

ORIGINAL ARTICLE

Provocation tests as measure of efficacy and dosage

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Abstract

Provocation and challenge tests have been used to understand the pathobiology of asthma, to facilitate diagnosis and to assess therapeutic efficacy and dosage. Current challenge tests expose the patient to 'natural conditions', for example, in an allergen chamber. For determining drug efficacy in asthma, allergen challenge has a moderate positive predictive value and an excellent negative predictive value. The best challenge tests are standardized, and the best bronchial challenge tests use a large allergen particle size. Allergen provocation tests are safe when performed by experienced investigators.

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The 2007 guidelines from the European Medicines Agency (EMA) (1) state that provocation tests such as conjunctival or bronchial provocation, allergen exposure in allergen chambers and/or clinical endpoints may be used as primary endpoints. Therefore, at the level of European regulation, provocation tests are allowed and considered a good tool to monitor SIT.

Provocation tests mimic natural exposure

The key question is whether provocation tests correspond to and mimic natural exposure. We performed challenge tests in two studies, one with cat (2) and one with house dust mite (3), using large, medium and small particles. With cat allergen in 10.3 μm particles, 13.5 ng of Fel d 1 per cubic metre induced a response by bronchial challenge test. From 50 samples, we determined the median level of Fel d 1 at home capable of inducing symptoms. A median of 14 ng per cubic metre had a median time of onset of symptoms of 30 min. Thus, at home, the amount of Fel d 1 needed to induce symptoms was 4.2 ng. This indicated that bronchial challenge with large particles of cat allergen corresponded closely to the levels of Fel d 1 that induce symptoms at home.

We obtained similar results for house dust mite in 37 patients. We know that 60 ng per cubic metre of Der p 1 are found domestically in the air after a disturbance and 80% are in large particles $> 10 \mu\text{m}$ (4, 5). The time for symptoms at

home was 30.8 min, and the estimated amount of Der p 1 to induce symptoms at home was 12 ng. When we perform bronchial challenge tests, we use 23 ng of Der p 1, so for mites, the levels are close to the natural exposure. Other studies found that levels of Fel d 1 or Der p 1 that produce symptoms in challenge tests and at home are very different. Therefore, particle size appears to be very important in challenge tests.

Provocation tests and drug efficacy

Another question is whether allergen challenge is a good test for measuring drug efficacy. One issue when using bronchial challenge tests to investigate drug efficacy is choosing the allergen. We did a performance study comparing cat, house dust mite and grass bronchial challenge test results (C. Barnig, unpublished data) (6). All allergens were on large particles and patients had immediate reactions. With Der p 1, 60% of patients had a late-phase reaction, which is considered close to chronic asthma. Therefore, to assess a drug for asthma, using a model with a high ratio of late-phase reactions is important. Using cat allergen, only 16% of patients had a late-phase reaction, so house dust mite is a better model for bronchial challenge test reactions.

Another question is the ability of a bronchial challenge test to assess the effectiveness of a drug. Not all drugs that attenuate allergen-induced responses have proven to be effective anti-asthma medicines. However, all drugs that did not

Table 1 Examples of currently available and newly developed drugs for asthma on allergen-induced airway responses in mild asthmatic subjects

True positives	True negatives	False positives	False negatives
All conventional inhaled corticosteroids (ICS)	Esterase-sensitive 'soft' steroids	Anti-CD11a hMab	None to date
Short-acting inhaled β_2 -agonists	Platelet-activating factor antagonists	Inhaled PGE ₂	
Long-acting inhaled β_2 -agonists (LABA)	Inhaled leukotriene receptor antagonists	PGE ₁ analogue	
Combination ICS/LABA	Thromboxane antagonists		
Oral leukotriene receptor antagonists	Ketotifen		
Anti-IgE			
Theophylline	Immunostimulatory sequence		
Prednisone			

