

Normal criteria for documentation of background and degree of sensitivity of BAT cannot be established before a well-documented BAT method has been agreed upon.

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Reply



To the Editor:

Dreborg¹ has expressed concerns regarding our recent article on the value of basophil activation test (BAT) for the evaluation of amoxicillin-clavulanic acid (AX-CLV) allergy.²

His main concern is the cutoff used for a positive result. As he correctly stated, *in vitro* testing for drug allergy evaluation is quite different from that for aeroallergens,³ requiring much higher concentrations for basophil activation. It is therefore widely accepted that the cutoff used for *in vitro* tests for

many allergens, the mean of blank tests + 3.3 S.D, is not valid for drugs.

Thus, other approaches must be considered, and a stimulation index (SI) of more than 2 is often used.^{3,4} Dreborg expressed specific concerns with our usage of an SI of 1.5, implying that we had chosen it to increase the sensitivity of our test without reducing the specificity. However, because no previous studies have investigated a sensitivity/specificity cutoff for the AX-CLV BAT, we performed receiver-operating characteristic curve analysis, using a large number of well-characterized allergic patients and (exposed) tolerant individuals, to choose the optimal cutoff⁵ and to spark research in this area. Receiver-operating characteristic curve analysis has been widely used when evaluating drug reactions by BAT,^{3,6} to balance sensitivity and specificity. Nevertheless, given the concerns of Dreborg, we reran the analysis using an SI of 2. The overall sensitivity of BAT was reduced from 54% to 42%, the sensitivity for AX remained at 41%, and the sensitivity for CLV decreased from 62% to 52%. Specificity values remained the same. On combining skin test and BAT results, the sensitivity became 75.9% for AX-allergic patients and 84.5% for CLV-allergic patients.

These values should however be viewed in the context of their clinical utility: although false-positive results are of course undesirable, because they result in unnecessary drug avoidance, false-negative results can have dramatic consequences, especially when dealing with severe reactions. Thus, physicians must make a decision after balancing the risk-benefit ratio for each individual case. We would argue that this means that in some circumstances they would prefer a cutoff that sacrifices specificity in favor of increasing sensitivity. Therefore, we still contend that for the data presented in our study, an SI of more than 1.5 is optimal (Figure 1, A). Of course, many more studies are required in this area to establish an optimal clinically valid cutoff.

Regarding the presentation of values with an SI of less than 1, these data show that degranulation was sometimes lower with the drug than observed spontaneously. Dreborg suggested that we change these negative values to 1 for statistical analysis. We reanalyzed the data taking this into account and the differences

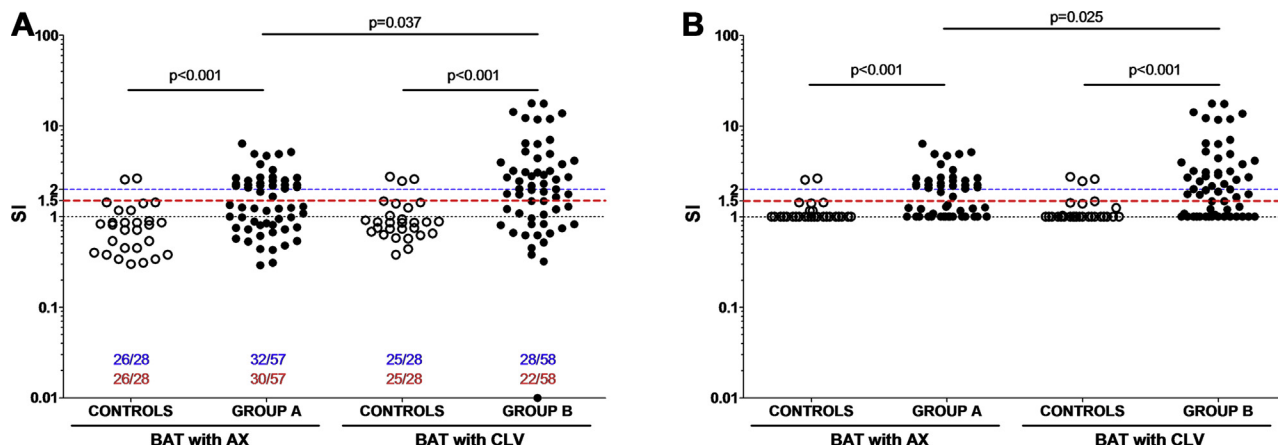


FIGURE 1. A, Copy of Figure 2, A, from the original communication.² Blue line indicates an SI value of 2 and blue numbers indicate negative results/total number using this cutoff. Red line indicates an SI value of 1.5 and red numbers indicate negative results/total number using this cutoff. B, Copy of Figure 2, A, from the original communication² assigning an SI value of 1 to all the individuals with values lower than 1. Blue line indicates an SI value of 2, and red line indicates an SI value of 1.5. Patients allergic to AX are represented as group A and patients allergic to CLV as group B. SI is represented on the Y-axis in logarithmic scale.

between groups became more significant, probably due to the dramatic loss of variance (Figure 1, B).

