Why is Pet (Cat/Dog) Allergen Immunotherapy (AIT) Such a Controversial Topic? Current Perspectives and Future Directions

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Abstract
Dogs and cats are the most common pets worldwide. In Italy, the prevalence of allergic sensitization to cats and dogs is 16% and 9% respectively. The limited standardization of allergenic extracts, especially for dogs, emphasizes the importance of Component Resolved Diagnosis (CRD) for accurate diagnosis and subsequent prescription of allergen immunotherapy (AIT).
However, this low standardization is the main factor contributing to the unsatisfactory clinical efficacy of traditional AIT, AIT with modified allergens, and intralymphatic allergen-specific immunotherapy (ILAIT). Emerging immunological approaches, particularly for controlling the primary cat allergen, show promise but are hindered by high costs (e.g., use of anti-Fel d 1 monoclonal antibodies in humans) or by exclusively targeting Fel d 1 produced by one's own animal (e.g., immunizing cats to induce neutralizing antibodies against Fel d 1 or including an egg product with anti Fel d 1 IgY antibodies in feline diet). Further studies are imperative for standardizing pet allergens, enhancing the efficacy of various AIT modalities, and exploring other immunological approaches, to optimize the relationship between pets and their owners and prevent distressing "forced removals."

Key words: Allergic sensitization, allergic rhinitis, bronchial asthma, cat, cat allergen, dog, dog allergen, hypersensitivity, immunotherapy, molecular diagnosis

Impact statement: Further studies are urgent both as regards the standardization of pet allergens and the improvement of the efficacy of the various modalities of the AIT and of other immunological approaches.

Background and General Aspects

Dogs and cats are the most prevalent pets globally. Recent data in Italy indicates that 44.7% of families own a dog, while 35.4% have a cat at home (Eurispes 2022) (1). Beyond the emotional connection, common pets drive substantial economic activities, including breeding, veterinary services, and new pet-related professions (e.g. pet sitters, groomers, pet shop workers, military units) (2) and pet product industries (e.g. pet-food, accessories)

The recent Italian Multicenter Study by Liccardi et al. (3) showed that allergic sensitization frequency to cats and dogs were 16% and 9% respectively. In Northern Europe and the US, higher pet ownership leads to much higher sensitization frequencies (up to 50%) (4). Conversely, China exhibits sensitization frequencies similar to Italy (14.9% for dogs and 9.3% for cats) (5). At present, both in dogs and in cats eight main allergens characterized by different molecular weights, biochemical properties, and biological functions have been identified (6). Notably, the primary cat allergen (Fel d 1) is responsible for over 90% of allergic sensitizations to cats, while dogs can have various allergens involved, such as Can f 1, Can f 2, and Can f 5 (7, 8). The distinct roles of common pet allergens in inducing sensitization underlie challenges in standardizing allergenic extracts and impact the clinical efficacy of allergen immunotherapy (AIT). Notably, the recently identified dog prostatic allergen (Can f 5) has become the most prevalent dog allergen in Italy (9) and globally (7,8). Furthermore, according to a previous Italian multicenter study by Liccardi et al (10), it has been showed that owning a male dog significantly increases the risk of mono-sensitization to Can f 5 compared to those exposed to female dogs or without direct contact with either gender. Polysensitization to dog and cat allergen components is associated with a high likelihood of allergic symptoms during exposure (11). Diagnosing dog allergies is particularly challenging due to difficulties in obtaining diagnostically accurate extracts with well-defined allergen compositions (12). The production of allergens (Can f 1-6) varies between dog breeds and anatomical sites, as well as between individual dogs of the same breed, introducing variability in natural extracts in terms of source, sampling, processing, and ultimately standardization and minimum allergen levels for accurate diagnosis and treatment (12).

