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LETTER TO THE EDITOR



Critical aspects in dog allergen immunotherapy (DAI). May Component Resolved Diagnosis (CRD) play a role in predicting the efficacy?

Gennaro Liccardi^{a,b}, Luigino Calzetta^{b,c}, Manlio Milanese^d, Carlo Lombardi^e, Eleonora Savi^f, Giovanni Passalacqua^g, and Paola Rogliani^{b,c}

^aDepartment of Pulmonology, Haematology and Oncology, Division of Pulmonology and Allergology, High Speciality “A.Cardarelli” Hospital, Naples, Italy; ^bPostgraduate School of Respiratory Medicine, Department of Experimental Medicine and Surgery, University of Rome “Tor Vergata”, Rome, Italy; ^cDepartment of Experimental Medicine and Surgery, University of Rome Tor Vergata, Rome, Italy; ^dDivision of Pneumology, S.Corona Hospital, Pietra Ligure (Savona), Italy; ^eDepartmental Unit of Allergy, Clinical Immunology and Respiratory Diseases, Fondazione Poliambulanza, Brescia, Italy; ^fDepartmental Unit of Allergology, Guglielmo da Saliceto Hospital, Piacenza, Italy; ^gAllergy and Respiratory Diseases, Policlinico San Martino, University of Genoa, Genoa, Italy

ABSTRACT

We hypothesize that a pivotal condition determining the efficacy of dog allergen immunotherapy (DAI) might be the mono-sensitization to dog lipocalins (Can f 1-2) in individuals not directly or indirectly exposed to other furry animals. In fact, the concomitant sensitization to lipocalins and/or albumins, especially in those patients directly exposed to furry animals, may potentially stimulate patient's airways by inducing persistent inflammation and, thus, clinical symptoms. In these conditions, it is likely that DAI alone could be inadequate to reduce airway inflammation mediated by inhalation of dog allergens in patients with simultaneous exposure to other furry animals. Can f 5 has been found as exclusive allergen in about one third of dog-sensitized individuals. Considering the presence of different allergenic materials in extract of mammalian origin, it is evident that a standard DAI is not likely to be effective in Can f 5 prevalent or mono-sensitized individuals. Moreover, we would underline the need of collecting detailed information on the possible exposures to furry animals (other than the common pets), an information that usually is neglected in clinical practice. Furthermore, a detailed clinical history exploring the real significance of dog sensitization (mono or poly-sensitization, induction of clinical symptoms after exposure etc.) should be performed before prescribing DAI. In some patients, with potential high susceptibility to animal allergens, the use of CRD is essential to verify the presence of concomitant allergic sensitization to lipocalins and/or albumins belonging to other furry animals. The availability of CRD introduced the possibility of a better targeted prescription of DAI because it might be useful for point out the primary allergens and for the exclusion of cross-reactive ones.

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To the editor

We read with interest the excellent article of Virtanen T.¹ showing the results of a thorough review of publications on allergic sensitization to pet allergens and pet allergen immunotherapy (PAI). We agree with authors' conclusions that “additional studies of allergen immunotherapy (AIT) for pet associated respiratory allergies are needed, because, as reported in this article, the number of patients is small” and there is the necessity of “possibly taking advantage of characterized recombinant allergens, novel adjuvants or alternative routes of delivery, ...”.

It is generally assumed that allergic sensitization to dog is characterized by the main allergens (Can f 1 and Can f 2), which can cross-react with those of other furry animals, whereas sensitization to cat is mainly due to Fel d 1, which

recognized by most of cat-allergic individuals and characterized by a lesser degree of cross-reactivity with other animal allergens.^{2,3} Based on these premises, we would suggest some particular but underestimated clinical conditions (based on our clinical and scientific experience) that might explain the poor clinical efficacy of dog allergen immunotherapy (DAI) in “real life”.

