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LETTER TO THE EDITOR

Low dose treatment of mice with bacterial extract (OM-85) for attenuation of experimental atopic asthma in mice – Reply

From the authors,

We thank Profs. Holt and Strickland for their interest in our study. In their Letter to the Editor following our publication, a series of issues were raised: (1) how we have chosen the treatment outcomes in our study; (2) interpretation of our lung function findings; and finally, (3) our results of lung cytokine responses in our model.

Lung inflammation (eosinophil airway influx) and airway hyperreactivity (AHR) have been considered the main outcomes in the ovalbumin (OVA) murine asthma model. Hence, the number of eosinophils in bronchoalveolar lavage (BAL) was defined as the main outcome of our study. The experimental model of allergic pulmonary response in mice sensitised by OVA is predominantly eosinophilic, with a stronger response than in humans, and in the authors' opinion, any novel therapies for this type of allergic asthma should demonstrate a significant decrease in the number of this effector cell in the lungs. This model historically shows a significantly decrease in lung eosinophils in response to well-established asthma treatments, such as corticosteroids.[1] Unlike what Holt and Strickland point out, our main results were presented in Figs. 2B and 3B, showing that regardless of the dose of OM-85 used with human-equivalent doses, eosinophil numbers in BAL are not reduced. Histological findings, as stated by Holt and Strickland as an important outcome, were considered mainly illustrative in our results, given that we had not performed any semi-quantitative analysis.

Lung function in this model has also some caveats. The measure of airway resistance by itself should not be used as a marker of therapy response in this model. We have shown that airway resistance was not significantly reduced by OM-85 treatment in this murine asthma model. However, although surrounded by controversies, the best approach for evaluating the physiological lung response to interventions in this model is the methacholine airway challenge, but we have not tested that in our protocol, which has been mentioned as one limitation of our study in our article.[2]

Cytokine tissue responses are always part of a complex scenario and should be interpreted with caution as a key marker of ''clinical'' response to treatments in this model or in human studies. Cytokine analyses are essential for understanding mechanisms of disease or for studying future therapy targets. However, discrepancies between cytokine levels, cell numbers, and other parameters are not uncommon in this model and should be hence interpreted with caution. We have shown that OM-85 significantly decreased IL-5 and IL-13 in BAL samples. These findings are interesting and should be better explored in future studies.

In this context, it has been widely discussed that the OVA-induced asthma murine model has translational limitations and is open to criticism, with strengths and weaknesses. However, this model is still extensively used, especially in pre-clinical studies.[1] The strengths of our study are the following: (1) we have treated animals with OM-85 prior to allergen sensitisation, an approach which is very attractive for translational purposes; (2) we have used doses of OM-85 for mice based on appropriate methods of dose translation between species[3] (previous studies do not mention on which basis the high doses used were calculated[4,5]); and finally, (3) we have chosen the analysis of the most important effector cell in the lungs of allergic asthma as our main outcome.

We acknowledge the fact that many studies have demonstrated the efficacy of OM-85 in reducing respiratory infections, and our original hypothesis of this study was indeed that OM-85 would reduce significantly the number of lung eosinophils. However, we assumed based on our results that early life (prior to sensitisation to OVA) treatment with OM-85 (in the doses we have used) seems not to inhibit the development of pulmonary eosinophilic response, which is the pivotal effector cell in Th-2 mediated asthma. In medical science, more than a couple of studies are always required to better answer clinical questions, and in this case, we believe that other mechanisms of disease such as AHR could be further explored as a target for the effectiveness of OM-85 in asthma.

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