

EDITORIAL

Clinical & Experimental Allergy

Inhaled allergen challenge in assessment of biologics for asthma

This editorial discusses the findings of the paper in this issue by H. Scheerens et al. [8] pp. 38–46.

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Inhaled allergen challenge of atopic asthmatic volunteers results in rapid airway narrowing measurable as a fall in FEV1 within a few minutes (early asthmatic reaction, EAR), which is followed in around 50% of subjects by a delayed fall in FEV1 between 3 and 8 h after challenge (the late asthmatic response, LAR) [1]. In those who have LAR, there is an associated increase in non-specific airway hyper-responsiveness (AHR) which can persist for 7 days or more. For many years, this technique has been used to study mechanisms and pharmacology in allergic asthma. It is advocated as a useful model of allergic asthma for screening novel therapeutics, with reasonable (but not infallible) positive predictive value and excellent negative predictive value for subsequent efficacy in control of clinical aspects of asthma [1]. It is potentially attractive because it is reproducible and relatively small numbers of subjects are required for studies [1].

Allergic asthma is associated with Th2-type, IgE-mediated eosinophilic airway inflammation, and allergen bronchoprovocation activates these pathways [2, 3]. However, asthma has been recognized as varied both clinically and mechanistically. Cluster analysis of clinical features of asthma identified several distinct clusters including an inflammation predominant atopic early-onset group and asthmatics with late-onset non-atopic asthma some with eosinophilic inflammation with few

symptoms and others with little inflammation but predominant symptoms, as well as a group of obese, predominantly female asthmatics [4, 5]. Gene expression analysis of airway epithelial cells from asthmatics identified a spectrum of expression of the IL-4-/IL-13-induced genes POSTN, CLCA-2, and SERPINB-2, which the authors used to classify subjects as 'Th2 high' and 'Th2-low' based on whether expression of these genes was elevated relative to non-asthmatic controls [6]. These findings suggest that the underlying pathology in asthma may be variable and that this may influence treatment response [6]. Potentially clinically applicable biomarkers for determining Th2-high and low phenotypes have been examined including serum periostin, as well as blood eosinophil counts and exhaled nitric oxide (FeNO) [7]. This is important as biologic therapies specific for individual cytokines are developed, as it will be important to target therapy of those who will benefit.

A number of biologic therapies have been tested in the inhaled allergen challenge model. In this edition of *Clinical & Experimental Allergy*, Scheerens and co-workers describe results from a study of the IL-13 blocking-mono-clonal antibody lebrikizumab [8]. What can we learn from studies of biologics for asthma in the allergen challenge model and from this study in particular?

Scheerens et al. studied 29 mild atopic asthmatics treated with as needed bronchodilator only in a multi-centre, double-blind trial. A screening allergen challenge was performed to select subjects with a LAR, who were then randomized to either 4 doses of subcutaneous lebrikizumab or placebo, given monthly over 12 weeks, after which a second allergen challenge was performed. The primary outcome was area under the curve for FEV1 between 2 and 8 h after challenge. The LAR (as AUC for FEV1 between 2 and 8 h) was 48% less in those subjects treated with lebrikizumab than that for placebo-treated volunteers: a difference that was not

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statistically significant. There was also a trend for reduction in maximal late fall in FEV1 in the lebrikizumab-treated patients compared with placebo, and there was a minimal (0.33 doubling dose) reduction in AHR but no change in EAR. As an exploratory endpoint, the investigators examined the effect of baseline expression of the biomarkers serum periostin, blood eosinophils, and FeNO (using cut-offs from previous large groups to define high and low values) to see whether these could be related to effect of treatment on LAR. These data did suggest that those with Th2-high markers at baseline tended to have a greater reduction in LAR after treatment with lebrikizumab than the Th2-low subjects.

This study supports a role for IL-13 in allergen-induced LAR, as expression studies and animal models had predicted and previous allergen challenge studies. Although studies are not strictly comparable, the protocols for allergen bronchoprovocation are well standardized, and it is striking that other studies targeting IL-13 [9] or the receptor for IL-4 and IL-13, IL-4R α [10], all show rather similar reductions in LAR, although in some cases also EAR (Table 1). As perhaps might have expected, targeting one (or two) cytokine produced a less dramatic effect than either inhaled corticosteroids or omalizumab (targeting IgE). The mechanism of the late fall in FEV1 after allergen challenge and the associated increase in AHR remain rather elusive. It had been postulated that both IgE-triggered mast cell activation and eosinophil degranulation played a role on both events, but blocking IL-5 with the antibody mepolizumab reduced airway eosinophils and had no effect on either LAR or AHR [11], whilst isolated LAR

was described after intradermal injection of allergen derived peptides, which did not activate mast cells [12]. Which action of IL-13 is responsible for the observed effect on LAR? Presumably it is not eosinophil related, but may be via IgE, epithelial cell, or smooth muscle changes. In the current report, AHR was not measured before and after allergen challenge so we do not know whether the allergen-induced increase in AHR was prevented by Lebrikizumab [8], as is the case of omalizumab and inhaled steroids [14, 15]. In animal models, blocking IL-4/IL-13 reduced AHR, but not specific IgE or eosinophils in an acute antigen challenge protocol [16]. In human studies, effects on AHR have been modest or lacking: either reflecting species differences as the authors here suggest or that the animal models do not model human asthmatic AHR.