Importance of Molecular Diagnosis (Component Resolved Diagnosis - CRD)

The limited standardization of allergenic extracts, particularly for dogs, has underscored the importance of molecular diagnostics (Component Resolved Diagnosis, CRD). It has been previously proposed that CRD is valuable in predicting the risk of sensitization to less common mammals, such as hamsters, rabbits, and horses, in individuals already sensitized to dogs or cats (13). Pre-existing sensitization to cats poses a lower risk due to the characteristics of its allergens, while sensitization risk is higher in individuals sensitized to dogs, attributed to cross-reactive allergens like lipocalins (13). Given the growing role of the dog-prostatic allergen (Can f 5) in sensitization compared to the well-known Can f 1 and Can f 2, we advocate for CRD prior to AIT prescription (14). If CRD reveals mono-sensitization to Can f 5, a common occurrence in dog-sensitized individuals (9, 10), a dog AIT containing a mix of allergens may have limited clinical efficacy (14). The EAACI Molecular Allergology User's Guide v.2 (15) has emphasized the importance of IgE anti Fel d 1 for identifying primary sensitization in cat allergy cases, while IgE anti Can f 1, Can f 2, and Can f 5 indicate primary sensitization in dog allergy cases. The presence of these allergens is considered crucial for an effective therapeutic response during AIT. Schoos et al. (16) also provide similar guidance on primary sensitization to pet allergens, recommending nasal challenge tests to refine the pet AIT, in cases of uncertain results. It is imperative that such tests are conducted in controlled medical environments to address the potential occurrence of bronchial obstruction, which can be common in asthmatic subjects (17).

Traditional Allergen Immunotherapy (AIT) and novel modalities of immunologic approach to cat / dog allergic sensitization.

Traditional Allergen Immunotherapy (AIT)

Data on cat / dog AIT in Italy

To provide current insights into subcutaneous (SCIT) or sublingual (SLIT) AIT for dog/cat allergens in Italy, we conducted an online survey encompassing both manufacturing companies and allergy centers evenly distributed across the country. We inquired with the manufacturing companies about the inclusion of AIT extracts for dogs/cats in their price lists, and gathered information from Italian allergists regarding the number of prescriptions issued in the last decade, as well as the clinical efficacy in managing respiratory symptoms. Six manufacturing companies and 30 allergy specialists from all Italian regions participated in the online survey. The

results are summarized in figure 1. As shown in figure 1 (B), one company does not manufacture allergenic extracts for cat/dog AIT. Only 2 out of six produce extracts for dog AIT, while 5 out of six offer extracts for cat AIT in their catalogues. Prescription trends over the last decade for pet AIT are highlighted in figure 1(A); they are notably higher for cat sensitization compared to dog sensitization, particularly in northern Italy as opposed to central and southern regions (likely influenced by reimbursement policies regarding AIT costs). Finally, figure 2 (C) illustrates that, in numerical terms, clinical efficacy is reported as more favorable in patients receiving cat allergenic extracts than those receiving dog allergenic extracts.

Actual aspects of cat / dog AIT

While AIT for dog/cat epithelia has demonstrated positive outcomes in atopic dermatitis treatment (18), its primary application is in respiratory allergy. AIT can be a potential add-on treatment option when conventional management proves infeasible or ineffective, and when there is specific IgE sensitization combined with a clear correlation between clinical symptoms and exposure to that particular allergen.

A pediatric-oriented EAACI Position Paper (19) and a Consensus Document on pet allergy (20) comprehensively reviewed the available literature spanning from the early 1980s to the middle of the second decade of the 2000s, affirming the actual clinical significance of AIT for cat/dog allergens. Alvaro-Lozano et al. (19) noted limited high-quality evidence supporting AIT for furry animals in children, with insufficient data on cost-effectiveness. Evidence for AIT in cat allergy is similarly limited, while data for its effectiveness in dog allergy is notably absent, likely due to the lack of standardized extracts and variability in sensitization profiles. Dàvila et al. (20) reported modest results concerning the clinical efficacy of AIT with dog extracts due to factors like the use of low-quality extracts, variations in allergenicity, and the complexity of the allergenic profile of dogs. In contrast, AIT with cat extracts showed both clinical and laboratory improvements. However, while there are double-blind placebo-controlled randomized clinical trials (21, 22), not all have optimal designs, and the patient cohorts tend to be limited. It's worth noting that each AIT product is distinct, making it unlikely that results achieved with one product can be generalized to others in the market with the same allergen.

The reduction of wheal area observed through skin prick tests (SPT) towards the allergen of AIT is a common finding after a suitable treatment period. In a preliminary report, it has been demonstrated that SLIT for dog allergen, after a year of treatment, not only induced positive clinical responses but also significantly reduced the areas of wheals assessed by SPT, not just against dog allergens, but also against those of other mammals like rabbit, horse, mouse, rat, hamster, and cow (23).

