Sublingual Immunotherapy with Monomeric Allergoid Tablets in Children and Adolescents Suffering from Cat Allergy. An Observational Study

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Abbreviations

AIT Specific immunotherapy
AR Adverse reaction
QoL Quality of life
RC Rhinoconjunctivitis
SAR serious adverse reaction
SLIT Sublingual immunotherapy

Introduction

Allergy is defined as an overreaction of the body's immune system to environmental substances, which leads to inflammatory reactions and hyper-reactivity in different parts of the organism. Amongst all forms of allergy, the sensitization to cat allergy is one of the most frequent causes for persistent allergy.

In many cases, sensitization to Feld 1, the major and most potent cat allergen, requires a multimodal therapeutic approach including the maintenance of hygiene standards, allergen avoidance, symptomatic treatment, allergen specific immunotherapy (AIT) and so on, to allow a comprehensive treatment of cat allergy.[1]

Even in homes that have never had cats indoors, the concentration of cat allergen particles are often present at a very high level above the sensitization- and asthma-threshold (>1µg/g and >8µg/g). [2] Ichikawa *et al* reported that the prevalence of cat allergy in children living in homes without cats was as high as 34%. [3]

Although different methods of AIT are available for the causal treatment of cat allergy, sublingual immunotherapy (SLIT) has proved to be a better option than subcutaneous immunotherapy, causing less local adverse reactions (AR), systemic reactions, and serious adverse reactions (SAR). The benefit of SLIT is the higher safety profile with immunogenic effects comparable to subcutaneous immunotherapy. [4,5,6,7,8]

Aiming to ensure a maximum immunological effect with a minimum of local and systemic AR, and to avoid SAR and fatalities altogether, SLIT with monomeric allergoid sublingual tablets may present a better form of causal treatment than the conventional types of AIT with native allergens. [9,10,11,12,13,14,15,16]

As the role of pet allergy, especially that of cat allergy in children, becomes a focal point in the fields of allergology, it was our objective to investigate the clinical outcome, safety and tolerability of monomeric allergoid SLIT in pediatric and adolescent patients with cat allergy suffering from rhinoconjunctivitis (RC) and/or allergic asthma.

Material and Methods

Study Design and Study Procedures

We conducted a retrospective observational cross-sectional survey by analyzing the records of interviews with pediatric and adolescent patients with cat allergy who had undergone a SLIT with monomeric allergoid tablets.

A questionnaire of 12 rubrics was designed to standardize the interviews that were performed by the physicians. It contained questions regarding the following:

- Patients' demographics
- Reasons for starting SLIT with monomeric allergoid tablets
- Data of the therapy e.g. duration of therapy, interruption of the therapy, discontinuation of the therapy
  - Therapies that had been applied for cat allergy before, prior to SLIT with monomeric allergoid tablets
  - Symptomatic therapy prior to SLIT with monomeric allergoid tablets
  - Allergy anamnesis incl. allergic symptoms, duration of the symptoms, mono- or polysensitization, allergen avoidance status, diagnostic of cat allergy
  - Application of the monomeric allergoid tablets including dosage and frequency, general tolerance during initial therapy phase and maintenance phase
  - Symptomatic medication at time of the questionnaire
  - Symptom classification (according to ARIA for rhinoconjucntivitis and GINA for asthma) for baseline and the therapy period, and first onset of symptom reduction
  - Quality of life
  - Compliance
  - Adverse reactions and serious adverse reactions

The survey did not interfere with the physicians' usual treatment strategies. It was performed from September 2013 to March 2014 and the retrospective observation period was from November 2006 to December 2013.

Patient Selection

Patients had been recruited from the pre-existing population of the physicians' practices and had been in therapy with monomeric allergoid sublingual tablets for at least three months prior to the study.

Inclusion criteria were the diagnosed sensitization to one of the major cat allergens and at least one of the main complaints such as rhinitis, conjunctivitis and allergic asthma.

Principal exclusion criteria were pregnancy, lactation period, diseases of the oral mucosa, age below 5, tumorous illnesses and other malignant diseases.

Medication

Patients were prescribed monomeric allergoid of cat extract tablets based on lactose for sublingual administration. All patients had been treated with an initial up-dosing phase (specify schedule), a subsequent maintenance phase with 1000 allergic units perennially taken at least twice a week.