Finally, Dreborg expressed his concern about the drug concentrations used in the test. Drugs do not activate basophils to the same degree as other allergens. Thus, optimal drug concentrations are generally much higher and effective ranges are much smaller,³ making dose-response curves mandatory to select the drug concentrations able to induce the response *in vitro* without cytotoxic effects. In our study, we have used drug concentrations that gave optimal results in dose-response curves produced previously.⁷

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Biologic Targeted Therapies for the Phenotypes of Type-2 High Severe Asthma



To the Editor:

We read with great interest the Pro/Con Review of Israel and Panettieri.¹ The authors clearly discussed and proposed the most appropriate phenotype-based mAb (anti-IgE or anti-IL-5) for 4 different cases with type-2 high severe asthma. We would like to share our clinical experience and opinions on this subject.

Indeed, despite all current knowledge, there is no consensus or algorithm to decide which mAb should be used as first-line therapy or an alternative therapy, or whether they could be used in combination.^{2,3} We recently shared our “in-house”

classification of asthma phenotypes and decision-making protocol that involves first-choice mAbs or potential alternative mAbs in severe asthma phenotypes particularly.⁴ One review² has proposed omalizumab for patients with an allergic phenotype regardless of their blood eosinophil count, and anti-IL-5 as an alternative in allergic patients with blood eosinophilia in whom omalizumab has failed. This article also recommended anti-IL-5 for patients with an eosinophilic phenotype and omalizumab as an alternative in patients in whom anti-IL-5 fails and IgE level is more than 30 IU/mL.² A good response is expected when mAbs are given to a correct asthma phenotype. If it is not working, an mAb used for another asthma phenotype should not be preferred as an alternative treatment option in my opinion. For example, benefit from anti-IgE treatment is expected in a patient with pure allergic rhinitis and atopic asthma, whether there is eosinophilia or not, because the allergic reaction in this asthma phenotype is based on early and delayed-type allergic inflammatory responses by allergen-specific IgEs and mast cell degranulation. If anti-IgE does not work in this phenotype (it would work if it is pure atopic asthma), alternative anti-IL-5 treatment would also not necessarily work just because there is eosinophilia. Thus, I think that possible alternative mAbs for this group of patients should include dupilumab. Cytokines such as IL-4, IL-5, and IL-13 have a major role in the pathophysiology of allergic inflammation in atopic asthma. IL-4 and IL-13 are the most important cytokines in specific IgE production. On the other hand, in eosinophilic asthma with chronic nasal polyposis, the most appropriate mAb would be an anti-IL-5 because the main mechanisms are leukotriene synthesis dysregulation and chronic epithelial activation (eg, superantigens and environmental pollutants) with expression of thymic stromal lymphopoietin, IL-25, and IL-33, which stimulate type 2 innate lymphoid cell activation and overproduction of IL-5.⁵⁻⁷ Therefore, anti-IgE treatment cannot be a good alternative in case of anti-IL-5 therapy failure, even if there is atopy, in this severe asthma phenotype. In eosinophilic asthma with chronic nasal polyposis and atopy, if there is partial response with anti-IL-5 therapy, instead of switching to anti-IgE and blocking only 1 mediator, combining these 2 mAbs would be expected to lead to better outcomes. Unfortunately, neither comparative efficacy or effectiveness trials of these 2 monotherapies nor trials of combination therapy with anti-IgE and anti-IL-5 are available, and these would be very valuable to support appropriate decision making in patients with asthma who require biologic therapy.

In conclusion, current or future biological mAbs for type-2 high severe asthma should be chosen wisely according to the most suitable phenotype. Although some logical recommendations can be made currently on the basis of mechanisms of action of the drugs and the underlying pathophysiology of various asthma phenotypes and endotypes, further studies are needed to support or refute these preliminary recommendations.

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