More recently, Uriarte and Sastre (24) investigated the effects of AIT for dogs and cats using an ultrarush (4 hours) SCIT schedule administered via subcutaneous infusion pump in patients with rhinitis and/or asthma. While no severe adverse reactions (ARs) were recorded, a greater number were noted compared to standard protocols, although this number was similar to that of longer rush protocols when patients were premedicated with antihistamine (25). The use of an infusion pump reduced the number of injections and could be applied when indicated in real-life settings under appropriate medical supervision.

Subsequently, the same authors explored the use of high-dose SCIT in patients with allergic rhinitis and asthma caused by exposure to cat and dog dander using real-life clinical practice extracts (Alutard SQ, Alk-Abelló). Allergenic extracts were administered via an infusion pump over 3 sessions as part of a rush protocol (24), followed by monthly administration over 12 months, at the following concentrations of major allergens: Fel d 1, 15 µg/mL; Can f 1, 3.21 µg/mL; Can f 5, 0.72 µg/mL (26). A significant improvement was observed in FEV1, symptoms of rhinitis and asthma, Quality of Life (QoL), use of medication, Visual Analog Scale (VAS) score, and Asthma Control Test score at 6 months and continued at 12 months. Clinical improvement with cat extract was significantly better than with dog extract.

The safety profile of the rush up-dosing and maintenance phases was generally good, as reported in previous studies (27).

Finally, Uriarte et al. (28) conducted a real-life study to assess clinical efficacy in terms of symptoms, QoL, asthma control, and pulmonary function in patients undergoing SCIT with ultrarush up-dosing using the same dog and cat extracts as in their previous studies (26). They compared the results and also evaluated the immunologic changes caused by cat/dog specific AIT. A significant improvement was observed in rhinitis and asthma symptoms and in QoL, use of medication, VAS, and ACT at 1 month; these improvements persisted at month 6. Cat-allergic patients had a better response to SCIT than dog-allergic patients, as also seen in our previous study (26). This finding may be attributed to the higher concentration of Fel d 1 relative to Can f 1 or other dog allergens not contained in the extracts used.

Intralymphatic allergen-specific immunotherapy (ILAIT).

Intralymphatic immunotherapy (ILAIT) administers allergen extract directly to lymph nodes to induce rapid and effective immunological tolerance. Three injections are provided at 12-week intervals, resulting in fewer injections, a shorter treatment duration, a reduction of expense and noncompliance with therapy (29). However, Park et al. (30) examined therapeutic efficacy and safety of ILAIT with L-tyrosine-adsorbed extracts of various allergens including those of cat / dog in patients with allergic rhinitis. After 4 months of treatment**,** ILAIT with L-tyrosine-adsorbed allergen extracts does not induce a significant therapeutic efficacy in allergic rhinitis but can provoke moderate-to-severe systemic reactions and cause pain at the injection site.

AIT with modified allergenic extracts

Since increasing the concentration of allergens during standard AIT increases the risk of possible adverse reactions, various strategies have been adopted, such as physical or chemical modifications of allergenic materials which allow the administration of larger amounts, minimizing the risk of adverse reactions.
Sola et al. (31) developed a new allergoid cat dander extract (ACD) (Probelte Pharma S.L.U., Spain.) from a native cat dander extract (NCD) by modification with glutaraldehyde, and the optimal process control was determined by SDS-PAGE, DOT BLOT and determination of free amine groups. The ACD showed a significant loss of allergenicity compared to NCD obtaining a good safety profile, while maintaining the IgG-binding capacity.
Calzada et al. (32) investigated a new dog dander allergoid (R&D Allergy & Immunology Unit, LETI Pharma, Madrid, Spain) containing Can f 1 and Can f 5, it exhibited a low capacity to bind IgE and to activate basophils in dog allergic patients. Furthermore, it showed potent activation of Th1 mediators and induction of tolerance through Treg activation. This allergoid could offer a safer profile than the native extract and could be an effective immunotherapy treatment for dog allergic patients.