Primary Criteria

The improvement of symptoms and hence the shift from one symptom classification to another was one of the primary endpoints. RC was classified in accordance to the ARIA documents as 'mild', 'moderate' or 'severe', and as 'intermittent' or 'persistent'. [17] 'No complaints' is scored with '0', 'intermittent mild' with '1', 'intermittent moderate/severe' with '2', 'persistent mild' with '3', and 'persistent moderate/severe' with '4'. Asthma was classified according to the GINA guidelines [18] and scored into 'no complaints' with '0', 'intermittent' with '1', 'mild-persistent' with '2', 'moderate-persistent' with '3', and 'severe-persistent' with '4'. Data prior to the therapy, during the first, the second and the third year of therapy were compared.

The second clinical primary endpoint was the symptom medication score. We compared the use of symptomatic medication prior to the SLIT with allergoid and during the conduct of our survey. Scores were allocated when the medication was taken 'several times per week', 'once per day' and 'several times per day' (**Table 1**).

Table 1. Distribution of the symptom medication score.

Medication	Score
Antihistamine nasal sprays	1
Antihistamine tablets	1
Leukotriene receptor antagonists	1
Beta-sympathomimetic asthma sprays	1
Corticosteroid nasal sprays	2
Corticosteroid asthma sprays	2
Corticosteroid tablets	3

The third primary endpoint was treatment safety and tolerability. Tolerability was classified as 'outstanding', 'good', 'moderate' and 'poor'. For the safety endpoint, ARs and SARs were documented. A SAR is any event that resulted in life-threatening conditions, death, hospitalization, use of epinephrine (or other medical interventions to prevent permanent impairment), birth defect or anomalies or persistent disability. [19]

Secondary Criteria

Secondary endpoints included quality of life (QoL), adherence and treatment contentment.

Quality of life was assessed through questions regarding the patients' current health, physical activity, social activity and the psychological state.

Adherence assessment was based on the patients' compliance, trust in and contentment with the immunotherapy and on the motivation to continue with the immunotherapy.

Statistical Analysis

Data were summarized and presented descriptively throughout the study. Statistical analysis was performed using IBM SPSS 22.

Results

Demographic and General Baseline Information

In total, 21 pediatric and adolescent patients completed the questionnaire. Of these patients, 11 were male and 10 female. The group of patients aged 6-11 consisted of 15 patients and the group aged 12-17 of 6 patients. The mean age of the patients was 10.62, the median 11 years.

Two patients were in the first, 7 in the second and 4 in the third year of therapy. Eight patients discontinued the immunotherapy, 1 due to lactose-based gastrointestinal discomfort, and 2 due to avoidance of the allergen. Five patients neglected the follow up or had skipped this part in the questionnaire. At baseline, 81% of the patients had symptoms of rhinitis. The complaints had been present for a mean of 2.88 and a median of 2 years. For conjunctivitis, 76.2% of the patients had symptoms at baseline, and the symptoms had been lasting for an average of 3 and a median of 2 years prior to therapy. At baseline, 76.2% of the patients had asthma. The mean duration of the complaint was 3.13, the median was 2 years. Of the 21 patients, 3 were monosensitized to cat allergens and 18 were polysensitized. A total of 8 patients had achieved a complete avoidance of the cat during immunotherapy. The majority (n=13) continued to have medium to intense contact with the allergen.

Maintenance Dose

Patients who only took the tablet twice a week represented the largest group with 15 individuals. Five patients took the tablet daily and one took it four times a week.

Symptom Improvement

General improvement of rhinitis, conjunctivitis and asthma was reported throughout the survey.

For rhinitis, a highly significant improvement of symptoms, perceived by a shift from one symptom classification to another, could be achieved from baseline with a score of 2.78 ± 1.17 (n=17) to the first year of therapy with 1.06 ± 0.77 (n=16), ($p \leq 0.001$) as well as from baseline to the second year of therapy with 0.33 ± 0.50 (n=9), ($p \leq 0.05$) and from baseline to the third year of therapy with 0.2 ± 0.45 (n=5), ($p \leq 0.05$).

For patients suffering from conjunctivitis, a highly significant improvement of the symptoms was achieved from baseline with 2.63 ± 1.15 (n=16) to the first year of therapy with 1.0 ± 0.78 (n=14), ($p \leq 0.001$). A significant improvement was achieved from baseline to the second year of therapy with 0.29 ± 0.49 (n=7), ($p \leq 0.05$). The Improvement from baseline to the third year of therapy with 0.25 ± 0.5 (n=4), ($p = 0.066$) showed a clear trend. During the third year of treatment there were only cases of 'intermittent mild' symptoms and 'no complaints'.

