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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



In a recent study from Rodrigues and colleagues published in this journal,¹ the authors reported that pre-treatment of mice with OM85 prior to sensitisation and challenge with OVA failed to prevent ensuing development of experimental atopic asthma. These findings contrasted with earlier results from our group using OM85 in rats,² and from others using the agent in mice.³ All three studies employed related experiment models involving intranasal challenge of pre-sensitised animals with relevant allergen to trigger asthma-like responses which were characterised by increased airways resistance accompanied by eosinophil recruitment. The key difference between the studies was that Rodrigues et al.¹ used much lower treatment dosages of OM85 which were derived by extrapolation on a mg/kg basis from those currently used in humans, as opposed to the much higher “pharmacological” dose ranges utilised earlier.^{1,2}

However, the crucial issue we wish to raise is that the treatment outcome (or lack thereof) claimed by the authors using these low OM85 dosages appears to be at variance with the data they actually show in the paper. As demonstrated in Fig. 3F from their publication,¹ peribronchiolar infiltrates of inflammatory cells (predominantly eosinophils) were indeed observed in lung sections from both OM-treated and untreated OVA-sensitised mice after intranasal challenge with OVA allergen, and this finding appears to be the basis for their conclusion that treatment was “ineffective in preventing experimental asthma development”. However, the important finding which was not addressed in detail by the authors in the paper was that while this cellular response was accompanied by a statistically significant increase in airways resistance (the physiological hallmark of the asthmatic response) in the untreated animals, *the corresponding physiological response in OM85 treated animals was at least halved, and the overall difference in airways resistance between these animals and untreated controls at the conclusion of the study did not achieve statistical significance* (Fig. 6 in Ref. [1]), i.e. according to the data shown, the allergen-challenged OM85-treated animals did

not express “experimental asthma”. At first sight, this finding may appear paradoxical. However, the accompanying BALF cytokine data from these treated animals shown in Fig. 5 (Ref. [1]) provides a highly plausible mechanistic explanation for this finding: notably a 90% reduction in local release of IL-5 in the airways of OM85 treated animals and an equivalent reduction in IL-13, consistent with earlier findings of treatment-associated attenuation of allergen-induced Th2 responses in models employing higher OM85 dosages.^{2,3} IL-5 in particular is the principal cytokine required for activation of recruited eosinophils, and in the absence of this signal these cells are likely to remain in a quiescent state, and this could readily account for the absence of the clinical response (increased airway resistance) in the treated animals (Fig. 6) despite the presence of the eosinophil infiltrate (Fig. 3F).

We are encouraged that these effects of OM85 are demonstrable at the low treatment doses employed by Rodrigues et al.¹, and plan to pursue these and other dosage issues in more detail in future studies in related experimental models, including those involving airways infection.⁴ In this regard our recent findings indicate that the mechanism-of-action of OM85 includes stimulation of the functional maturation of mucosal-homing T-regulatory cells within local lymphoid tissues in the small intestine, which subsequently migrate to the airways.² This implies that the key issues related to determination of optimal OM85 dosages in different species involve the relative concentrations of agent achieved at the intestinal mucosal surface, the length of time it remains available for local uptake within this microenvironment, and the efficiency of its subsequent accumulation in adjacent lymphoid structure such as Peyer's Patches. There is currently no consensus on how potential interspecies differences in these parameters can be modelled, and hence independent dose ranging studies must inevitably be performed in each species of interest, rather than reliance on interspecies extrapolations.

Conflict of interest

The authors acknowledge OM Pharma for supply of drug used in our earlier studies cited below, and for supplementary funding of laboratory consumables, but certify that the relevant work, data analysis, interpretation and paper writing were independent of the company.

References

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