

Allergy Vaccination With Peptides – SIT With Major Cat Allergen Fel d 1 Peptides: Safety, Tolerability and Dose Responses

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Introduction

The prevalence of type I allergies has been continuously increasing. Cat is among the most frequent elicitors of inhalant allergies besides grass and birch pollen. Specific immunotherapy (SIT) is the only causal approach for the long-term treatment of IgE mediated allergies. Until now whole allergen extracts and more recently recombinant allergens have been used for SIT. Other therapeutical concepts consider the use of peptides as therapeutic vaccines to treat allergic diseases. These concepts are based on the knowledge that T cell receptors recognize short linear peptides (9–15 amino acids long) which have been processed by antigen presenting cells and complex to the major histocompatibility complex (MHC). One approach is to treat patients with such synthetic peptides that correspond to the major T cell epitopes of the allergen. An advantage of this approach is the avoidance of IgE mediated mast cell/basophil activation and the presentation of the allergen derived T cell epitopes by quiescent antigen presenting cells. Such quiescent APCs may generate regulatory T cell responses including the generation of regulatory T cells like Foxp3 and Treg (Fig. 1).

The concept of using cat peptides for specific immunotherapy was first introduced by Briner et al in 1993 [1]. This group has shown for the first time that peripheral T cell tolerance can be induced in naive and primed mice by subcutaneous injection of peptides from the major cat allergen *Fel d 1*. Consecutively a few clinical studies by using two immunodominant peptides with a length of 27 amino acids were used in different clinical studies. The dosages which have been used in these early studies were between 15 and 6000 µg. Approximately 300 patients were studied within these clinical studies [2–5]. The data from these studies indicated clinical efficacy by improvement of the symptom scores after cat room challenge [2], reduced allergen provocation dose [3] and improved FEV₁ [4]. However, the study by Simons et al. [5] indicated no change in the size of cutaneous reactions after peptide-based SIT. The largest study by Maguire et al. [4] in which, besides placebo, 75 and 750 µg of

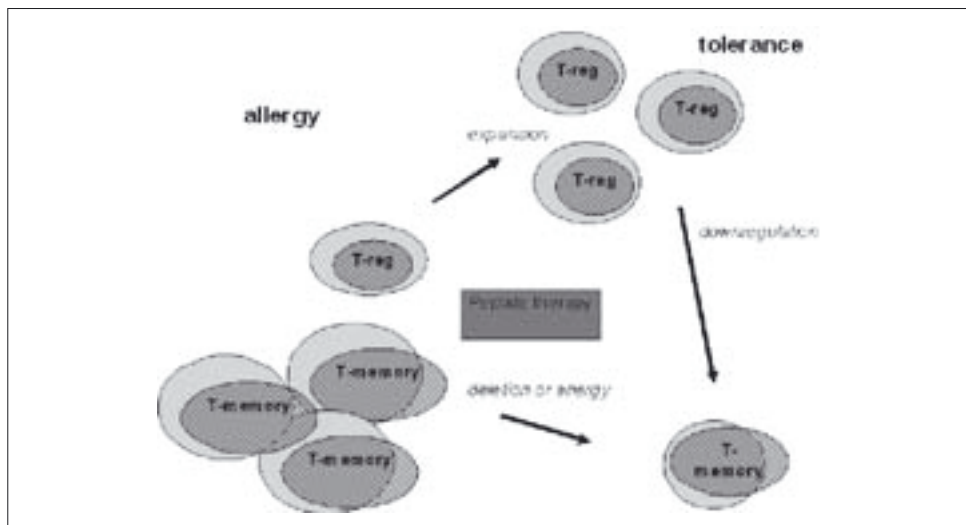


Fig. 1. Concept of peptide-based therapeutic vaccines for allergic diseases.

cat peptides were used, indicated a large proportion of adverse events which were mainly restricted to the respiratory tract. These adverse reactions occurred frequently as late phase responses whereas early onset symptoms were not significantly different from the control group.

These findings indicated that cat peptide based treatment is possible and to some extent are efficacious. However, in particular higher dosages of peptides may lead to an increase of unwanted late phase side effects. This indicates that the optimal dose window using peptides for SIT needs to be identified and is probably narrow if tolerance rather than an inflammatory effect is aimed to be induced.