For asthma, a highly significant improvement of symptoms was recorded from baseline with 2.59 ± 1.18 (n=16) to the first year of therapy with 1.13 ± 0.89 (n=16), ($p \leq 0.001$). A significant improvement from baseline to the second

year of therapy with 0.5 ± 0.71 (n=10), ($p \leq 0.05$), as well as from baseline to the third year of therapy with 0.6 ± 0.89 (n=5), ($p \leq 0.05$). The overall shifts from one symptom classification of rhinitis, conjunctivitis and asthma to another are presented in **Figure 1-3**.

Legends explanations for figures 1 to 3: general improvement of symptoms in rhinoconjunctivitis (RC) and asthma patients. RC patients: 'no complaints'=0, 'intermittent mild'=1, 'intermittent moderate/severe'=2, 'persistent mild'=3, 'persistent moderate/severe'=4.
Asthmatic patients: 0='no complaints', 1='intermittent', 2='mild-persistent', 3='moderate-persistent', 4='severe persistent'.

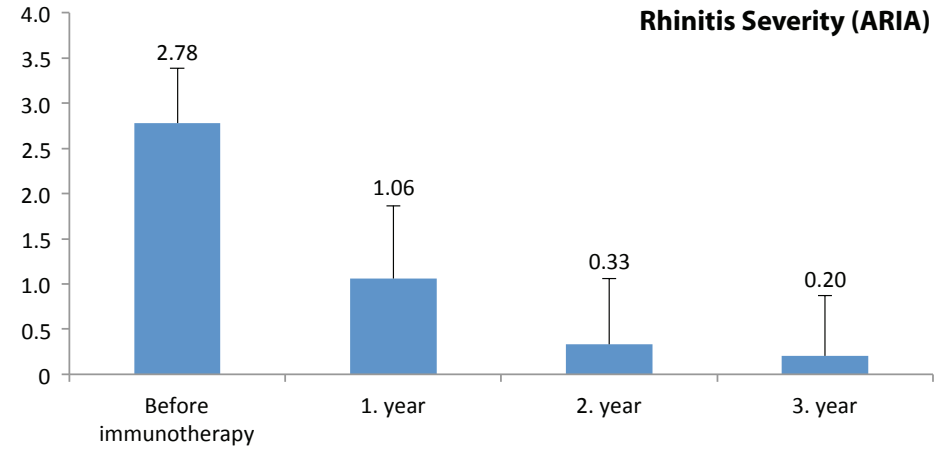

Figure 1. Rhinitis severity according to ARIA. Shift of symptom classification, from baseline to the third year of SLIT with monomeric allergoid tablets.

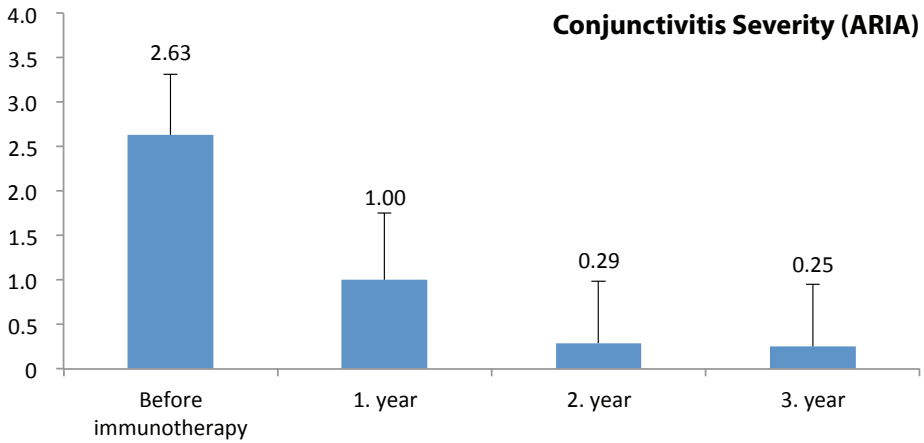

Figure 2. Conjunctivitis severity according to ARIA. Shift of symptom classification, from baseline to the third year of SLIT with monomeric allergoid tablets.