As mentioned above, mepolizumab (which blocks IL-5) had no effect on the LAR or other aspects of inhaled allergen challenge [11]. However, this trial had small numbers in each group and may be non-informative rather than negative for an effect on blocking IL-5 on the LAR [17]. Targeted trials of this agent in severe asthmatics with residual airway eosinophilia despite high-dose inhaled corticosteroids (ICS) and long-acting bronchodilators (LABA) achieved a reduction in exacerbation rates of 50% [18], a value similar to that seen with omalizumab (anti-IgE) [19], which did block EAR, LAR, and AHR in a challenge protocol [13]. Neither drug had effects on asthma symptoms or lung function. In the case of lebrikizumab, a long-term study in moderate/severe asthmatics also with symptoms despite ICS and LABA showed a significant improvement in lung function and a trend for reduction in exacerbation rates [20]. Any monoclonal antibody therapy for asthma is likely to be directed to the small but very significant proportion of asthmatics who remain uncontrolled despite high-dose ICS and LABA or who need long-term oral corticosteroids to control disease. This is a different setting to the mild atopic asthmatics studied in allergen challenge studies. It will be of interest to try to establish whether results from allergen challenge studies can be related to any of the clinical outcomes in severe asthma. Is it a useful model of asthma exacerbation? The data from mepolizumab might argue that it is not as this drug had no effect on LAR but reduced exacerbation rates (in selected patients). However, the trial has been criticized [17], and perhaps it would be hasty to exclude the allergen challenge protocol as a model of asthma exacerbations on this basis. Many exacerbations are associated with viral infections (which also induced Th2 cytokines and eosinophilia) and viral challenge models (possibly together with allergen) may be informative [21]. However, such protocols are complex; the safety is not yet established,

Table 1. Selected allergen challenge studies: effect of treatment on the Late Asthmatic Response (LAR), as mean maximal percentage fall in FEV1 from baseline or area under curve (AUC) of FEV1 during the LAR after treatment, with mean differences from statistical comparison of actively and placebo-treated subjects

Drug	Active	Placebo	Difference	P value	Ref
Inhaled corticosteroids					
BDP	6.2	21.8	Not stated	0.05	14
BUD	6.6	23.7	Not stated	0.02	15
Omalizumab (IgE)	9.0	24	Not stated	0.02	13
Mepolizumab (IL-5)	32.8	32.5	-0.3	1.0	11
Pitrakinra (IL-4/IL13)					
S/C	17.1	23.0	6.0	0.24	10
(AUC)	19.2	17.6	-1.6	0.054	
INH	16.1	27.6	11.5	0.0009	
(AUC)	21.6	18.4	-3.1	0.0006	
IMA 638 (IL-13)	12.8	19.3	-6.4	0.09	9
(AUC)	25.5	49.3	-23.8	0.04	
Lebrikizumab (IL-13)	13.8	16.4	-15.9	Ns	8
(AUC)	26.3	50.5	-47.9	Ns	

Ns, not significant; S/C, subcutaneous; INH, inhaled.

and they will have to be validated to gain a place in drug development.

One important aspect of the Scheerens study is the preliminary look at the relationship between baseline biomarker expression and the effect of lebrikizumab on the LAR. Although not powered for statistical analysis, there was a suggestion that those with high baseline Th2-high markers (serum periostin, blood eosinophils, or FeNO) had a more marked reduction in LAR when treated with lebrikizumab. Higher expression of these markers also was associated with increased lung function in response to lebrikizumab in the longer term study of severe asthmatics [19] and with greater reduction in exacerbation rates with omalizumab treatment in the recent EXTRA study [18]. Whilst the concept of subgroups suitable for treatment with biologics is becoming familiar in severe asthma with clinical use of omalizumab (restricted to atopic asthmatics with a certain total IgE and frequent exacerbations) and trials of mepolizumab and lebrikizumab, the suggestion that there may be subgroups of Th2 high and Th2 low in an allergen challenge study is perhaps surprising. One might have expected mild atopic asthmatics selected for LAR to all be 'Th2 high', but on a closer look at the data (some of which is in the supplemental data for the Scheerens study) on such subdivisions of asthma, they

may not simply relate to atopic status or eosinophilic inflammation. This may imply that further pre-screening and larger studies are required for allergen challenge studies of biologics. Further experience with biomarkers and gene expression profiling in asthma and how it relates to clinical responses to difference treatments should clarify this area.

What then is the position of allergen challenge studies in development of biologics for asthma? They may have a useful role for investigational studies to confirm that the agent does what was expected (for example, reduce eosinophilia in the case of mepolizumab) and for investigating mechanisms. However, allergen challenge may not be necessary for such investigations. Do they shed light on potential for clinical benefit? Maybe for exacerbations, possibly together with viral challenge studies, but such studies will need to be tempered by the possible need for selection on the basis of biomarker expression and by further data on which clinical outcome the model is informative for (if any). Will go/no-go decisions rest on allergen challenge study results? Personally I doubt it, but they may give useful guidance along the development pathway.

Conflict of interest: Dr Robinson has received consulting fees and speaking fees from Roche/Genentech.

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