Novel modalities of immunologic approach to cat / dog allergic sensitization

Use of anti-Fel d 1 monoclonal antibodies in humans

AIT has been utilized for over a century, yet the prevailing protective mechanism remains poorly understood. One consistent observation is that increased allergen-specific IgG can competitively block allergen binding to IgE (33). Orengo et al. (34) investigated the contribution of allergen-specific blocking IgG as the protective mechanism of AIT using pre-selected monoclonal anti-allergen-blocking antibodies to suppress allergic symptoms. To explore this fundamental point, they generated two fully human IgG4 antibodies, REGN1908 and REGN1909, specific for Fel d 1, the major cat allergen. They reported that recombinant, allergen-specific blocking IgG antibodies perform comparably to allergen-specific IgG isolated from patients who successfully completed AIT. This effect translates to a rapid and sustained reduction in clinical symptoms in patients with cat allergy thereby offering evidence that allergen-specific blocking IgG play an important role in the protective mechanism of SCIT, and may be a potential new and more rapid treatment approach for allergies (34).
Shamje et al. (35) showed that a single subcutaneous prophylactic dose of a combination of two anti–Fel d 1 (Felis domesticus allergen 1) monoclonal antibodies (REGN1908–1909) reduced nasal symptoms in cat-allergic patients challenged with cat allergen by suppressing FceRI-, FceRII-, and Th2-mediated allergic responses. Finally, the efficacy of these therapies have been demonstrated also in asthmatic patients with cat allergy. It has been suggested that passive administration of neutralizing mAbs targeting the predominant cat allergen Fel d 1 alone, but not Fel d 2, 4, 7, or 8, can prevent cat allergen–triggered asthma responses and may inhibit type 1 immediate IgE-mediated responses (36). Notably, REGN1908/1909 was generally well tolerated, with profound and rapid effects that can last for at least 85 days (36).

Immunization of cats to induce neutralizing antibodies against Fel d 1

Thoms et al. (37) within the "One Health" (http://www.onehealthinitiative.com) paradigm, propose to reduce or prevent cat allergy in human subjects by immunizing cats against their own allergen. The rationale of this method is based on the fact that the major cat allergen (Fel d 1) is recognized by over 90% of cat allergic patients (38).
The authors conjugate vaccine consisting of recombinant Fel d 1 and a virus-like particle derived from the cucumber mosaic virus containing the tetanus toxin–derived universal T-cell epitope tt830-843 (CuMVTT) was used to immunize cats. Vaccinating cats against Fel d 1 induces specific antibodies capable of neutralizing the molecule in situ (ie, in saliva or tears), making cats less allergenic to Fel d 1–sensitive human subjects (37). The same authors demonstrate that allergic symptoms of cat allergic owners were alleviated after the immunization of their cats (39). As a result of the owner being less burdened by their allergy, the QoL of their cat may be improved. The ability of allergic cat owners to better tolerate and increase the duration of their interactions with their pet can benefit the animal through better training and socialization and awareness of the animals' overall health. It is also important to note that, from a veterinary perspective, the overall health status of the cats was not compromised by the induction of auto-antibodies against Fel d 1 (39).

Feline diet with an egg product containing anti Fel d 1 IgY antibodies

Satyaraj et al. (40) demonstrated that it is feasible to reduce the immunologically active Fel d1 allergen from cats by incorporating anti-Fel d1 polyclonal IgY from chicken eggs into their diet.
In fact, it has been demonstrated the efficacy of a rabbit polyclonal and an allergen-specific chicken IgY to bind to Fel d1 in cat saliva and block Fel d1-IgE binding and IgE-mediated basophil degranulation. These Fel d1 blocking antibodies present a novel approach for neutralizing cat allergens and potentially offer a safe and noninvasive method to reduce cat allergenicity (41). The anti-Fel d 1 IgY is safe for cats, based on a comprehensive safety study that fed an egg product ingredient with multiple levels of anti-Fel d 1 IgY, including levels much higher than those used in efficacy studies (42). In addition, based on the principle of allergen load reduction, complete elimination of Fel d 1 production is not necessary, as the approach described does not neutralize 100% of the cat's Fel d 1. Essentially, it transforms moderate and high Fel d 1-producing cats to the equivalent of low or moderate producers without altering the cat's overall production of the allergen (43).
However, it is important to underline that the benefits for cat allergic patients, deriving from the use of monoclonal or IgY antibodies against Fel d 1, strictly concern the cat owned and in contact with the subject. Obviously, these benefits do not extend to other cats the patient may encounter, nor do they address "passive exposure" to cat allergens through various carriers such as clothing, hair, etc. (44, 45).

