10. **Could the authors add a comment in discussion on whether there was an effect of asthma severity in their analysis and if there was any attempt to monitor steroid compliance over the year.**

We agree with the reviewer that asthma severity may be an important factor in the response to ICS. In line with this, it is important to mention that at baseline there were no differences in asthma severity between the smoking groups. There were no differences in FEV₁, reversibility to bronchodilators and bronchial hyperresponsiveness. However, since it has previously been shown that the baseline value of variable is the most important predictor of response (i.e. patients with a low value have more room for improvement than patients with an almost normal baseline value, Meijer et al. Clin Exp Allergy. 2002 Jul;32(7):1096-103), we corrected for this baseline value in all corticosteroid response analyses.

At each visit the study medication had to be returned by the patients. The medication was then checked to see if the patients had used them. However, there was no formal compliance registration.
Point by point response to the comments of the reviewers

Reviewer 3

Reviewer 3 provided no comments