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Can dog allergen immunotherapy reduce concomitant allergic sensitization to other furry animals? A preliminary experience

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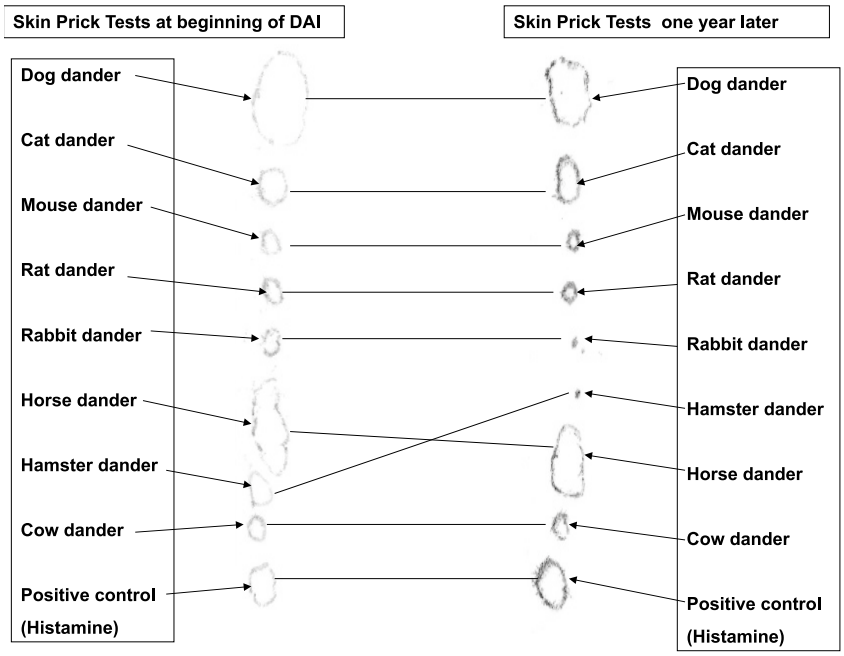
Summary
It has been shown that allergen immunotherapy (AIT) is effective in reducing symptoms of allergic asthma and rhinitis. Data on the efficacy are less convincing with regard to AIT for allergens of common pets (cats/dogs).
We describe a case of dog allergy in which we explored if dog AIT (DAI) could reduce a concomitant allergic sensitization to other allergens of furry animals. Our case demonstrates the efficacy of sublingual DAI on SPTs, symptom score, and spirometric responses despite persistent exposure to dog allergens at home in a patient sensitized, but not exposed, to several other furry animals. Moreover, 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.
We recommend an accurate anamnesis and diagnosis of dog allergy before prescribing DAI. In particular, the use of ImmunoCAP ISAC is essential to verify the presence of IgE to lipocalins / albumins belonging to other furry animals.
Obviously further studies carried out by using different DAI schedules, allergen amount and time of re-evaluation, laboratory procedure should be performed to confirm our findings.

To The Editor

International Consensus Reports have shown that allergen immunotherapy (AIT) is effective in reducing symptoms of allergic asthma and rhinitis, improving the quality of life of allergy sufferers and potentially modifying the underlying course of disease (1). Relevant allergens are the major contributors to the safety and efficacy of the allergenic extracts used for AIT. Most of the currently available data address mites, selected pollens, and animal dander. On the other hand, less is known concerning the efficacy and safety of mould or cockroach allergens. Double-blind, placebo controlled trials with both subcutaneous AIT (SCIT) and sub-lingual AIT (SLIT) in patients with perennial dust mite allergic asthma have provided more robust evidence of efficacy. The literature data are less convincing with regard to AIT for allergens of common pets (cats/dogs) (1). In particular, Smith and Coop (2) reviewed medical literature on dog AIT (DAI) in patients with hypersensitivity to dog. They demonstrated the poor and conflicting results of clinical efficacy, correlated with the poor-quality extracts and the inherent complex allergenic profile of dog materials. However, we believe that further important factors can be involved. For example, it