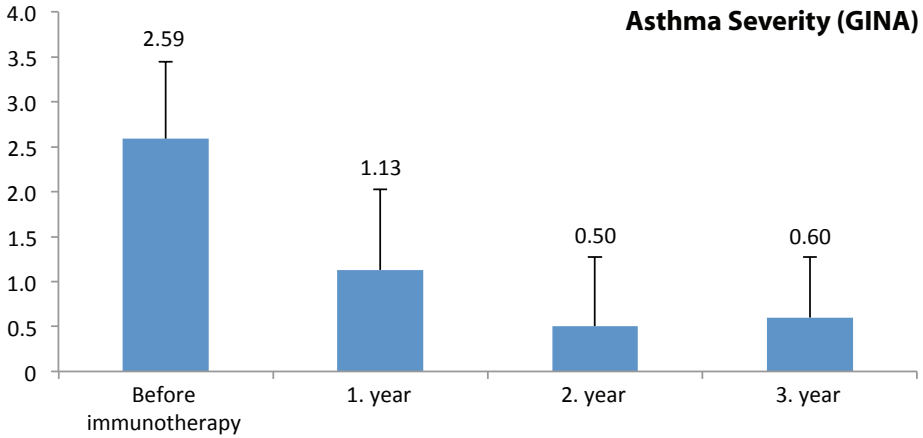

Figure 3. Asthma severity according to GINA guidelines. Shift of symptom classifications, from baseline to the third year of SLIT with monomeric allergoid.

Although the *p*-values seem to increase from the first to the second year of therapy, it is important to note, that the number of patients remaining in second and third year of therapy decreased and thus resulted in rising *p*-values. Nevertheless, all p-values are significant except for the improvement in patients suffering from conjunctivitis during the third year.

Nine patients noticed the beginning of a symptom reduction during the first year of therapy, seven patients during the initial therapy, and one patient during the second year of therapy. One patient has not noticed any symptom improvements yet.

Medication Score

The general symptomatic medication usage decreased with a score of 1.05 ± 1.6 at baseline to 0.56 ± 0.92 at the time the questionnaire was filled in ($p \geq 0.05$).

The use of asthma medication was also reduced from 1.56 ± 1.54 at baseline to 1.06 ± 1.44 at the time of questionnaire was filled in ($p \geq 0.05$).

It was shown that due to polysensitization, many patients had to continue with their symptomatic therapy regime.

Safety and Tolerability

No cases of death, no anaphylactic reaction, no usage of epinephrine, and no other SAR were documented. According to the WAO Grading System for SLIT, besides one local AR, no systemic reactions were reported in this study.

Only local AR was reported among 21 children and adolescents, which had been gastrointestinal discomfort due to lactose-intolerance during the first year of maintenance therapy. This incidence led to discontinuation of the immunotherapy.

Subjectively, the majority of the patients experienced an outstanding to good tolerability throughout the immunotherapy. During the initiation phase 76.2% of the patients rated their tolerability as ‘outstanding’ and 23.8% as ‘good’. None assessed the tolerability as ‘moderate’ or ‘poor’. During the first year of the maintenance phase 85.7% of the patients rated their tolerability as ‘outstanding’, 4.8% (n=1) as good, 4.8% (n=1) as moderate and 4.8% (n=1) patient did not

participate in the follow up. Of the remaining 12 patients in the second year of the maintenance phase, 11 patients reported an outstanding, one a good and none a 'moderate' or 'poor' tolerability. During the third year of the maintenance phase all remaining patients assessed the tolerability as 'outstanding'.

Quality of Life

The majority of the participants experienced an increase of physical activity, social activity and an improvement of the psychological state during the therapy with monomeric allergoid tablets. Although there were patients that had not noticed any improvements yet, none had reported a decrease in QoL (**Table 2**).

Table 2. Changes in QoL through SLIT.

	Very reduced/reduced	Same as before	Moderate increase	High increase
Physical activity	none	11.8%	11.8%	76.4%
Social Activity	none	29.4%	0.0%	70.6%
Psychological State	none	17.6%	5.9%	76.5%

Additionally, 76.2% of the patients reported a significant improvement of their general health condition.

Adherence

The SLIT tablet was taken regularly and the visits followed punctually by 90% of the patients, all being compliant. 76.2% of the patients expressed high confidence in the therapy with monomeric allergoid tablets and 66.7% of the patients declare a high motivation to continue with the therapy.

Therapy Contentment and Trust

The contentment with the therapy was certified by 81% of the patients, while 14.3% of the patients were not content. The contentment of one patient (4.8%) could not be assessed, because this patient had been in therapy for less than three months. A high trust in the SLIT was expressed by 76.2% of the patients. A moderate trust by 9.5% and no trust by another 9.5% of the patients.

One patient did not answer the questions of this section.

Discussion

This survey was mainly conducted in order to evaluate the clinical outcome and the safety of SLIT with monomeric allergoid to treat cat allergy.

