

Clinical & Experimental Allergy

LABAs (again), asthma exacerbations and anaphylaxis

G. Roberts^{1,2,3}

¹Clinical and Experimental Sciences and Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, UK, ²NIHR Southampton Respiratory Biomedical Research Unit, University Hospital Southampton NHS Foundation Trust, Southampton, UK and ³The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight, UK

Last month I highlighted a randomized controlled trial (RCT) that suggested that salmeterol was not associated with an increased incidence of asthma-related death and hospitalization in a large group of, mainly adult, asthma patients [1, 2]. So the headline was 'A clean bill of health for LABAs?' Now there was a question mark perhaps anticipating a more recent, paediatric study from Turner et al. They assessed whether a Gly-to-Arg substitution (rs1042713) in the β 2-adrenoceptor gene (ADRB2) is associated with asthma exacerbations in children receiving long-acting β -agonist (LABA) therapy [3]. In a large meta-analysis, they utilized data from 5 observational studies including 4226 children. The odds ratio for an exacerbation of asthma was 1.52 (95% CI, 1.17–1.99; $P < 0.002$, $n = 637$) for each copy of the A allele when treated with inhaled corticosteroids plus LABAs. This was not seen for other combinations of therapy, including, interestingly, treatment with inhaled corticosteroids, LABA and leukotriene receptor antagonist (OR 0.94, 95% confidence interval 0.73–1.22, $n = 569$). This study raises questions without being able to provide a definitive answer. There is no obvious mechanism by which the additional of a leukotriene receptor antagonist could negate the

negative impact of this Gly-to-Arg substitution. Additionally, these data are observational, and the therapy that each child received is likely to have been associated with their underlying asthma control meaning that these results may be completely confounded by severity. However, given that nearly two-thirds of the population have at least one A allele, the authors rightly call for clinical trials to focus on this question. Genotyping participants in the recent large RCT LABA trials and assessing whether specific genotypes are associated with increased exacerbations would be a good start.

Continuing on the theme of exacerbations of asthma, Sekiya et al. have used a cluster approach to look for specific subgroups of adults with severe or life-



Kiyoshi Sekiya

Correspondence:

G. Roberts, Paediatric Allergy and Respiratory Medicine (MP803), Clinical & Experimental Sciences & Human Development in Health Academic Units University of Southampton, Faculty of Medicine & University Hospital Southampton, Southampton SO17 1BJ, UK.

E-mail: g.c.roberts@soton.ac.uk

Cite this as: G. Roberts, *Clinical & Experimental Allergy*, 2016 (46) 1020–1021.

Caption to cover illustration: Molecular surface representation of Ara h 2 showing a consensus epitope site centred on Y63 (red) [see figure 3 in X. Chen et al. (pp. 1120–1128)].

EB This logo highlights the Editor-in-Chief Editorial articles on the cover and the first page of each of the articles.