Concluding remarks

As shown in Figure 2 allergic sensitization to common pets, particularly dogs and cats, is a complex puzzle influenced by many different factors related to individuals, living environments, modes of exposure, and the animals themselves. The limited standardization of allergenic materials, especially for dogs, remains the primary factor contributing to the unsatisfactory clinical efficacy of traditional AIT, AIT with modified allergens, as well as ILAIT. While new immunological approaches, particularly for controlling the primary cat allergen such as the use of anti-Fel d 1 monoclonal antibodies in humans, immunization of cats to induce neutralizing antibodies against Fel d 1 and feline diet with an egg product containing anti-Fel d 1 IgY antibodies show great promise, they have significant costs (e.g. monoclonal antibodies) or the limitation of exclusively targeting one's own animal's Fel d 1.
The need for further studies is evident, encompassing both the standardization of pet allergens and the enhancement of the efficacy of various AIT modalities. This is crucial to optimize the relationship between animals and their owners and prevent the distressing necessity of "forced removals".

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References

1. Thirty-fourth Institute of Political, Economic and Social Studies (EURISPES) Report 2022. www.eurispes.eu

2. Kesici GG, Karataþ A, Ünlü Y, Tutkun E. Occupational allergy to dog among police dog trainers. Eur Ann Allergy Clin Immunol. 2019 Nov;51(6):265-273. doi: 10.23822/EurAnnACI.1764-1489.102.

3. Liccardi G, Bilò MB, Calzetta L, Milanese M, Martini M, Bresciani M, et al. Pest sensitization to cockroach, mouse, and rat: An Italian multicenter study. Allergy. 2023 May;78(5):1360-1363. doi: 10.1111/all.15586.

4. Liccardi G, Triggiani M, Piccolo A, Salzillo A, Parente R, Manzi F et al. Sensitization to Common and Uncommon Pets or Other Furry Animals: Which May Be Common Mechanisms? Transl Med UniSa. 2016 May 16;14 : 9-14.

5. Zhu H, Huang Z, Liu T, An N, Gan H, Huang D, et al. Sensitization to Furry Animals in Patients with Suspected Allergic Disease in China: A Multicenter Study. J Asthma Allergy. 2022 Nov 24;15: 1701-1712. doi: 10.2147/JAA.S390473.

6. van Hage M, Käck U, Asarnoj A, Konradsen JR. An update on the prevalence and diagnosis of cat and dog allergy - Emphasizing the role of molecular allergy diagnostics. Mol Immunol. 2023 May; 157:1-7. doi: 10.1016/j.molimm.2023.03.003.

7. Roger A, Lazo C, Arias N, Quirant B, Albert N, Gómez M, et al. Using Component-Resolved Diagnosis to Characterize the Sensitization to Specific Cat and Dog Allergens in Patients with Allergic Respiratory Diseases in Catalonia, Spain. Int Arch Allergy Immunol. 2023;184 (5):440-446. doi: 10.1159/000528643.

8. Özuygur Ermis SS, Borres MP, Basna R, Ekerljung L, Malmhäll C, Goksör E, et al. Sensitization to molecular dog allergens in an adult population: Results from the West Sweden Asthma Study. Clin Exp Allergy. 2023 Jan;53(1):88-104. doi: 10.1111/cea.14216.

9. Villalta D, Milanese M, Da Re M, Sabatino G, Sforza M, Calzetta L, et al. Frequency of allergic sensitization to Can f 5 in North East Italy. An analysis of 1403 ISACs 112 (Component Resolved Diagnosis) collected retrospectively. Eur Ann Allergy Clin Immunol. 2019 Jul; 51 (4):186-189. doi: 10.23822/EurAnnACI.1764-1489.89.

10. Liccardi G, Calzetta L, Bilò MB, Brusca I, Cecchi L, Costantino MT, et al. A prevalent exposure to male dog is a risk factor for exclusive allergic sensitization to Can f 5: An Italian multicenter study. J Allergy Clin Immunol Pract. 2020 Jul-Aug;8(7):2399-2401. doi: 10.1016/j.jaip.2020.02.041.

11. Kang SY, Yang MS, Borres MP, Andersson M, Lee SM, Lee SP. The association between specific IgE antibodies to component allergens and allergic symptoms on dog and cat exposure among Korean pet exhibition participants. World Allergy Organ J. 2022 Oct 12;15(11):100709. doi: 10.1016/j.waojou.2022.100709.

12. Wintersand A, Asplund K, Binnmyr J, Holmgren E, Nilsson OB, Gafvelin G, et al. Allergens in dog extracts: Implication for diagnosis and treatment. Allergy. 2019 Aug;74(8):1472-1479. doi: 10.1111/all.13785.

