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A clean bill of health for LABAs?

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There have been persisting concerns about the safety of long-acting beta-agonists (LABAs) in asthma. In 2008, the US Food and Drug Administration asked manufacturers to look at their data. In studies comparing salmeterol with other therapy, a meta-analysis demonstrated a higher incidence of asthma-related death and hospitalization in participants receiving salmeterol; the results were difficult to interpret as many participants had not received concurrent inhaled corticosteroid therapy. GlaxoSmithKline has therefore undertaken a huge study, recently published in the New England Journal of Medicine, to assess whether there are safety issues when a combination inhaler is used, comparing Seretide with fluticasone (ClinicalTrials.gov number, NCT01475721) [1]. A randomized, double-blind trial approach was taken recruiting 11 679 participants with persistent asthma, who had a recent history of a severe exacerbation and aged from 12 years. Over 6 months of follow-up, 67 participants had serious asthma-related events (defined as death, endotracheal intubation or hospitalization) with a hazard ratio for the fluticasone–salmeterol group of 1.03 (95% confidence interval 0.64 to 1.66). This met the prespecified criterion for a non-important difference. Additionally, the risk of a severe asthma exacerbation was lower in the fluticasone–

salmeterol group (8% versus 10%, hazard ratio 0.79; 0.70 to 0.89). So a huge effort is required to find a null difference in serious asthma-related events. It is extremely important, though, given our dependence on combination inhalers to manage severe persistent asthma. Do we finally have a clean bill of health for LABAs?

In this issue of Clinical and Experimental Allergy, Norredam *et al.* have used Danish patient registry data to explore whether migration has an impact on the risk of anaphylaxis [2]. Non-Western immigrants had a much lower risk of hospital attendance for anaphylaxis than Danish-born people (RR=0.64; 95% CI: 0.52; 0.80). This reduced risk seems to disappear with increasing time in Denmark. These data might be explained by the lower rate of allergic disease in the immigrants' countries of origin. Another explanation might be that migrant groups were less likely to access hospital care when experiencing severe allergic reactions; the authors discount this on the basis of other Danish data. The increasing tendency of migrants to lose this protection with time in Denmark suggests that a Danish *exposure* is responsible for the increased likelihood of anaphylaxis. But what is the nature of that exposure?

Moulds represent important triggers for allergic disease. Kespohl *et al.* have looked at how different commercial mould skin prick test (SPT) solutions compare with each other [3]. They included a heterogeneous group of 168 patients with mould exposure with or without mould-induced respiratory symptoms. Importantly, for many of the mould SPT solutions, the concordance between two tests with the same commercial solution was <80%. This strongly suggests that mould



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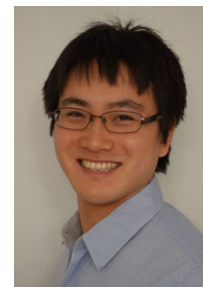
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Caption to cover illustration: An overview of the function and regulation of dendritic cells (DCs) in human allergic rhinitis. [see figure 1 in P.-P. Cao. *et al.* (pp. 894–906)].

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SPT should be undertaken in duplicate or at least repeated where the result does not fit the clinical presentation. Looking at each mould, individuals' results were not the same for all commercial mould SPT solutions. For example, of the 43 who reacted to *Aspergillus fumigatus*, 14 reacted to only one manufacturer's solution, 8 reacted for 2 solutions, 6 to 3 solutions, only 15 reacted to all 4 solutions (≥ 1.5 mm weal cut-off). The investigators also explored the diagnostic accuracy of each solution using the specific IgE result as their gold standard; while they all performed reasonably well, there were differences between the individual manufacturers.

Handa *et al.* have examined how IgG production impacts on the relationship between house dust mite exposure and susceptibility to the IgE-mediated allergic response using a mouse model [4]. Adoptive transfer of total IgG from mice sensitized to house dust mite prevented mice from developing a severe allergic response to the allergen. This suggests that the very high levels of specific IgG seen in specific allergen immunotherapy are protective.



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References

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- 4 Hirai T, Yoshioka Y, Takahashi H *et al.* High-dose cutaneous exposure to mite allergen induces IgG-mediated protection against anaphylaxis. *Clin Exp Allergy* 2016; **46**:992–1003.