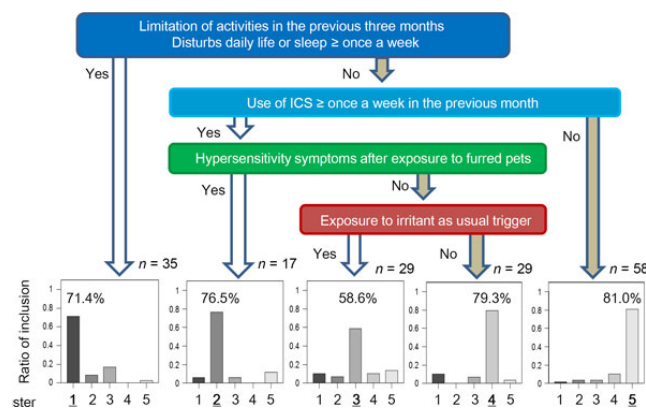


Figure 1



Raymond Mullins

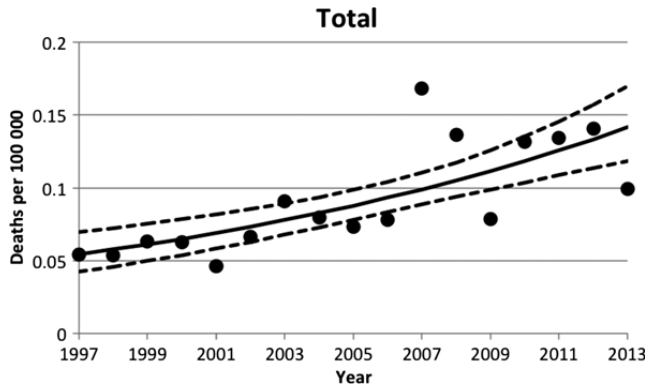


Figure 2

threatening exacerbations [4]. In a data set of 168 patients, they identified five distinct clusters: (i) younger-onset, severe persistent asthma, high frequency of current smoking; (ii) younger-onset, allergic asthma; (iii) older patients with severe disease and frequent comorbidities; (iv) older patients with less severe disease; and (v) mild disease severity who less prior asthma medication usage (Fig. 1). The next step will be to see whether these distinct subgroups are characterized by different exacerbation pathophysiologies with resulting implications for acute therapy.

In these issues, Mullins et al. have examined trends in fatalities from anaphylaxis in Australia (free access) [5]. They used routine data from the Australian Bureau of Statistics and data from coroners' inquests to provide information from at least a subgroup of fatalities. From 1997 to 2013, fatal anaphylaxis rates increased by 6.2%/year (95% confidence interval 3.8 to 8.6%, $P < 0.0001$) (Fig. 2). For food-associated cases, there was an increase of 9.7%/year (95% confidence interval



Rosa Muñoz Cano and Mariona Pascal

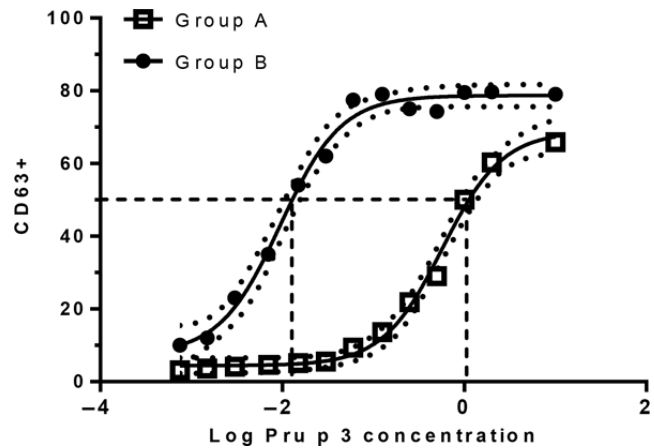


Figure 3

0.25–20%, $P = 0.04$). Which leads us to ask why? Is this a real increase or, with better awareness of allergy, are cases more likely to be recognized as anaphylaxis?

Pascal et al. have examined whether non-selective and selective cyclooxygenase (COX) inhibitors impact on basophil activation by peach lipid transfer protein (Pru p 3) [6]. They looked at patients with Pru p 3-induced anaphylaxis with and without a history of NSAID as a cofactor. Basophils from patients with food-dependent NSAID-induced anaphylaxis (FDNIA) were less reactive and sensitive to Pru p 3 than the non-FDNIA group (Fig. 3 – group A: FDNIA; group B: anaphylaxis without NSAIDs involvement). A non-selective cyclooxygenase (COX) inhibitor increase basophil activation in both Pru p 3-allergic groups. This provides a pathophysiological mechanism for NSAID as cofactors in anaphylaxis and might provide a new diagnostic approach.

References

- 1 Stempel DA, Raphiou IH, Kral KM *et al.* Serious asthma events with fluticasone plus salmeterol versus fluticasone alone. *N Engl J Med* 2016; 374:1822–30.
- 2 Roberts G. A clean bill of health for LABAs? *Clin Exp Allergy* 2016; 46:892–3.
- 3 Turner S, Francis B, Vijverberg S *et al.* Childhood asthma exacerbations and the Arg16 β 2-receptor polymorphism: a meta-analysis stratified by treatment. *J Allergy Clin Immunol* 2016; 138:107–13.
- 4 Sekiya K, Nakatani E, Fukutomi Y *et al.* Severe or life-threatening asthma exacerbation: patient heterogeneity identified by cluster analysis. *Clin Exp Allergy* 2016; 46:1043–55.
- 5 Mullins R, Wainstein B, Barnes E, Liew WK, Campbell D. Increases in anaphylaxis fatalities in Australia 1997 to 2013. *Clin Exp Allergy* 2016; 46:1099–1110.
- 6 Pascal M, Muñoz-Cano R, Mila J *et al.* Nonsteroidal anti-inflammatory drugs enhance IgE-mediated activation of human basophils in patients with food anaphylaxis dependent and independent of nonsteroidal anti-inflammatory drugs. *Clin Exp Allergy* 2016; 46:1111–9.