Author’s response to reviews

Title: Concordance for Changes in Allergic Asthma Domain Variables after Short-term Corticosteroid Therapy

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Author’s response to reviews:

1. Editor comments

Major points

REVIEWER COMMENT

RESPONSE

It is not specified in the inclusion criteria whether patients with asthma were taking inhaled or systemic steroids prior to admission to the study. Clarifying this point is mandatory.

Answer: To be eligible, all subjects were required to be off corticosteroids or any other asthma controller for prescribed periods before the study. This has been clarified in the revised manuscript in the methods section (page 6).

It is not clear whether patients with asthma were taking short or long-acting bronchodilators. This condition must be declared as being able to modify lung function.

Answer: All subjects who did not have a rescue medication were prescribed a short-acting bronchodilator (albuterol metered dose inhaler 1-2 actuations or albuterol Inhalation Solution 0.083%-unit dose; 4-6 times daily via nebulizer), as needed. This has been clarified in the revised manuscript in the methods section (page 6).
The percentage of subjects with atopy is not reported as well as the clinical condition responsible for the aggravation of asthma. These conditions are associated with FeNO levels both in baseline and after steroid therapy.

Answer: Based on the commonest terms captured via medical history at screening, food allergy was present in 30.1%, nasal allergies in 18.1% and atopic dermatitis in 3.5%. This information has been added to Table 1. We did not capture the etiology of the asthma worsening and this has been clarified on Page 6 line 98. The etiology could have been due to allergic exacerbation, viral illness, non-compliance with therapy or other causes. Eligibility was not restricted to any particular etiologies.

Knowing all this information can improve understanding the different behavior of FeNO, lung function and ACQ in response to steroid therapy.

Answer: This is acknowledged

Minor points

The score of the ASX questionnaire is not clearly described.

Answer: The ASX consisted of symptom questions regarding wheezing, coughing, tightness of the chest, breathlessness, and activity limitation during the day and wheezing, coughing, tightness of the chest, breathlessness during the night each scored from 0-4 making a total potential score (TASX) of 36 for day and night together. A description has been added to the methods section (page 6-7)

The years of asthma duration as well as the age of onset of asthma are important conditions for assessing the degree of reversibility and the presence of airway remodeling which, as the authors report in the discussion (lines 257-8), can justify the discrepancy in the failure to improve lung function with respect to respiratory symptoms and FeNO.

Answer: The duration and age of onset of asthma have been added to Table 1.

It is also not reported how many subjects take cortisone systemically and what dose is administered.

Answer: Only 3 subjects were started on prednisone at V1. This information has been added to the results section (page 9)

The Authors should evaluate whether the results of the study change as a function of route of steroid administration (oral vs intravenous), age (young vs adults), atopy (allergic vs non-allergic...
asthma), sex (men vs women). They should perform a multivariable analysis as well as subgroup analysis, the latter as a sensitivity analysis.

Answer: We had already included the concordance in the adult and the pediatric subsets in the report. On consideration of this comment, subset analysis would result in much smaller sample sizes, so we don’t think subset analyses would add to the manuscript.

Reviewer 1

I am not sure that ASX, a new questionnaire instrument, is adding so much to the present paper. As it is a novel instrument, it deserves a separate paper to be validated. In the present form, a non-validated instrument, which is not described in detail, is not strengthening the present manuscript.

Answer: We agree that the instrument is novel and unvalidated. However, the scores showed highly significant changes from V1 to V2 and concordance with the ACQ, which anchors the instrument. We therefore respectfully prefer to keep this endpoint in the manuscript as it adds to our understanding regarding the relationship between different asthma domains.

ACQ-6 should have been used instead of ACQ-7 if the authors wanted to disentangle symptoms from lung function. I suggest the authors to make the same analyses for ACQ-6.

Answer: We have now completely rewritten the manuscript based on the ACQ6. In general, there were few changes in the findings reported.

Doses of ICS and proportion of subjects starting OCS should be presented

Answer: Only 3 subjects were started on prednisone at V1. This information has been added to the results section (page 9)

Is there any information available on IgE sensitization? If yes, this should be included.

Answer: IgE and specific IgE were not assessed in this study. Based on the commonest terms captured via medical history at screening, food allergy was present in 30.1%, nasal allergies in 18.1% and atopic dermatitis in 3.5%. This information has been added to Table 1.

Is there any information available on adherence to medication? If yes, this should be included.

Answer: Self-reported daily compliance with the corticosteroid therapy was captured by subjects or their caregivers for children in the asthma diaries. On review of this data, 84 of 85 subjects complied with corticosteroid therapy started at V1. Only one subject appears to be non-
compliant across all 14 days of study. We have added compliance data to the manuscript (page 9).

A reference regarding validation of Fenom PRO towards other FeNO instruments should be included.

Answer: We have added reference to a recently published manuscript comparing Fenom Pro to other analyzers[1].

Reference 13 is not about anti-IgE treatment, but about optimized anti-inflammatory treatment (ICS +/- LTRA).

Answer: The author is correct, and we have removed this reference.

Reviewer 2:

Introduction clear and without references

Answer: We have added references.

The aim of the study is not clear

The focus of this report is an analysis of concordance for separate asthma domains based on a study performed for regulatory objectives.

Answer: The objectives of the study are outlined at the end of the introduction on page 4 and in the methods section on Page 5.

The rationale for including only patients with high FeNO levels is not clear and far from real clinical practice

Answer: It is increasingly recognized that FeNO is predominantly a marker for Type-2 asthma (eosinophilic asthma). The design of a study required for the regulatory approval of a novel FeNO monitor in the US requires that the Sponsor demonstrate a significant reduction in FeNO before and after corticosteroid therapy in conjunction with assessment of changes in asthma control and lung function. If Subjects with a normal FeNO were included (presumably non-Type 2 subjects), a fall in FeNO would not be anticipated. We have explained this in the methods section on Page 6.

Figure 2, I would not show the machine
Answer: We would like to keep this figure in the manuscript if acceptable.