

Correspondence

Graded Challenge (whenever possible, according to risk stratification) prior to the indication of desensitization.

Once all the previous matters have been clarified, we summarize by highlighting: 10-step RCUH RD standard protocol has been successfully used for different drugs (oxaliplatin, carboplatin, paclitaxel, docetaxel, cyclophosphamide and rituximab) and for different types of immediate reactions (IgE-dependent and IgE-independent) with an excellent safety profile (and improved compliance with our institutional hazardous drugs handling guidelines) in a significant number of patients from our population, allowing for single-morning desensitizations (approximately 4 h). Additionally, we present a specific practical approach other groups may adopt for their local populations, and we report the first important series of desensitizations to oxaliplatin, along with cutting-edge data on a novel diagnostic tool for these patients: oxaliplatin-specific IgE determination.

‘Eppur si muove’, Galileo Galilei (3).

Author contributions

All of the authors, in agreement with all co-authors of the original article, have contributed to the design of the article, and/or to the interpretation of data, and/or to the drafting and critical revision of the article for important intellectual content, and/or to the final approval of the version to be published of this reply letter.

Conflicts of interest

There are no potential conflicts of interest for any of the authors regarding this article. There are no financial interests.

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Diversity of allergens contained in dog saliva

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Most individuals sensitized to cats react to Fel d 1, and standardized extracts are based on particular concentrations of this allergen. In contrast, a distinctive major dog allergen recognized by the specific IgE of dog-sensitized individuals has not been identified. Several dog allergens, including Can f 1, Can f 2, and Can f 3, have been traditionally considered relevant to particular individuals sensitized to dogs, with Can f 2 (lipocalin) and Can f 3 (albumin) being responsible for cross-reactivity among mammals. More recently, other dog allergens (Can f 4, Can f 5, and Can f 6) have been identified and proven clinically relevant to particular individuals and also responsible for cross-reactivity among species (1–3).

Mammalian allergens can occur in a variety of sources, and different raw materials are used for the production of allergenic extracts. These materials include dander, hair, epithelium, pelt, skin scrapings, and hides. Dog raw materials differ in allergenic composition, with dander containing greater Can f 1 concentrations than epithelia. Dander is the

most common material used for the preparation of dog allergenic extracts.

The fact that no major clinically relevant dog allergens that affect most sensitized individuals exist, combined with the heterogenic composition of dog raw materials, is responsible for the presence of a number of products in the market with differential diagnostic value. Standardized allergenic extracts for immunotherapy are lacking.

In the May issue of *Allergy*, Polovic et al. (4) described the interesting finding that dog saliva contains allergens, not previously identified in dander, and suggested that saliva could have an increased diagnosis potential, compared with other materials. The authors of this article collected saliva samples from 14 individual dogs belonging to 11 different breeds and compared their allergenic content with that measured in a dog dander sample commercially obtained.

As expected, a large variation of different allergen concentrations was detected between individual dogs, and the authors propose that particular dog breeds could be less

allergenic than others, based on selective allergenic content in saliva, and therefore, particular breeds could be recommended to dog-sensitized individuals. While this theory has been previously proposed, based on Can f 1 content measured in dander (5), due to the multiple factors responsible for dog allergen production and accumulation, the allergenic content in saliva may not correlate with that present in dander, and findings should not be extrapolated.

Studies that investigate the environmental components responsible for allergen accumulation are very difficult to perform due to a number of confounding factors involved. In fact, an attempt to determine the validity of the proposition that dog-sensitized individuals can tolerate some dog breeds better than others concluded that scientific evidence is lacking to provide recommendations in that regard (6).

The findings described in the article by Polovic et al. (4) should be verified using a larger sample size, and the nature of the differential allergens detected in saliva should be identified, particularly those common to different breeds. From a manufacturing and regulatory perspective, the qualitative and quantitative allergen compositions of raw materials are the critical parameters responsible for the quality and consistency of the associated allergenic extracts.

While the finding of large allergen diversity in dog saliva is scientifically interesting, this material may not be suitable for

the production of allergenic extracts due to the potentially associated challenges of obtaining consistent formulations comprising a number of allergens. The intrinsic nature of sensitization to dog allergens is unique, and consistent diagnostic tools are needed. The production of individual dog allergens is an emerging technology with applications for diagnosis and treatment to target specific patient populations.

Author contribution

R. Codina is the only author of this Correspondence article, which represents her sole opinion.

Conflicts of interest

The author has no conflicts of interest associated with any potential economic or scientific outcomes resulting from its publication.

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REPLY

We thank Dr. Codina for her comments regarding our article (1) and highlighting our findings. We investigated saliva from 14 dogs of 11 breeds and noted that there was a great variation in the IgE-binding profile, including cases with fewer IgE binding proteins in saliva from some breeds indicating that some dogs could be better tolerated by allergic subjects than others. Dr. Codina states that due to the multiple factors responsible for dog allergen production and accumulation, the allergenic content in saliva may not correlate with that present in dander, and therefore particular breeds could not be recommended to dog-sensitized individuals based on the allergenic content in saliva. Our objective was to evaluate dog saliva as allergen source for improved diagnostics of dog allergy. We agree that the allergenic content in dog saliva is not the same

as in dog dander. Based on LC-MS/MS we observed that dog saliva in addition to the known dog allergens Can f 1, Can f 2, Can f 3 and Can f 6 also contains novel IgE-binding proteins (BPIFA2, Mucin-5B, ANGPTL5 and the IgA heavy chain constant region) (1–6). We also noted that there was a modest correlation between IgE responses to saliva and dander ($r^2 = 0.48$, $P < 0.0001$) where several dog dander sensitized patients had higher IgE responses to saliva than to dander. Interestingly, about 20% of 55 patients with symptoms to dog, but lacking IgE antibodies to dog dander, were IgE positive to dog saliva. The results indicate that dog dander alone as an allergen source may not identify all dog sensitized patients. However, we also noted that not all dog dander sensitized patients could be identified by dog saliva (44/55 patients).

Dr. Codina further comments that the nature of the different allergens should be identified, particularly those common to different breeds. Our data are in agreement with the generally acknowledged challenges of qualitative and quantitative allergen compositions of raw materials from dog dander extract for diagnosis and treatment. The IgE binding proteins we observed from a dog saliva pool ($n = 14$) from 11 breeds should be replicated in a greater number of dogs and larger number of breeds. Nevertheless, the identification of these novel candidate allergens may now allow detailed studies using recombinant technology to improve allergen production and allergy diagnostics, and possibly improve the allergen compositions for treatment.

In conclusion, there is a difference in allergen content in dog saliva and dander and not all patients reporting symptoms to dog can be identified with dog dander only. We suggest that dog saliva is an important additional source to dander for improvement of dog allergy diagnostics.

Conflicts of interest

The authors declare no conflicts of interest.

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