Prevalent sensitization to major dog allergens (Can f 2 and Can f 2) or multiple sensitization to other allergens of furry animals

We previously reported that pet (cat or dog) ownership, or their presence in indoor environments, cannot be considered the main criterion to assess the exposure to furry animals. The

CONTACT Gennaro Liccardi MD  gennaro.liccardi@tin.it  Department of Pulmonology, Haematology and Oncology, Division of Pulmonology and Allergology, High Speciality “A. Cardarelli” Hospital, Piazzetta Arenella n° 7, 80128, Naples, Italy - Postgraduate School of Respiratory Medicine. Department of Experimental Medicine and Surgery, University of Rome “Tor Vergata”, Rome, Italy.

On behalf of Italian Allergic Respiratory Diseases Task Force (CRD Working Group).

Italian Allergic Respiratory Diseases Task Force (other components): Ilaria Baiardini, Caterina Bucca, Giorgio Walter Canonica, Maria Teresa Costantino, Maria Angiola Crivellaro, Stefano Del Giacco, Enrico Heffler, Stefania La Grutta, Vincenzo Patella, Francesca Puggioni, Erminia Ridolo, Giovanni Rolla, Oliviero Rossi, Gianenrico Senna, Bruno Sposato, Carlo Filippo Tesi, Giovanni Viegi.

use of this criterion represents a potential bias of underestimation in clinical practice and in large epidemiological studies.⁴⁻⁸ In fact, exposure to dogs and cats can occur also by indirect modalities, such as pet allergen-contaminated items.^{9,10} The indirect modality of exposure may explain the common findings that dog allergens (Can f 1 and Can f 2) can be detected in indoor environments where dogs are not present.¹¹ In developed countries, the consequence of pet allergen ubiquity may induce a persistent stimulation of airways similar, for instance, to that of dust mite, and consequently increase the risk of allergic sensitization.¹²

For example, in Naples area, less than fifty percent of patients sensitized to cats/dogs or other animals such as horses, rats, mouse, rabbits, hamsters and cows are directly exposed, whereas a significant percentage of subjects are indirectly exposed or not exposed to these allergens.¹³ A plausible explanation for allergic sensitization in these latter case is a cross-reaction mechanism involving some families of allergenic proteins such as lipocalins [the major allergenic materials derived from dog (Can f 1–2), cattle (Bos d 2), horse (Equ c 1), rat (Rat n 1), mouse (Mus m 1), guinea pig (Cav p 1), rabbit (Ory c 1), hamster (Pho s 21)] and albumins (SA).^{14,15} Moreover, we have shown, by using an *in vivo* (skin prick test – SPTs) and *in vitro* model (the micro-array technique ImmunoCAP ISAC), that exposure and allergic sensitization to common pets may increase the risk of developing sensitization to other furry animals.^{16,17}

Considering this background, we hypothesize that a crucial condition determining the efficacy of DAI may be the mono-sensitization to dog lipocalins (Can f 1–2) in individuals not directly or indirectly exposed to other furry animals. The concomitant sensitization to lipocalins and/or albumins, especially in those patients directly exposed to furry animals, may potentially stimulate patient's airways by inducing persistent inflammation and, thus, clinical symptoms. In other word, DAI alone could be inadequate to reduce airway inflammation mediated by inhalation of dog allergens in patients with simultaneous exposure to other furry animals although the sensitization to ≥ 2 molecules or to pet albumins was associated with more severe respiratory symptoms.¹⁸

Exclusive or prevalent sensitization to dog prostatic kallikrein allergen Can f 5

Dog allergens are a common cause of allergic sensitization and triggering respiratory symptoms worldwide. The impact of dog allergens is particularly relevant in geographical areas characterized by an high level of pet ownership such as US and Northern Europe.^{19,20}

Common described dog allergens belong to lipocalins (Can f 1, Can f 2, Can f 4 and Can f 6) or albumins (Can f 3) families of proteins.¹⁴ In 2009 Mattson et al.²¹ identified a new dog allergen named Can f 5, a prostatic kallikrein which is an androgen-regulated protein expressed in the prostate and detectable only in male dogs (small amounts might also be present in dog epithelia). Recent studies have highlighted the increasing importance of allergic sensitization to Can f 5 which has been found as exclusive allergen in about a third²¹ until 37% of dog-sensitized

individuals.²² However, further studies should confirm the real value of Can f 5 sensitization in “real life”.²³