13. Liccardi G, Bilò MB, Manzi F, Piccolo A, Di Maro E, Salzillo A. What could be the role of molecular-based allergy diagnostics in detecting the risk of developing allergic sensitization to furry animals? Eur Ann Allergy Clin Immunol. 2015 Sep;47(5):163-7.

14. Liccardi G, Calzetta L, Milanese M, Lombardi C, Savi E, Passalacqua G, et al. Critical aspects in dog allergen immunotherapy (DAI). May Component Resolved Diagnosis (CRD) play a role in predicting the efficacy? Hum Vaccin Immunother. 2018 Jun 3; 14 (6):1438-1441. doi: 10.1080/21645515.2018.1434383.

15. Dramburg S, Hilger C, Santos AF, de Las Vecillas L, Aalberse RC, Acevedo N, et al. EAACI Molecular Allergology User's Guide 2.0. Pediatr Allergy Immunol. 2023 Mar;34 Suppl 28: e13854. doi: 10.1111/pai.13854.PMID: 37186333

16. Schoos AM, Nwaru BI, Borres MP. Component-resolved diagnostics in pet allergy: Current perspectives and future directions. .J Allergy Clin Immunol. 2021 Apr; 147 (4):1164-1173. doi: 10.1016/j.jaci.2020.12.640.

17. Liccardi G, Calzetta L, Milanese M, Bilò MB, Rogliani P. Sensitization to Cat: Why Not Use Molecular Diagnostics instead of the Nasal Challenge in Clinical Practice? Int Arch Allergy Immunol. 2019;180(2):142-143. doi: 10.1159/000501796.

18. Chu H, Park KH, Kim SM, Lee JH, Park JW, Lee KH, et al. Allergen-specific immunotherapy for patients with atopic dermatitis sensitized to animal dander. Immun Inflamm Dis. 2020 Jun;8(2):165-169, doi: 10.1002/iid3.291.

19. Alvaro-Lozano M, Akdis CA, Akdis M, Alviani C, Angier E, Arasi S, et al.
EAACI Allergen Immunotherapy User's Guide. Pediatr Allergy Immunol. 2020 May;31 Suppl 25(Suppl 25):1-101. doi: 10.1111/pai.13189.

20. Dávila I, Domínguez-Ortega J, Navarro-Pulido A, Alonso A, Antolín-Amerigo D, González-Mancebo E, et al. Consensus document on dog and cat allergy. Allergy. 2018 Jun;73(6):1206-1222. DOI: 10.1111/all.13391.

21. Van Metre TE Jr, Marsh DG, Adkinson NF Jr, Kagey-Sobotka A, Khattignavong A, Norman PS Jr, Rosenberg GL. Immunotherapy for cat asthma. J Allergy Clin Immunol. 1988 Dec;82(6):1055-68. doi: 10.1016/0091-6749(88)90144-3. PMID: 2462581

22. Valovirta E, Viander M, Koivikko A, Vanto T, Ingeman L. Immunotherapy in allergy to dog. Immunologic and clinical findings of a double-blind study. Ann Allergy 1986 Sep;57(3):173-9. PMID: 3752618

23. Liccardi G, Calzetta L, Salzillo A, Billeri L, Lucà G, Rogliani P. Letter to the Editor: Can dog allergen immunotherapy reduce concomitant allergic sensitization to other furry animals? A preliminary experience. Eur Ann Allergy Clin Immunol. 2017 Mar; 49 (2):92-96. PMID: 28294591

24. Uriarte S, Sastre J. Safety of an Ultrarush (4 Hours) Subcutaneous Immunotherapy Schedule With Cat and Dog Extracts Using an Infusion Pump. J Investig Allergol Clin Immunol. 2018 Dec;28(6):430-432
DOI: 10.18176/jiaci.0307.

25. Cox L. Advantages and disadvantages accelerated immunotherapy schedules. J Allergy Clin Immunol. 2008 Aug;122(2):432-4. doi: 10.1016/j.jaci.2008.06.007. Epub 2008 Jul 10.

26. Uriarte SA, Sastre J. Subcutaneous Immunotherapy With High-Dose Cat and Dog Extracts: A Real-life Study. J Investig Allergol Clin Immunol. 2020; 30 (3):169-174 DOI: 10.18176/jiaci.0415

27. Uriarte SA, Sastre J. Safety of rush subcutaneous immunotherapy administered in real life using an infusion pump. Ann Allergy Asthma Immunol. 2015 Dec;115(6):527-9. doi: 10.1016/j.anai.2015.09.004.

