Carbamylated monomeric allergoids as a therapeutic option for sublingual immunotherapy of dust mite– and grass pollen–induced allergic rhinoconjunctivitis: a systematic review of published trials with a meta-analysis of treatment using Lais® tablets

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SUMMARY

Lais® allergoid tablets contain allergens that are modified by carbamylation. Due to their modified chemical structure, they are suitable for sublingual immunotherapy (SLIT). Based on their small molecule size of 12 to 40 kDa, they can be easily absorbed via the oral mucosa. In this review, we studied the efficacy of SLIT with carbamylated monomeric allergoid tablets in the treatment of grass pollen– and dust mite–induced allergic rhinoconjunctivitis on the basis of symptom and medication score improvements.

Following a selective internet and databank search, six trials—some placebo-controlled—regarding the treatment of grass pollen– (n = 266) and dust mite–induced (n = 241) allergic rhinoconjunctivitis were used to draw conclusions regarding the clinical efficacy of allergoid tablets. The primary endpoints in these trials were decreases in the need for allergy medications and/or reductions in the occurrence of rhinoconjunctivitis symptoms. Data was recorded from patient diaries regarding their symptoms and medications used and conclusions were then drawn about the effectiveness and tolerabieity of Lais® tablets.

The average improvement in symptom score in three trials of grass pollen allergy treatment was 34% in comparison to the placebo group. The treatment of dust mite–induced rhinoconjunctivitis produced an average symptom score improvement of 22% compared to the placebo or control groups. The intake of symptomatic rescue medication during allergoid tablet therapy declined. Treatment of grass pollen allergies and dust mite–induced rhinoconjunctivitis showed an average medication score improvement of 49% and 24%, respectively.

Few side effects were documented in the trials and predominantly local effects were observed. Severe systemic side effects did not occur. On the basis of the trial results summarized in this review, we suggest that SLIT using Lais® sublingual tablets is an effective and well-tolerated form of treatment.

KEY WORDS

sublingual immunotherapy, allergic rhinoconjunctivitis, Lais® allergoid tablets, grass pollen allergy, dust mite allergy

Introduction

Apart from the avoidance of allergens, specific immunotherapy represents the only causal and preventive therapy approach for the treatment of IgE-mediated allergic diseases. Regular administration of the triggering allergen induces a tolerance toward it through systemic immunological changes. Symptoms and medication use are reduced as the immune response is attenuated (1).

In the past 20 years, new methods have been sought for administering immunotherapy that was previously applied subcutaneously (subcutaneous immunotherapy, or SCIT). Patients often find SCIT to be unpleasant and painful. Local reactions frequently appear at the injection site (swelling, redness). In rare cases, systemic side effects occur to the point of anaphylactic reactions with a lethal outcome. The sublingual means of application is a new and effective therapeutic alternative to SCIT (2). Potential advantages of sublingual immunotherapy (SLIT) include a smaller spectrum of side effects, improved compliance, and improvement in the treatment of children that are afraid of injections.

Carbamylated monomeric allergoids

Allergoids are purified, modified allergens with an altered protein structure (3). They are changed externally by chemically treating native allergens, for example by polymerization with glutaraldehyde or formaldehyde. This weakens their allergenic potency. The immunological properties, however, remain completely the same. In comparison to native allergens, a less pronounced allergic reaction occurs with allergoids because IgE binding sites become inactive on account of their altered chemical structure and, overall, fewer IgE antibodies can therefore be bonded. Allergoids thus exhibit lower allergenicity at the same level of immunogenicity.

Unlike conventional allergoids that are polymerized with formaldehyde or glutaraldehyde, carbamylated monomeric allergoids undergo carbamylation of the lysine groups. Compared to conventionally manufactured allergoids, which typically have a molecular weight of over 1,000 kDa, carbamylated monomeric allergoids (Lais®, Lofarma, Milan, Italy) are 25 to 80 times smaller (12–40 kDa). This enables easier absorption through the oral mucosa and increases their stability when mixed with proteolytic enzymes contained in saliva. The allergoid-containing tablets are taken orally and dissolve in the patient's mouth within one to two minutes.

Objective

The published data on SLIT with carbamylated monomeric allergoids for the treatment of rhinoconjunctivitis induced by grass pollen or dust mite allergens shall be presented and evaluated in a systematic review.

Methods

Search strategies

In order to identify relevant publications on SLIT using carbamylated monomeric allergoids in tablet form, the user interface PubMed and the DIMDI search service were used. A manual search of respected medical journals and a search for gray literature were also conducted. The reference lists of selected papers were also scanned for further citations. The search limitations for suitable materials were set to include only those written in English, German, Italian, and Spanish on the subject of SLIT using carbamylated monomeric allergoids in tablet form for the treatment of human subjects with grass pollen– or dust mite–induced allergic rhinoconjunctivitis. Symptom and/or medication scores were the outcome parameters used to measure the clinical efficacy of SLIT. There were no restrictions as to the publication period and the duration of the trial. Double-blind and placebo-controlled trials were preferred, but observational studies, randomized controlled trials, open controlled studies, and retrospective trials were also included.