True positives are drugs that attenuate allergen-induced responses and are effective in asthma; true negatives are drugs that did not attenuate allergen responses and failed clinical trials in asthma; false positives are drugs that attenuated allergen responses, but may not be useful in asthma; and false negatives are drugs that did not attenuate allergen responses and were effective in asthma.

attenuate allergen-induced airway responses were subsequently proven to be ineffective in asthma in large clinical studies (7). Thus, the bronchial challenge tests are good at finding true negatives, or drugs that will not turn out to be efficient in large clinical tests, for example, platelet-activating factor antagonists. Bronchial challenge tests have generated false positives, or drugs that were found to be efficient by bronchial challenge test but not efficient during large clinical tests, such as inhaled PGE₂. No examples exist of bronchial challenge test false negatives, or drugs that were not efficient in bronchial challenge test but found to be efficient during large clinical trials. Therefore, the negative predictive value of bronchial challenge test is very important. For immunotherapy, several studies with house dust mite and cat have demonstrated efficacy using bronchial challenge (8), but all with immediate reaction, not with late-phase reactions.

For nasal provocation tests measuring rhinitis, the issue is deciding the threshold. We conducted small preliminary studies on 31 patients, 20–66 years old, who experience perennial intermittent and persistent rhinitis, and have a positive skin test to mite allergen. Using an evaluation published by the German Society of Allergy, we found that 100% of the patients had a positive nasal provocation test. This result was different from other studies (9, 10) using a higher threshold. Thus, the problem with nasal provocation tests is setting the threshold.

Efficacy of immunotherapy was assessed in a Spanish study (11) of sublingual immunotherapy including 50 patients with rhinitis and asthma from cat allergy. Efficacy was assessed using a cat room for bronchial and nasal symptoms. A decrease was seen compared with placebo. Therefore, challenge tests can be used to monitor immunotherapy. Another method is conjunctival tests. A study of cat allergen (12) showed increased response with increased immunotherapy dose, as measured by conjunctival provocation test.

Allergen chambers

Rhinitis and conjunctivitis antigen challenge chambers expose patients to standardized levels of allergens in a large chamber

(13). The first was developed at the Johns Hopkins University but was not standardized. In Vienna in 1987, a chamber was used with standardized amounts of grass pollen. Currently, several allergen chambers are in use in Europe, North America and Japan, and they can be used to assess dose effects and onset of action. For example, in a study of 16 patients with allergic rhinitis to grass pollen (14), the dose effect and onset of action of a corticosteroid was assessed with an allergen challenge chamber. In measuring time to onset of action, a difference was seen after 7 days of treatment and a significant difference after 14 days. So in this case, onset and duration of action could be studied. Significant differences were also seen in onset of action, measured as symptoms, after 2 and 4 months with Stallergenes Oralair immunotherapy.

In conclusion, allergen challenge is useful at the early stage of development of a drug and possibly for monitoring of immunotherapy (Table 1). For asthma, it has an important negative predictive value. For rhinitis and conjunctivitis, the results are likely the same as obtained for asthma. Bronchial and nasal provocation tests are useful for studying immunological markers, although we are still searching for good surrogate markers. Several methods for allergen challenge are available. The best are those that are standardized. The bronchial challenge test is well standardized, and large particle sizes should be used because this better resembles natural exposure. Nasal provocation tests are useful, but a threshold must be carefully chosen to avoid false positive results. Allergen chambers are usually used for grass pollen because measuring pollen grain levels in the room is relatively easy. However, they are difficult for indoor allergens, because of the length of time needed to measure allergen levels in the chamber.

Conflict of interest

Frédéric de Blay has received a research grant from Chiesi Lab, funding for clinical studies from AB Sciences, Allergopharma, ALK-Abelló, Amgen, GSK and Stallergenes Labs, consultancy fees from ALK, Stallergenes, Mundipharma and Novartis as well as a lecture fee from ALK-Abelló.

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