It is well known that literature data on dog allergen immunotherapy (DAI) demonstrated poor and conflicting results on clinical efficacy, probably correlated with the poor-quality extracts and the inherent complex allergenic profile of dog materials.^{24,25} As a consequence of this and considering the presence of different allergenic materials in extract of mammalian origin, it is evident that a standard DAI is not likely to be effective in Can f 5 prevalent or mono-sensitized individuals. In addition to this probable effect on the efficacy of DAI, patients suffering from this specific sensitization might experience either favourable or unfavourable clinical conditions in “real life”.²⁶ (Table 1).

The role of CRD as preparatory procedure before prescribing DAI

The component resolved diagnosis (CRD) can be considered a prototype of “Precision Medicine”, since it would allow a better targeted prescription of AIT, by discriminating against primary and cross-sensitization allergens.²⁷ In patients, with potential high susceptibility to animal allergens, the use of ImmunoCAP ISAC is essential to verify the presence of concomitant allergic sensitization to lipocalins and/or albumins belonging to other furry animals.^{28,29}

It is reasonable to assume that individuals with a prevalent or exclusive sensitization to primary dog allergens (Can f 1, Can f 2) have more chances for effective clinical effects following DAI.

Possible future perspectives

Our group previously described a case of dog allergy in which we explored if DAI could interfere with a concomitant allergic sensitization to other allergens of furry animals.³⁰ This demonstrated the efficacy of sublingual DAI on SPTs, symptom score, and pulmonary function, despite the persistent exposure to dog

Table 1. Possible favourable or unfavourable conditions of being exclusively or prevalently sensitized to dog allergen Can f 5 in “real life”. (Adapted from Liccardi G. et al. Eur Ann Allergy Clin Immunol – 2017).²⁶

Possible favourable conditions:

- Reduction of the risk of cross-reactivity with other common animal allergens.
 - Can f 5 should not cross-react to other mammalian “pan-allergens” belonging to albumins or lipocalins family.²⁶
- Possible reduction of the occurrence of dog allergen «ubiquity» and consequent effects.
 - To the best of our knowledge, no studies have previously demonstrated a passive transport of Can f 5 in dog-free indoor environments.²⁶
- Possibility to own a female dog.
 - Dog-allergic patients mono-sensitized to Can f 5 seem to tolerate female dogs.³¹ It could to fulfill the wish to get a dog in the house especially in children.
- Possible utility of castration of male dog ?
 - Studies are needed.
- Possible Unfavourable Conditions:
 - Increased risk for allergic sensitization to human seminal fluid.
 - This condition has been well documented^{32–34}
 - Possible necessity of re-location of the male dog
 - In the case of documented occurrence of respiratory symptoms only after exposure to male dogs and not after contact with female dogs.^{26,31}
 - Possible reduced efficacy of dog AIT ?
 - Further studies are needed^{26,30}

AIT = Allergen Immunotherapy.