Description of identified source materials

The literature survey was carried out according to the criteria described in the search strategies, and it initially identified 60 trials of SLIT conducted using tablets for the treatment of dust mite allergies and 91 trials of SLIT using tablets for the treatment of grass pollen allergies. Trials in which patients were not treated using carbamylated monomeric allergoid tablets (n = 82 for grass pollen and n = 53 for dust mites) and studies in which carbamylated monomeric allergoid drops (n = 1 for dust mites) were used for treatment were not taken into closer consideration on the basis of the exclusion criteria. Likewise, studies that did not document scores were omitted (n = 3 for grass pollen). The number of relevant articles was thereby reduced to six cases of grass pollen allergy treatment and six cases of dust mite allergy treatment.

Efficacy results of SLIT using tablets containing carbamylated monomeric allergoids for grass pollen–induced rhinoconjunctivitis

Four double-blind, placebo-controlled studies (4–7), one open controlled study (8), and one observational study (9) were used to draw conclusions regarding the clinical efficacy.

In three of the trials, significant symptom-specific improvements in symptom score were observed (7–9). Typical rhinoconjunctivitis symptoms such as rhinorrhea, conjunctivitis, and sneezing improved significantly in patients treated with carbamylated monomeric allergoid tablets ($p < 0.001$ [9], $p < 0.03$ [7]). Significant improvements in concomitant asthma symptoms and rhinitis were also observed in another 3-year study of allergoid treatment ($p < 0.01$; 8). In three of the six trials compared, the authors described improvement in symptom scores in comparison to the placebo group (4–6). The improvement averaged 34% compared to placebo. In these trials, the absolute improvement in symptom score between the time "before therapy" and "after end of treatment" averaged 46% (placebo: 13%).

An assessment of efficacy based on medication scores for treatment with carbamylated monomeric allergoid tablets was described in two of the studies (2, 6). During treatment, a significant reduction in the use of PRN allergy medication (medication that is prescribed by a practitioner to be administered on "as needed basis") was achieved, averaging 49% in comparison to the placebo group. In the other trials, an overall trend toward the decreased use of allergy medication was noted.

Efficacy of SLIT using tablets containing carbamylated monomeric allergoids for dust mite–induced rhinoconjunctivitis

Two double-blind, placebo-controlled studies (10, 11), two open trials (12, 13), one retrospective study (14), and one open randomized trial (5) were used to evaluate clinical efficacy.

A positive therapeutic effect was registered in all studies. Three of the trials determined improvements in symptom score averaging 22% compared to the placebo group (10–12).

In two studies, more precise details regarding changes in the use of PRN allergy medications were given in terms of medication scores (11, 12). An average improvement of 24% in the medication scores was achieved as compared to the placebo or control groups. In the observational study, a significant reduction in the need for bronchodilators was shown during the two-year treatment period ($p < 0.001$; 13). The retrospective observational study did not uncover a significant difference between SLIT and conventional SCIT. SLIT and SCIT proved to be similarly effective with regard to score improvement.

Meta-analysis of the efficacy of SLIT using tablets containing carbamylated monomeric allergoids for dust mite–induced rhinoconjunctivitis

Two placebo-controlled, double-blind clinical studies by Passalacqua et al. from 1998 and 2006 were combined in a meta-analysis (10, 11). These were studies lasting more than two years in which symptom scores were recorded during perennial treatment with allergoid tablets.

A review of the studies showed homogeneity in both years of investigation based on the chi-square test (year 1: $p = 0.02$; year 2: $p = 0.16$), wherein the fixed effect model was used for calculating the pooled estimate. The combined standardized mean difference (SMD) was −2.35 (−3.89; −0.80) in the first year of the trial and −1.55 (−2.08; −1.02) in the second year. Numerically speaking, this data favors the use of SLIT therapy (cf. Figs. 1 and 2). A significant advantage over placebo was proven (year 1: $p = 0.003$, year 2: $p < 0.00001$). In the course of the in-depth study, the