Although an eminent number of patients suffering from moderate to severe persistent asthma were treated with monomeric allergoid tablets, only one local AR was reported. According to the review of Calderon *et al*. in 2012, patients with uncontrolled asthma are more susceptible for systemic AR or SAR. [20] This patient population is at a specific risk of developing pronounced adverse events such as anaphylactic reactions and/or acute asthma attacks in extreme cases [21,22], or such as wheezing in milder cases. [23] In this survey, however, no events of death, no anaphylactic reactions, no use of epinephrine, no systemic AR, and only one case of gastrointestinal discomfort due to lactose intolerance have been reported.

This is due to the promoting characteristics of monomeric allergoid, namely the low binding affinity to the IgE-binding site, rarely leading to local reactions of the mucosa which have been reported for tablets containing birch pollen, grass pollen, and house-dust-mite monomeric allergoid. [24,25,26,27] Furthermore, the results from our survey are in accordance with the findings from a placebo-controlled randomized trial with monomeric allergoid tablets for grass pollen in children, in which safety was outstanding as 24 patients in the active treatment group did not suffer from any systemic or local AR. [28]

Compared with this, many previous trials for SLIT with native allergens have shown more AR amongst pediatric patients. In the trial of Fiocchi *et al*. in 2005, 11 out of 65 pediatric patients aged three to seven years experienced 13 adverse reactions. [29] La Rosa *et al*. reported 12 out of 16 patients in the active allergen immunotherapy group experiencing one or more adverse events. [30] Another randomized controlled study of Blaiss *et al*. from 2011 reported that more than eighty percent of the patients experienced a local AR, including one case of epinephrine-rescue due to angioedema, dysphagia and cough. [31] Although many AR of SLIT with native allergens are not serious, they have the potential to minimize the adherence and satisfaction with the therapy and thus lead to discontinuation and low compliance.

Another advantage of monomeric allergoid tablets is the enhanced bio-availability which leads to improved clinical effects. In our survey on cat-allergic patients, the symptoms have improved significantly. Additionally a decrease of medication usage was reported, leading to an outstanding contentment and trust level for the allergoid immunotherapy. Our results on clinical effects may also be reflected by the results on efficacy in previous trials on SLIT with native allergens for grass pollen allergy, house-dust-mite allergy, and tree pollen allergy. [32,33,34,35,36] Likewise, results of a previously mentioned placebo-controlled randomized trial by Caffarelli *et al*. displayed significantly lower total symptom scores and symptom medication scores in the active treatment group compared to the placebo group, both under high pollen exposure.

Despite the satisfying results for clinical effects and safety, there are limitations to this study, too. In the present survey with sublingual monomeric allergoid tablets, there was no control group. The sample size is also relatively small in comparison to other studies on AIT. However, this study exclusively aimed to prove clinical effectiveness and safety in cat-allergic pediatric patients, therefore, the number of patients has an adequate size. It is also worth noticing that the retrospective approach led to a recall bias. Despite these limitations, the aims of the study were not affected, and we have found viable results for the treatment of cat allergy.

This retrospective survey demonstrates an outstanding safety of SLIT with monomeric allergoid tablets, a significant positive shift of symptom classifications, a reduction of symptomatic medication, an improvement in QoL, and a high compliance rate in real-life settings. No observational study evaluating the efficacy, safety and QoL of allergoid SLIT with cat-allergic patients only has been available yet. However, several studies are available on SLIT

with standardized cat allergen extracts to provide evidence of the effectiveness. In 2001, a Spanish study of Sanchez Palacio *et al*. reported clinical effects and an overall good tolerance in 20 patients that had received SLIT with natural cat dander extracts for one year. [37] Alvarez-Cuesta *et al*. reported in a randomized double-blind placebo-controlled study in 2007 a symptom reduction of 62% during the natural exposure challenge test with $p < 0.001$, an improvement of the peak expiratory flow with $p < 0.05$, and both no changes in the placebo group. [38] As a result, our retrospective survey on SLIT with monomeric allergoid tablets for cat allergic patients may support clinical evidence of these previous studies. **Taking into account the high impact that allergic rhinitis and asthma can have on QoL and the general well being of patients [39,40], as well as the potential of causing severe adverse reactions under treatment with standardized allergen extracts [41], monomeric allergoid SLIT may be a considerable alternative for the causal treatment of this chronic immunological disorder. In conclusion, we highly suggest SLIT with monomeric allergoid tablets for pediatric patients suffering from RC and asthma due to cat allergy.**

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