Figure 1 *- Wheals of SPTs for animal allergens at the beginning and one year after DAI. The profile of the wheals was outlined using a fine-point marking pen and transferred by adhesive tape onto patient's form.*



has been shown that allergic sensitization to common pets, and likely to other furry animals, can be induced by both direct and indirect exposure. In fact, it has been widely recognized that cat and dog allergens should be considered as ubiquitous, since they are found not only in indoor environments containing these animals but also in other indoor private / public places where cats/dogs have been never kept (3,4). 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 or not exposed (3). A plausible explanation for allergic sensitization in these last cases 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 serum albumins (SA) (5,6). Moreover, we have shown, by using an *in vivo* (skin prick test) 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 (allergic phenotype?) (7,8). It is likely that the concomitant sensitization to lipocalins and/or serum albumins of other furry animals, especially in those patients directly exposed, could be the crucial condition which determines the efficacy of DAI in dog-sensitized individuals (9). The availability of molecular-based diagnosis (CRD) introduced the possibility of better targeted prescription of AIT because it might be useful for excluding cross-reactive allergens. In fact, it has been demonstrated that AIT has to be presently considered a prototype of so-called "Precision Medicine" (10) because CRD helps to improve the selection of the allergen product for AIT of an individual patient.

Since, at the best of our knowledge, no studies have assessed the relationship between DAI and sensitization to other furry animals, we describe briefly a case of dog allergy in which we explored if DAI could reduce a concomitant allergic sensitization to other furry animals as assessed by using skin prick test (SPTs). A 38 year old man sensitized to dog, cat, rabbit, horse, mouse, rat, hamster, cow and *Parietaria* allergens, underwent sublingual DAI (ALK Group Milan Italy) because he refused to relocate his dog for family reasons. He had declared no direct or significant indirect exposure to cat and other furry animals. Diagnosis was done by using SPTs, evaluating specific IgE (CAP System and ImmunoCAP ISAC), symptom score and spirometry. One year after having begun DAI, we re-evaluated SPTs and found a significant reduction of wheal diameters (expressed in mm) of dog, horse, cow, mouse, rat, abolished skin response to rabbit / hamster, and no significant change of wheal diameters of cat (**figure 1**). This last finding can be easily explained because the main cat allergen Fel d 1 does not belong to lipocalins' family and, in

Table 1 *- Clinical and diagnostic data at the beginning and one year after DAI.*

At the beginning of DAI	**One year after DAI**
SPTs (wheal diameters expressed in mm)	SPTs (wheal diameters expressed in mm)
Dog allergen: 13 x 15	Dog allergen: 9 x 10
Cat allergen: 6 x 6	Cat allergen: 5 x 7
Mouse allergen: 4 x 4	Mouse allergen: 2 x 2[1]
Rat allergen: 4 x 4	Rat allergen: 2 x 2[1]
Rabbit allergen: 4 x 4	Rabbit allergen: 0 x 0 (no SPT response)
Hamster allergen: 5 x 6	Hamster allergen: 0 x 0 (no SPT response)
Horse allergen: 8 x 16	Horse allergen: 7 x 11
Cow allergen: 4 x 4	Cow allergen: 3 x 3
Positive control (Histamine): 6 x 7	Positive control (Histamine): 7 x 7
(T-paired test results: t = 2.4062; p = 0.0470. This difference is considered statistically significant.)	
Serological data	
Evaluation total IgE: 263 kUL (n.v. < 100 kUL)	n.a.[2]
Evaluation specific IgE (CAP System) (value)	
Dog epithelia: 51.1 kUL (Very high)	n.a.
Cat allergen: 7.27 kUL (High)	n.a.
Mouse allergen: 2.19 kUL (Moderate)	n.a.
Rat allergen: 1.28 kUL (Moderate)	n.a.
Rabbit allergen: 0.15 kUL (Low)	n.a.
Hamster allergen: n.a	n.a.
Horse allergen: 2.24 kUL (Moderate)	n.a.
Cow allergen: 2.37 kUL (Moderate)	n.a.
Evaluation specific IgE (ImmunoCAP ISAC) (value)	
rCan f 1 (Lipocalin): 36 ISU-E (Very high)	n.a.
rCan f 2 (Lipocalin): 12 ISU-E (High)	n.a.
rCan f 5 (Arginin esterase): 1.9 ISU-E (Moderate)	n.a.
rEqu c 1 (Lipocalin): 3.5 ISU-E (High)	n.a.
rFel d 1 (Uteroglobulin): 0.6 ISU-E (Low)	n.a.
nCan f 3 (Serum albumin): 22 ISU-E (Very high)	n.a.
nEqu c 3 (Serum albumin): 3.5 ISU-E (High)	n.a.
nFel d 2 (Serum albumin): 18 ISU-E (Very high)	n.a
Fel d 4 (Lipocalin): < 0.3 ISU-E (Negative)	n.a.
Mus m 1 (Lipocalin): < 0.3 ISU-E (Negative)	n.a.
Bos d 1 (serum albumin): < 0.3 ISU-E (Negative)	n.a.
(Statistical evaluation not applicable)	
Symptom score (Nov 2012 - Mar 2013)	Symptom score (Nov 2013 - Mar 2014)[3]

