Allergen-specific Immunotherapy and the Importance of choosing the right Serological Allergy tests

Canine atopic dermatitis (CAD) is a genetically predisposed inflammatory and pruritic allergic skin disease, associated with IgE antibodies against environmental allergens. This means that CAD is a chronic disease and its genetic condition makes it nearly impossible to cure, since contact with the environmental allergens cannot be avoided. It is, however, possible to control it and to provide a good quality of life for the affected animal.

Allergen-specific Immunotherapy: the only possible curative treatment

Allergen-specific Immunotherapy (ASIT) is the only treatment that can change the course of the disease and it is the only possible curative treatment option. ASIT can re-educate (instruct) the immune system and transform it from hyper-reactive to dormant against the allergens to which the animal is sensitized. ASIT is an effective and safe way to reduce the clinical signs of AD in dogs, cats and horses, and there is substantial evidence to support the use of ASIT as a treatment against canine, feline and equine environmental allergy (AD). Desensitization is effective in approximately 50–75% of atopic animals.

The onset of the beneficial effects may be delayed for months, however, and anti-inflammatory/anti-pruritic drugs should be given as needed to maintain good quality of life until the ASIT is judged to be effective. In order to evaluate the effect of the ASIT, a reduction or withdrawing of the medical treatment is needed, when possible.

The need to identify the allergens to formulate ASIT

To formulate an Allergen-specific Immunotherapy (ASIT), it is necessary to identify the allergens against which the animal is hyper-reactive. IgE serology or intradermal tests (IDT) are used to select allergens to be included in the ASIT. Both tests are adequate for that purpose, and no difference has been seen in the efficacy of the ASIT whichever test is used.

Currently, IgE serology is preferred, as only a small amount of blood is needed to run the test.

Disadvantages of IDT are many: the necessity of sedating the animal (higher risk); the necessity of clipping the hair of the lateral thorax; the impossibility to run the test in the presence of lesions; the short expiration date of the allergens (increased costs); the possible difficulty in reading and interpreting the test; and finally, the lack of standardization of the allergens and its performance, which leads to substantial variation in results, even between specialists within the same geographical region.

As for the IgE serological tests; their reliability depends on two principal points:

1. Sensitivity and specificity for the identification of IgE (with lack of cross-reactivity with IgG) and
2. Identification and blocking of cross-reactive carbohydrate determinants (CCD).

The substantial variation between laboratories, basically results from the increased number of false positive results due to the cross-reactivity of the IgE detecting reagent with IgG and the detection of IgE anti-CCD reactions leading to multi-positive pollen results.

False positive results affect the composition of the ASIT and its treatment efficacy.

LABOKLIN IgE serological tests avoid the problem of false positive results by:

1. Using a unique recombinant fragment of the extracellular portion of the human high affinity IgE receptor alpha-subunit (FccR1α) (Heska Allercept) which has shown a strong affinity for canine IgE and a lack of cross-reactivity with IgG. 
2. IgE detection against CCDs (carbohydrate cross-reacting determinants) and
3. IgE anti-CCD blocking system for IgE anti-CCD positive samples

Additionally, an independent study on test variability showed an exceptional level of intra- and inter-assay reproducibility and an identical level of performance obtained in the dogs and cats.

Absolute specificity of IgE detection: the IgE receptor alpha-subunit (FccR1α)

The use of the Fc-ε receptor alpha chain (FccR1α) overcomes the potential problem of cross-reactivity with IgG, which is the major and most current problem when using polyclonal and monoclonal antibodies.

IgE are the specific antibodies related to hypersensitivity, and are the only ones relevant for the evaluation of the allergic response. IgG are also produced and they are present in the serum in concentrations that are 10.000 to 100.000 times higher than IgE. The capacity to distinguish the IgE molecules from IgG at these ratios is very difficult, and the specificity of the IgE detecting reagent is critical.

The binding strength and avidity of the Fc-ε receptor for IgE is one of the strongest found in nature. Its dissociation constant (Kd) is 10x10⁻¹⁰ M in most animal species, assuring the sensitivity and specificity of these tests.
What are cross-reactive carbohydrate determinants (CCD)?

Pollen allergens are composed of specific proteins and common carbohydrate chains. Cross-reactive carbohydrate determinants are defined carbohydrate portions of glycoprotein cell surface molecules common in many plant and insect species. Mammalian species recognize CCD as foreign antigens and can mount humoral immune responses against them.

Anti-CCD IgE are clinically irrelevant, but 20 to 37% of all people and animals allergic to grass and insect venom develop anti-CCD IgE.

Insect venoms are also potent inducers of CCD-specific IgE antibodies, and positive results to pollen allergens can also be found in non-atopic persons with insect venom allergy.

Allergic patients produce specific IgE against the specific proteins of the offending allergen. Anti-CCD-IgE can also be produced, but are not relevant for the allergic disease and induce false positive results.

Relevance of identifying anti-CCD IgEs

Anti-CCD IgE reactions are not allergen specific, they are not related to clinical disease and produce false multi positive results. They lead to very high IgE values in pollen and insect assays.

Testing positive for anti-CCD IgE leads to false positive results. The inclusion of irrelevant allergens in the ASIT affects the efficacy of the hyposensibilization therapy.
How can false positive results associated with CCD be avoided?

LABOKLIN uses the unique CHO-test, an Fc-epsilon-receptor test, to identify the anti-CCD IgE. When the CHO detects anti-CCD IgE in the serum of the patient, a new test is run in which the CCD reaction is blocked. The CHO-test and the blockage of the CCD reaction are used in samples from dogs and cats for all serological tests of seasonal and hymenoptera allergens. On a trial performed on 500 cases from all over Europe, an anti CCD-IgE were detected in 30% of the cases. The sensitivity of the test is higher than 88% and the specificity over 94%.

Blocking of the IgE-CCD assures that only IgE to protein allergens are detected. A previous strongly positive result will be transformed into a weaker true positive result or into a true negative result.

The results with and without blocking are explained in the following figures:

These situations will lead to a specific IgE reaction which is not clinically relevant. The result of the IgE test cannot be interpreted.
Conclusions

1. ASIT is an effective and safe way to reduce the clinical signs of AD in dogs, cats and horses and the only treatment option that can be curative.

2. To formulate the ASIT, it is necessary to identify the allergens against which the animal is allergic.

3. Serological tests are easy to perform and just as suitable as IDT for selecting the ingredients for the ASIT.

4. The choice of IgE test may have a major influence on the positive/negative results and ensuing treatment recommendations.

5. The use of the unique Fc-ε receptor alpha chain (FcεR1α) overcomes the potential problem of cross-reactivity with IgG.

6. The identification of anti-CCD IgE by our CHO test and its blockage avoids false positive results and makes our serological tests the most reliable on the market.

7. LABOKLIN makes the diagnosis and treatment of allergies easier for you and your patients.

Bibliography