28. Uriarte SA, Grönlund H, Wintersand A, Bronge J, Sastre J. Clinical and Immunologic Changes due to Subcutaneous Immunotherapy With Cat and Dog Extracts Using an Ultrarush Up-Dosing Phase: A Real-Life Study. J Investig Allergol Clin Immunol. 2022 Apr 19; 32 (2):133-140 DOI: 10.18176/jiaci.0656.

29. Jiang S, Xie S, Tang Q, Zhang H, Xie Z, Zhang J, Jiang W. Evaluation of Intralymphatic Immunotherapy in Allergic Rhinitis Patients: A Systematic Review and Meta-analysis. Mediators Inflamm. 2023 May 8; 2023:9377518. doi: 10.1155/2023/9377518.

30. Park HJ, Kim SH, Shin YS, Park CH, Cho ES, Choi SJ, et al. Intralymphatic immunotherapy with tyrosine-adsorbed allergens: a double-blind, placebo-controlled trial. Respir Res. 2021 Jun 4;22(1):170. doi: 10.1186/s12931-021-01766-0.

31. Sola JP, Pedreño Y, Cerezo A, Peñalver-Mellado M. Development and characterization of an allergoid of cat dander for immunotherapy. Allergol Immunopathol (Madr). 2018 Sep-Oct;46(5):491-498. doi: 10.1016/j.aller.2017.12.003.

32. Calzada D, Aranda T, M Gallego G, Escutia MR, Balsa D, Álvarez J, et al. Immunological mechanisms involved in the human response to a dog dander allergoid. Mol Immunol. 2022 May; 145:88-96. doi: 10.1016/j.molimm.2022.02.020.

33. Wachholz PA, Durham SR. Mechanisms of immunotherapy: IgG revisited. Curr Opin Allergy Clin Immunol. 2004 Aug; 4 (4):313-8. doi: 10.1097/01.all.0000136753.35948.c0.

34. Orengo JM, Radin AR, Kamat V, Badithe A, Ben LH, Bennett BL, et al. Treating cat allergy with monoclonal IgG antibodies that bind allergen and prevent IgE engagement. Nat Commun. 2018 Apr 12; 9 (1):1421. doi: 10.1038/s41467-018-03636-8.

35. Shamji MH, Singh I, Layhadi JA, Ito C, Karamani A, Kouser L, et al. Passive Prophylactic Administration with a Single Dose of Anti-Fel d 1 Monoclonal Antibodies REGN1908-1909 in Cat Allergen-induced Allergic Rhinitis: A Randomized, Double-Blind, Placebo-controlled Clinical Trial. Am J Respir Crit Care Med. 2021 Jul 1;204(1):23-33. doi: 10.1164/rccm.202011-4107OC.

36. de Blay FJ, Gherasim A, Domis N, Meier P, Shawki F, Wang CQ, et al. REGN1908/1909 prevented cat allergen-induced early asthmatic responses in an environmental exposure unit. J Allergy Clin Immunol. 2022 Dec; 150 (6):1437-1446. doi: 10.1016/j.jaci.2022.06.025.

37. Thoms F, Jennings GT, Maudrich M, Vogel M, Haas S, Zeltins A, et al. Immunization of cats to induce neutralizing antibodies against Fel d 1, the major feline allergen in human subjects. J Allergy Clin Immunol. 2019 Jul;144(1):193-203. doi: 10.1016/j.jaci.2019.01.050.

38. van Ree R, van Leeuwen WA, Bulder I, Bond J, Aalberse RC. Purified natural and recombinant Fel d 1 and cat albumin in in vitro diagnostics for cat allergy. J Allergy Clin Immunol 1999 Dec;104(6):1223-30. doi: 10.1016/s0091-6749(99)70017-5

39. Thoms F, Haas S, Erhart A, Nett CS, Rüfenacht S, Graf N, et al. Immunization of cats against Fel d 1 results in reduced allergic symptoms of owners. Viruses. 2020 Mar 6;12(3):288. doi: 10.3390/v12030288.