Cat toleromune – early clinical studies

Cat toleromune is a 7-peptide mix covering 115 residues of *Fel d 1* chains 1 and 2 (CAT-PEPTIDE MIXTURE). Previous data indicated that these peptides induce T cell proliferation, while not inducing histamine release (unpublished data). Initial clinical studies using these peptides by Oldfield [6,7] and Alexander [8,9] (Table 1) indicated that after intradermal application of 12 peptides with a length of 16 amino acids resulted in reduced cutaneous late phase reaction, reduced TH1/TH2 cytokine responses and increased IL-10 production. Furthermore, reduced airway hyperreactivity and cutaneous late phase reactions were determined showing an increase of CD4 positive / interferon γ positive cells in the skin. The studies by Alexander et al. [8,9] showed also an improvement of nasal symptoms and late asthmatic reactions after allergen challenge. These studies [6–9] indicate immunological, but also clinical efficacy by these peptide mixtures after intradermal application. Therefore, a clinical study with an escalating single intradermal or subcutaneous application of these peptides in cat allergic patients was initiated.

Table 1. *Previously published clinical studies with cat peptides*

Author	Ref.	No. and length of peptides	dose	route	n	outcome measures
Norman	2	2 × 27	30–3000 µg	sc	95	Improved symptom scores after cat room Challenge
Simons	5	2 × 27	1000 µg	sc	42	no change in cutaneous challenge
Pène	3	2 × 27	15–4500 µg	sc	31	Improved allergen PD ₂₀ compared with baseline
Maguire	4	2 × 27	6000 µg	sc	133	Improved FEV ₁ (with reduced baseline)
Oldfield	6	12 × 16/17	5 µg	id	24	Reduced cutaneous late-phase reaction
Oldfield	7	12 × 16/17	90 µg	id	24	Reduced cutaneous reaction, TH1/TH2 cytokines reduced, IL-10 increased
Alexander	8	11 × 16/17	40.1 µg	id	8	Reduced airway hyperactivity and cutaneous late-phase reaction, increase in CD4 ⁺ IFN- γ ⁺ cells in skin
Alexander	9	12 × 16/17	131–341 µg	id	28	Improved nasal symptoms and late asthmatic reaction after allergen challenge

Current clinical study

This latest monocenter clinical study aimed to assess the safety and tolerability of cat peptide mixtures in cat allergic subjects. The secondary objectives were to evaluate the relationship between the dose of the cat PEPTIDE MIXTURE (given intradermally or subcutaneously) and the size of late phase skin response to whole cat allergen. These data should provide information to identify optimal immunologically effective dose for subsequent studies.

Within the study, different dosages of the cat peptide mixture were applied to the patients either intradermally or subcutaneously. Within the study, 132 cat allergic patients were identified with a late phase skin reaction >30 mm. Interestingly, we identified a correlation between the size of the intradermal reaction and cat-specific IgE levels (Fig. 2).

The tolerability in all cat PEPTIDE MIXTURE intradermal cohorts was very good and the preliminary data assessment revealed a mean reduction of late phase skin responses following intradermal injection of cat peptide mixture compared to placebo. No serious adverse events occurred and the overall tolerability was excellent.

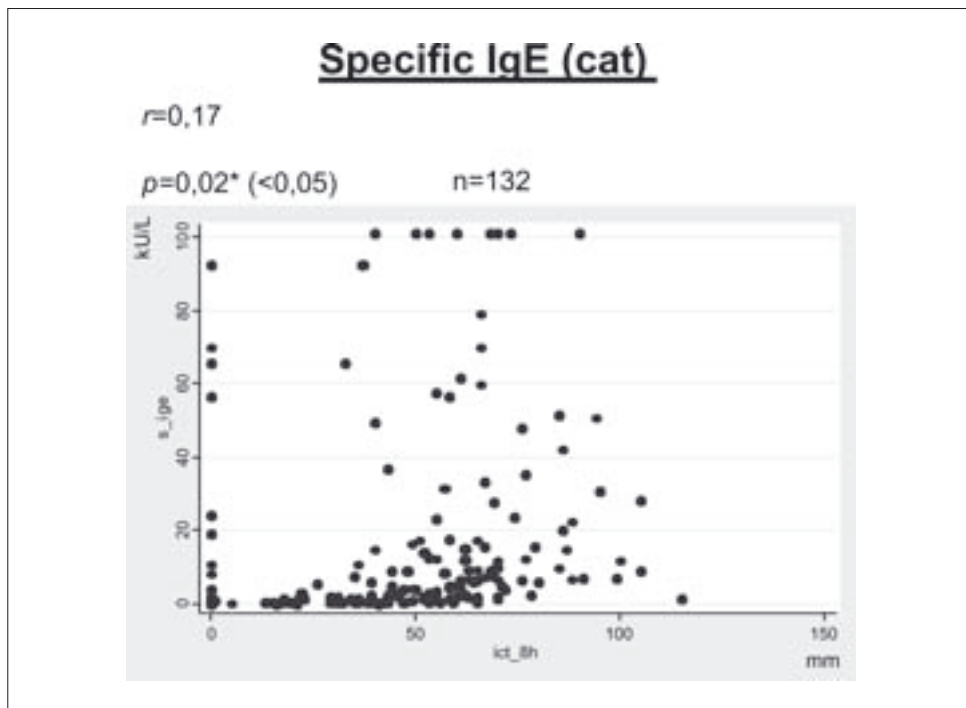


Fig. 2. Correlation of cat specific IgE and the late phase skin response.

