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CORRESPONDENCE

Serum IgE-targeted elimination diets for treating eosinophilic esophagitis: things are not what they seem

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We have eagerly read the article by Rodríguez-Sánchez et al. (1) recently published in *Allergy*. The authors described an observational and descriptive (but not comparative) study carried out in adult patients suffering from eosinophilic esophagitis (EoE): Forty-three patients underwent food-specific serum IgE (sIgE) testing against the six food groups comprising an empiric six-food elimination diet (SFED) (2). Those patients with positive sIgE results (considered ≥0.1 kU/l) followed a targeted food exclusion diet (n = 26), while patients with negative results were treated with an empirical SFED (n = 17). Histological remission (<15 eos/hpf) was achieved in 19 and 9 EoE patients, respectively.

Even when the study strategy posed by the authors seems an interesting option to simplify schemes for managing EoE, we have serious concerns regarding the study concept and design, its methodology, and results, which affect the validity of the authors' conclusions. In fact, the design of this study prevents to directly compare the effectiveness of two dietary interventions (specific sIgE-targeted elimination diet [sIgE-ED] and SFED), which can only be done by a well-designed longitudinal study or by a randomized clinical trial: This paper is a descriptive study that only shows the result of a common initial treatment strategy carried out in all patients and based on specific sIgE determination, followed by a latter decision node according to the results obtained.

The overall 'efficacy' of the sIgE-ED of 73% (19/26 patients) is one of the most important misconceptions included in this paper, by committing an evident bias when the authors exclusively considered patients with positive sIgE results, and excluded those with a negative one. When the whole series of EoE patients are considered, the response rate dropped to only 44% (19/43), significantly lower to that reported for SFEDs (3). Furthermore, total sIgE levels were not considered; specific sIgE were exclusively tested for foods included in a SFED, instead to every potential food allergen, which makes all patients highly susceptible of having responded to a SFED. The additional exclusion of rice and corn in case of sIgE levels against wheat were demonstrated cannot be justified by cross-reactivity between those cereals. These facts make from this sIgE-ED not a targeted but an empirical dietary approach.

The authors also claim a reduction in the cutoff point of serum IgE from 0.35 to 0.1 kU/l in order 'to increase the sensitivity and thus to detect not only serum food-specific IgE-mediated but also non-IgE-mediated allergic reactions as well'. We really wonder how IgE-based tests are able to detect a non-IgE-mediated reaction. The fact that skin prick test results were not taken into account when designing exclusion diets provides an additional proof on the subjective use that authors made of IgE-based tests in their paper.

Authors provide sensitivity and specificity figures for specific serum IgE in the 14 patients who completed the sequential food reintroduction protocol. Interestingly, whereas a larger number of patients underwent sIgE-ED compared with SFED, the ability of these tests to determine the triggering food was very low and similar to that obtained in a previous study on a full cohort of EoE patients from the same geographic region (2) (Table 1).

To summarize, the conclusions made by Rodrígez-Sánchez on the utility of sIgE-targeted elimination diet set forth a confusing scenario that should be interpreted with caution. Research efforts in EoE should be directed to assay simplified dietary strategies with a demonstrated effectiveness and to identify the true biological mediators of the immune

Table 1. Sensitivity and specificity for specific serum IgE measurements in comparison with food challenge results evaluated by recurrence of inflammation in histology in adult EoE patients included in two different studies. A: research by Rodríguez-Sánchez et al. (1); B: research by Lucendo et al. (2)

	Sensitivity (%)			Specificity (%)		
	A* (n = 14)	B† (n = 42)	P‡	A* (n = 14)	B† (n = 42)	P‡
Milk	66.7	30	0.147	100	92.3	0.528
Wheat	75	50	0.797	70	52.4	0.589
Egg	50	20	>0.999	75	90.5	0.491
Legume	50	62.5	0.628	66.7	73.3	0.956
Overall	60.4	40.6	–	77.9	77.2	–

Positivity thresholds were defined as *0.1 kU/l and †≥0.35 kU/l, respectively.
‡Chi-square test.

response laying beneath the esophageal eosinophilic infiltration in these patients (4), especially when firm evidences have repeatedly questioned the involvement of IgE in the pathophysiology of EoE (5–7).