40. Satyaraj E, Li Q, Sun P, Sherrill S. Anti-Fel d1 immunoglobulin Y antibody-containing egg ingredient lowers allergen levels in cat saliva.J Feline Med Surg. 2019 Oct; 21 (10):875-881. doi: 10.1177/1098612X19861218.

41. Satyaraj E, Sun P, Sherrill S. Fel d1 Blocking Antibodies: A Novel Method to Reduce IgE-Mediated Allergy to Cats. J Immunol Res. 2021 Jun 19; 2021:5545173. doi: 10.1155/2021/5545173.

42. Matulka RA, Thompson L, Corley D. Multi-Level Safety Studies of Anti Fel d 1 IgY Ingredient in Cat Food. Front Vet Sci. 2020 Jan 8;6: 477. doi: 10.3389/fvets.2019.00477.

43. Satyaraj E, Wedner HJ, Bousquet J. Keep the cat, change the care pathway: A transformational approach to managing Fel d 1, the major cat allergen. Allergy. 2019 Oct;74 Suppl 107(Suppl 107):5-17. doi: 10.1111/all.14013.

44. D'Amato G, Liccardi G, Russo M, Barber D, D'Amato M, Carreira J. Clothing is a carrier of cat allergens. J Allergy Clin Immunol. 1997 Apr;99(4):577-8. doi: 10.1016/s0091-6749(97)70088-5.

45. Liccardi G, Barber D, Russo M, D'Amato M, D'Amato G. Human hair: an unexpected source of cat allergen exposure. Int Arch Allergy Immunol. 2005 Jun;137(2):141-4. doi: 10.1159/000085793.

Figure 1.
An overview on the state of Allergen Immunotherapy for cat / dog in Italy in terms of prescription (A), manufacturers (B), and reported efficacy (C).

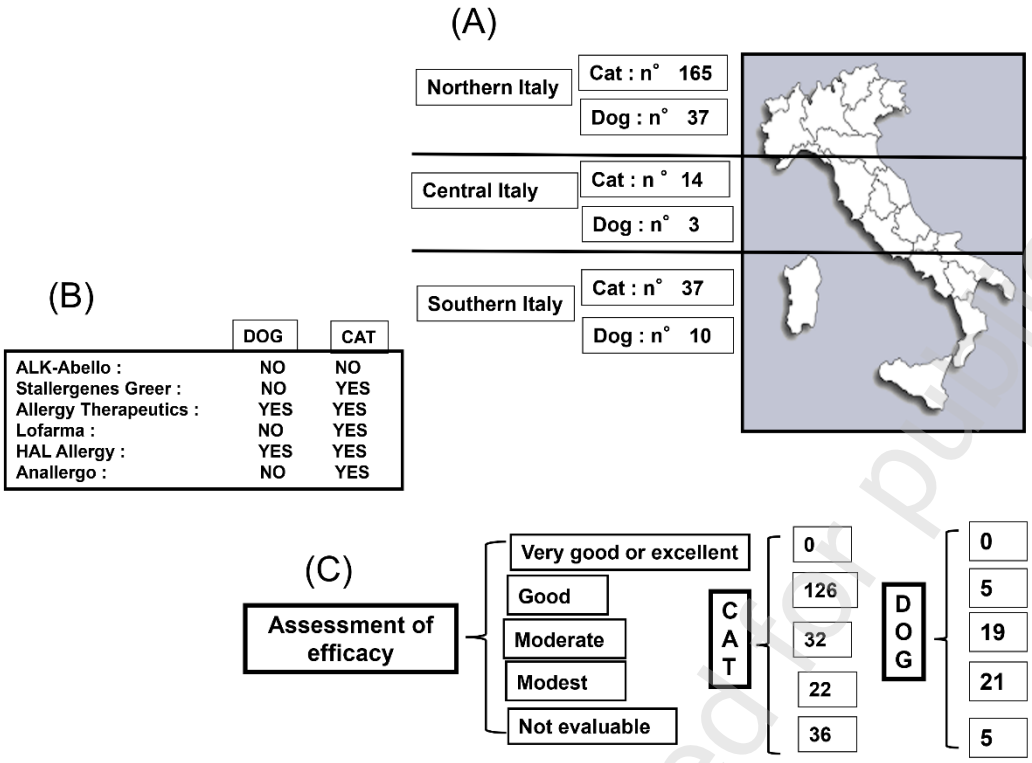

Figure 2.
The "puzzle" of allergic sensitization to common pet allergens.