At the beginning of DAI	One year after DAI
ANOVA test for all nasal / bronchial symptoms (running nose, stuffy nose, nasal congestion, itchy nose, sneezing, cough, wheezing, dyspnea) and following multiple rank test:	
F = 93.53; P < 0.001	
Multiple rank test has been carried out by using LSD of Fisher.	
Significant statistical difference for: running nose, stuffy nose, sneezing and dyspnea.	
Spirometric evaluation[4]	
Once a month from Nov 2012 to Mar 2013	Once a month from Nov 2013 to Mar 2014
Mild obstruction at lower airways:	Mild obstruction at lower airways:
(in 4 out of 5 monthly controls)	(in 1 control, the remain 4 controls: normal values)

[1]Values below usual limits of positivity (3 x 3 mm)
[2]n.a. = not available
[3]These periods have been chosen because out of *Parietaria* pollen season.
[4]These periods have been chosen because out of *Parietaria* pollen season.
SPTs = Skin Prick Tests
LSD = Least Significant Difference

the case of our patient, for the high presence of IgE against nFel d 2 (cat SA). Nasal and bronchial symptom scores showed a statistical significant difference, spirometric evaluations showed normal values in 4 out of 5 controls (see additional materials for details). Unfortunately, the patient refused to continue DAI and undergo the second blood sample, so we have no data on specific IgE levels to dog and other animals.

Our case demonstrates the efficacy of sublingual DAI on SPTs, symptom score, and spirometric responses despite persistent exposure to dog allergens at home in a patient sensitized, but not exposed, to several other furry animals. 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. Since our patient denied any direct / indirect contact with all animals (excluded the dog), perhaps the clinical influence of this finding could be negligible for him. We cannot exclude that, in patients sensitized and exposed to several animal species, the clinical effectiveness of DAI may be of great extent. The limitations of our study, carried out in "real life" by using commercially available extracts, are related with the time of re-examination and the lack of serological data, merely due to the patient's decision.

In conclusion, our preliminary experience on DAI suggests that this therapeutic approach is effective on symptoms related to dog allergy, but could be potentially useful also to reduce allergic sensitization to other animal allergens as assessed by SPTs. We recommend an accurate anamnesis and diagnosis of dog allergy before prescribing DAI. In particular, the use of ImmunoCAP ISAC is essential to verify the presence of IgE to lipocalins / SA belonging to other furry animals (11), as these allergens are likely to stimulate patient's airways inducing clinical symptoms. 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.

Summary statement

Our preliminary experience suggests that the effects of dog allergen immunotherapy could be potentially useful also to reduce allergic sensitization to other animal allergens as assessed by SPTs.

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