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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REPLY

We kindly thank the interest of Lucendo et al. in our recent study (1). These authors provide a thorough dissection of the article, criticizing pre-selection of patients for serum IgE-targeted elimination diet (sIgE-ED) upon IgE sensitization, the real *'overall'* efficacy of sIgE-ED, '*not considering total serum IgE levels*', '*eliminating rice and corn in patients in case a sIgE levels against wheat*' and using known ineffective diagnostic tools, instead of *'simplifying dietary strategies with a demonstrated effectiveness'* and '*identifying the true biological mediators of the immune response in EoE*'.

In our study, 43 adult EoE patients were allocated to undergo sIgE-ED (n = 26) or SFED (n = 17), upon the presence or absence of IgE-mediated food sensitization, respectively. Selection bias was already acknowledged as the main limitation of the study (1). Lucendo et al. point out that the '*whole*' efficacy of sIgE-ED is 44% (19/43), much lower than that reported for six-food elimination diet (SFED). This figure is false and can only be misconstrued presupposing than those 17 patients allocated to SFED had failed to sIgE-ED. Testing-directed elimination diets consists of eliminating foods with positive test results, but its efficacy does not apply to patients with negative test results (40% in our study). In fact, the group led by Dr Lucendo did not assume this premise in their recent meta-analysis on dietary interventions for EoE (2).

Testing only foods included in SFED precisely aimed to simplify dietary restriction in *'a dietary strategy with a demonstrated effectiveness'*, like SFED. Thus, our goal was to streamline dietary restriction in an empiric effective but highly restrictive diet, where just 1 or 2 food triggers are identified after food reintroduction in 65–85% of adult EoE patients (3, 4). Total serum IgE levels were not considered as they are not useful to diagnose and monitor EoE (5). Although previously reported (6), additional exclusion of rice and corn in wheat-sensitized patients was not based on sIgE-wheat positive result, but empirically due to well know potential cross-reactivity between these grains (7).

Some other issues related to IgE-based testing are reasonably questionable (using sIgE and not SPT for designing food restriction, the proposed cutoff point for sIgE). We also agree with the low ability of IgE-based testing to determine the triggering food, in accordance with Lucendo′s previous findings (4). Indeed, we pointed out that full agreement between sIgE and food challenge results for cow′s milk in IgE-sensitized adult patients was the main finding in our study.

Finally, Lucendo et al. encourage us 'to *identify the true biological mediators of the immune response in EoE'*. In an elegant upcoming study (8), adult EoE is firstly presented as an IgG4-mediated and not an IgE-mediated disorder. This landmark study speculates that EoE might be IgE-associated or mediated initially, becoming then an IgG4-associated process with repeated trigger food exposure. Nevertheless, the authors acknowledge that '*it is plausible that a few adult or long-term EoE adult patients might retain IgE reactivity and*

lack an IgG4 response, similarly to some cases of failure of IgG4 antibodies to develop in patients with filariasis or with allergen desensitization therapy' (8).

In conclusion, our results, despite impaired by selection bias and methodological issues, are straightforward and cannot be misinterpreted. EoE is a mixed IgE and non-IgE-mediated disease and our study points to the existence of a subset of adult EoE patients which may benefit from IgE-based testing. Whether our results might be transferable to pediatric population, with a less debated IgE profile, will need to be further addressed. Currently, EoE food triggers can only be identified trough individual food reintroduction and subsequent endoscopy. Therefore, efforts targeted to find novel or improve current diagnostic tools, either IgE or non-IgE mediated, are undoubtedly warranted.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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