The data from this phase 2 clinical study indicates that peptide based specific immunotherapy is immunologically effective and tolerable using these peptide mixtures by an intradermal route. Whether these findings are associated to clinical efficacy will need to be proven in further clinical studies.

References

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Discussion

Saxon: How did you pick the peptides for this study? I know there have been several iterations from this group for which peptide to use. What were the criteria for this set of peptides?

Worm: The criteria for using these peptides were based of course on the immunological data, but also based on the characteristics of the peptides. You really need to achieve a certain stability in order to use them in patients.

de Blay: Do you think that the length of the sequence, i.e. the number of amino acids in the peptides, is important for the efficacy? So, is the efficacy depending on whether there are 10 or 20 amino acids?

Worm: The question is whether you need 12 amino acids and also whether you need the mixture?

de Blay: No, in the beginning I thought that you had selected some sequences corresponding to, e.g., IgG or IgE epitopes. But I do not know whether the efficacy depends on probably 1000, 100 or 10 amino acids or is the efficacy very similar in each case? I do not know whether you have results on it.

Worm: I guess those peptides were chosen based on the data obtained either in T cell responses or histamine release data of the effector cells. And so, on the one hand you want to have as few peptides as possible, on the other hand you want to have a range of peptides which are also able to consider the MHC diversity.

Frew: Margitta, I think I learnt just a little bit about the background. I think they tried to cover the whole range and they cut it down to T cell length so that they would probably fit all the different HLA peptides. They had to leave out certain things because they were not soluble, so some of the sequences did not work. I do not think it was related to histamine release, it had more to do with just trying to get a cocktail, which was practical and would cover as much of the protein as they could.

Chapman: Just a sort of a follow-up on that. In the original Allervax study, the peptide had 27 amino acids or so and that was thought to be a reason why there were these reactions that you described. I thought Mark Larché's rationale was going with 12-residue peptides in the study, but it appeared, at least when you showed the slide, that the chain 2 peptide actually had about 20 amino acids or more. So, I guess what we all are looking for is a real rationale for why these particular peptides are being

picked because I think there were 4 or 5 peptides on chain one and then only one peptide on chain two.

Worm: First, I have to admit I am not an immunologist. But as far as I know, in order to trigger the T cells, you need to have at least a certain number of amino acids and this is considered to be something like 12. So that is the approximate size you really need. And of course it might be possible that if you then go to an individual, in some cases one amino acid more or one less would be better. I guess the immune response is not the same in every person.

Robinson: You showed the data comparing the intradermal and subcutaneous routes. As far as I know this is the first time these peptides have been given subcutaneously. Do you think you have got enough data here to say that they do not work subcutaneously? Or do you think you just happened to pick patients who did not have the right MHC to react to these peptides? Has that made the company to switch to intradermal and if so, why? Are we injecting immunotherapy in the wrong place?

Worm: Well, we have heard many things about dendritic cells in the skin. So one can imagine that the concept, which is probably relevant here, is different. I have no difficulties to understand why it did not work in the subcutaneous group. The concept of using peptides is different, here you want to target T cells and maybe the response in the skin is of importance here.

Robinson: Do you actually have any data on the T cell responses of individual patients to these peptides that are in the same study or is it just a kind of a generic assumption because the T cell peptides have been mapped in populations that have been worked with the ones that are in the test group?

Worm: An important question. We did not do any genetic analysis before the study. So, this was just a random collective.

Robinson: I mean the *in vitro* T cell stimulation.

Worm: This was done with T cell lines, but it was not done with T cells from the patients that were in the trial.

Kleine-Tebbe: With regard to subcutaneous versus intradermal injection: all these pilot studies had been done intradermally and it is believed that there are many more interactions. Some people even believe that subcutaneous immunotherapy might work through intradermal injection, particularly if you do not change the needle after sucking up the allergen fluid. But it had never been demonstrated that that practice might lead to an enhanced efficacy of subcutaneous immunotherapy.

Worm: I think the data is nicely demonstrating that whenever we develop a new treatment concept we also have to consider where we want to meet the immune system. The response of the immune system also depends on where it happens. I guess it is important to address that. It needs consideration in clinical studies, as well.