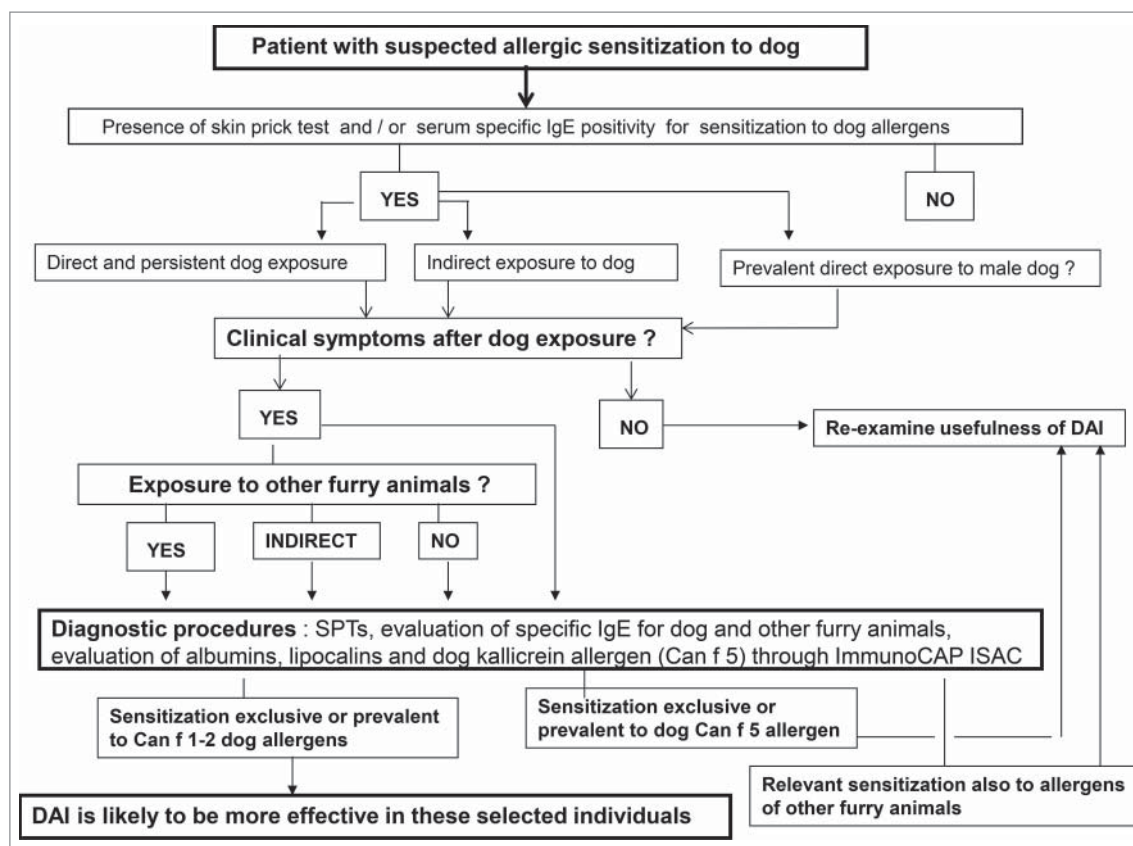


Figure 1. Suggested flow chart to select individuals with higher possibility of positive response to DAI.

allergens at home in a patient sensitized, but not exposed, to other furry animals. At the best of our knowledge this is the first report suggesting that DAI is able to reduce SPTs responses not only to dog, but also to other furry animals such as rabbit, horse, mouse, rat, hamster, cow. No significant change of wheal diameters induced by cat allergenic extract was acknowledged. This last finding can be easily explained because the primary cat allergen Fel d 1 does not belong to lipocalins' family and, in the case of our patient, for the high presence of IgE against nFel d 2 (cat SA). Obviously further studies carried out by using different DAI schedules, allergen amount and time of re-evaluation, an adequate number of patients and laboratory evaluation should be performed to confirm our findings.

Concluding remarks

Based on our clinical and scientific experience, we would underline the need of collecting detailed information on the possible exposures to furry animals (other than the common pets), an information that usually is neglected in clinical practice. Furthermore, a detailed clinical history exploring the real significance of dog sensitization (mono or poly-sensitization, induction of clinical symptoms after exposure etc.) should be performed before prescribing DAI. In some patients, with potential high susceptibility to animal allergens, the use of CRD is essential to verify the presence of concomitant allergic sensitization to lipocalins and/or albumins belonging to other furry animals. The availability of CRD introduced the possibility of a better targeted prescription of DAI because it might be useful for point out the primary allergens and for the exclusion

of cross-reactive ones. Finally, in [Figure 1](#), we propose a flow chart to select individuals with higher possibility of positive clinical responses to DAI.

Summary statement

Some important issues might explain the frequent poor clinical results following the use of DAI in clinical practice.

Disclosure of potential conflicts of interest

All authors declare that they have no conflict of interest and that the study has been carried out without any financial support.

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Author contributions

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