Author’s response to reviews

Title: Elevated serum OX40L is a biomarker for identifying corticosteroid resistance in pediatric asthma patients

Authors:

Su-Li Ma (m950094@qq.com)
Lei Zhang (taizhouzl680511@126.com)

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Author’s response to reviews:
Reviewer reports:

Kirsten Kloepfer (Reviewer 1): This is an interesting look at utilizing serum OX40L to determine if it can be used as a biomarker for corticosteroid resistance. I have a few questions/comments about this article.

1. A native English speaker should proofread the paper. There are numerous grammatical errors.

Reply: The manuscript was edited by a native English speaker to reduce the number of grammatical errors as much as possible.

3. Consider making your hypothesis stronger. Instead of stating that it "may be associated" you may want to chose a side and state that "it will be associated" or "it won't be associated."

Reply: We revised the sentence about hypothesis (Page 5 line 4).

4. Choose one way to refer to study subjects and use it throughout the manuscript. For example, use "subjects, patients, or participants."

Reply: We have unified study subjects as "patients" throughout the manuscript.

5. Page 5 line 46 reads, "all patients received inhaled corticosteroid (ICS) therapy," but this includes the healthy age-matched control patients. Did everyone receive ICS or only those in the asthma group?

Reply: All 192 pediatric asthmatic patients received inhaled corticosteroid (ICS) therapy, but the healthy control subject received no treatment.
6. How did you chose 10% improvement within one week as a marker of steroid sensitivity? Is this based on previous studies in the literature?

Reply: In our study, steroid-sensitive asthma was defined as more than 10% improvement in FEV1, and steroid-resistant asthma was defined as less than 10% improvement in FEV1. This is based on one previous report and we added it as reference 14.

7. I have seen definitions for steroid sensitivity in the literature with a definition based on response to oral corticosteroids for 7 days rather than ICS/LABA for 7 days. Please site your reference(s) for your methods.

Reply: Because Inhaled corticosteroids (ICS) are widely used in pediatric asthmatic patients, we chosen patients with ICS as study population. This is based on reference 13.

8. Table 1: Unable to determine difference between * and #. Consider including cell counts in absolute numbers, particularly the absolute eosinophil count.

Reply: We made a mistake and redefined * and #. We added absolute numbers of eosinophils, neutrophils, monocytes and lymphocytes.

9. Page 9, lines 32 states, "patients with high OX40L required higher doses of corticosteroids for the initial ICS response." I did not see this reported in the results.

Reply: This is a conjecture and we made a slight revision to make the meaning more clear.

10. Page 9, line 56-page 10 line 12. I do not understand how these sentences about IL-6 support one another.

Reply: Serum OX40L shows positive correlation with IL-6 in asthmatic patients, so its is one potential indicator of corticosteroid resistance. The mechanism underlying corticosteroid resistance by IL-6 may be associated with Th2/Th17-mediated airway inflammation and airway hyperresponsiveness. We revised these sentences.

11. Page 10, line 10. "Therefore pour results indicted an obvious..." This is an overstatement. You may consider replacing it with, "our results suggest/support OX40L..."

Reply: We revised this sentence and thanks for your suggestion.

12. Page 11 lines 5-7: "Moreover steroid can be combined...." Does this already exist? or are you suggesting this as a next step in your research?
Reply: As OX40L is a potent contributor of airway hyperresponsiveness and corticosteroid resistance, we speculate that inhibitors of OX40L is potential agents for SSA patients.

13. Page 11 line 29: "The limitations of the present study are incomplete data..." What data is incomplete?

Reply: Incomplete data means that this study only shows the association between OX40L and corticosteroid resistance, with no cause and effect analysis. This expression may be inappropriate, so we deleted this word.

14. You may consider expanding your strengths and limitations paragraph.

Reply: We revised this paragraph according to your suggestion. Thanks.

Yvonne Huang, MD (Reviewer 2): Overall an interesting scientific premise to examine OX40L levels in a clinical cohort to explore relationships to steroid-responsive vs. -resistant asthma. However, there are a number of issues that need to be addressed.

1. The Ethics statement is not sufficient in that it potentially conflicts with the described study design, specifically the statement of ICS/salbutamol administration in Methods (page 5 lines 46-49) to determine steroid sensitivity by ICS. Please readdress and in consideration of point #2 below.

Reply: This is a retrospective clinical study and relied on frozen serum and medical records. In our clinical practice, pediatric asthmatic patients received inhaled corticosteroids (ICS) therapy. This study did not provide intervention on patients. The steroid sensitivity by ICS was determined based on reference 14.

2. Per above in Methods, need to better describe what ICS therapy (type, dose) was administered, and was this standardized (the same) for all subjects or patients? Differences in this may impact the results. What was the context for this intervention (clinical or investigational design)? Also what was the rationale for determining response by ICS and the criteria used to determine responsiveness? Typically oral (or systemic) administration of steroid has been used in clinical trials. Finally there is typo regarding definition of SRA (line 54).

Reply: We add detailed information to better describe type and dose of ICS therapy. This retrospective study did not provide intervention on patients and divided into groups according to response to ICS therapy. The rationale and criteria for determining response by ICS was based on reference 14. In pediatric asthmatic patients, inhaled corticosteroids (ICS) are more widely used compared with oral or systemic corticosteroids.
3. Please highlight subheadings for each section in the Results, perhaps in bold or underline. Also spell out abbreviations on initial mention, e.g. VDBP.

Reply: We highlighted subheadings for each section in the Methods and Results, and added full name of VDBP.

4. Finally, it is strongly suggested that assistance be obtained from a native English writer to review and proofread for language edits. There are a number of grammatical, typographical, or syntax errors that need to be corrected.

Reply: The language was edited by a native English writer to reduce the number of grammatical, typographical, or syntax errors as much as possible.