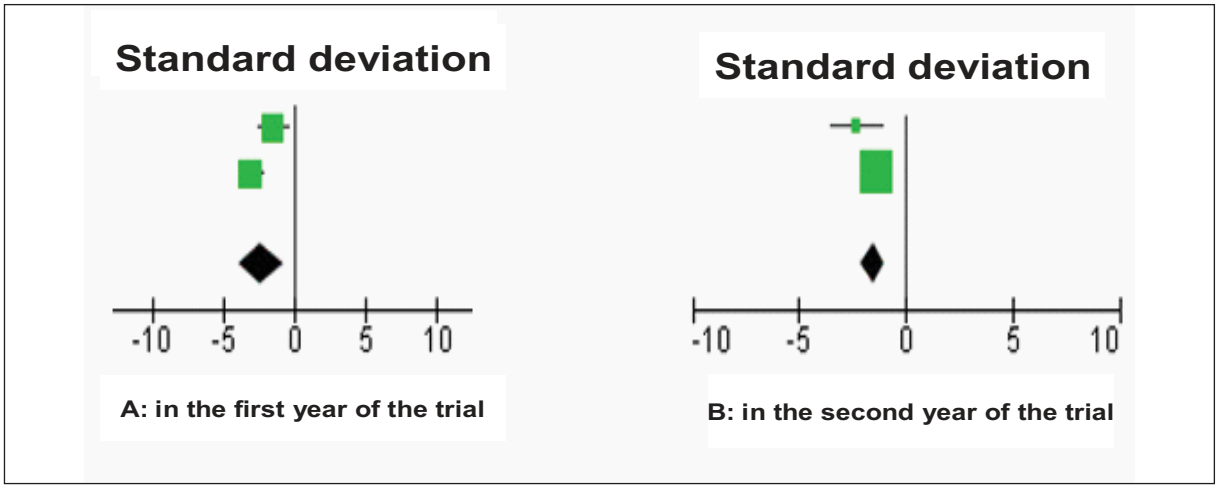


Figure 1. Reduction of Symptom score under allergoid therapy of house dust mite administered on an "as needed basis").

symptom score under treatment using carbamylated monomeric allergoid tablets significantly improved in both trials in the first as well as the second year. A direct comparison between SLIT and placebo effects according to medication scores could not be performed due to insufficient data.

Side effects

No severe, life-threatening systemic reactions occurred during the controlled efficacy and safety trials of SLIT with carbamylated monomeric allergoids for grass pollen and dust mite allergies. Only isolated local irritations such as itching or swelling of the oral mucosa were observed, which, however, did not require discontinuation of treatment.

Of the 155 patients who suffered from grass pollen–induced rhinoconjunctivitis, only three patients complained of side effects during treatment with allergoid tablets. This corresponds to an occurrence of adverse drug reactions in 2% of patients. During treatment of dust mite–induced rhinoconjunctivitis, itching of the oral mucosa occurred in one case (10). In another trial by Passalacqua et al., side effects were observed in 11 of 28 patients (11). Those side effects predominantly consisted of asthma attacks, coughing, rhinitis, and flu-like symptoms. Those symptoms could not be directly connected to the treatment. Similar side effects were observed in 16 of the 28 patients in the placebo group.

Dose

The duration of treatment and the medication dose varied depending on the trial. The administration of SLIT using carbamylated monomeric allergoid tablets took place pre-seasonally in all trials investigating grass pollen allergy and perennially in those for dust mite allergy.

Starting from the lowest dosage level, the dose was raised incrementally during the titration phase (duration depending on the study: three to 14 weeks) until the maximum maintenance dose was reached. This dose, ranging from 1,000 to 3,000 AU (allergenic units) per week for grass pollen allergy and from 300 to 4,000 AU per week for dust mite allergy, was then taken until the end of treatment. The doses administered in the titration phase displayed differences in the level, frequency of application, and frequency of intake until the next dose increase. The cumulative allergen dose consumed over the entire study duration ranged between 36,000 and 40,500 AU in the treatment of grass pollen allergy and between 23,775 and 176,500 AU in the treatment of dust mite allergy.

Dose-effect relationship

In three trials of SLIT with carbamylated monomeric allergoid tablets for dust mite–induced rhinoconjunctivitis (10–12), it was possible to compare the dose and efficacy by examining symptom scores compared with the placebo and control group scores. The improvement in symptom score compared with the placebo and control groups increased in connection with higher weekly maintenance doses. The study by Cosmi et al. (12) showed an improvement in symptom score of 2% compared to the control group at a weekly maintenance dose of 1,000 AU per week. In two trials by Passalacqua et al. (10, 11), a symptom score improvement of 14% was achieved at a dose of 2,000 AU per week and 48% at 4,000 AU per week compared to the control group (Figs. 2 and 3).

A linear correlation showing increased score improvement in connection with higher weekly maintenance doses could not be depicted in the same manner for the results of treatment of grass pollen–induced rhinoconjunctivitis. One study that reported symptom scores showed a score improvement of 39% even with a weekly maintenance dose of only 1,000 AU (4). Two other studies, each having 3,000 AU as the weekly maintenance dose, showed symptom score improvements of 30% and 32% respectively (5, 6).

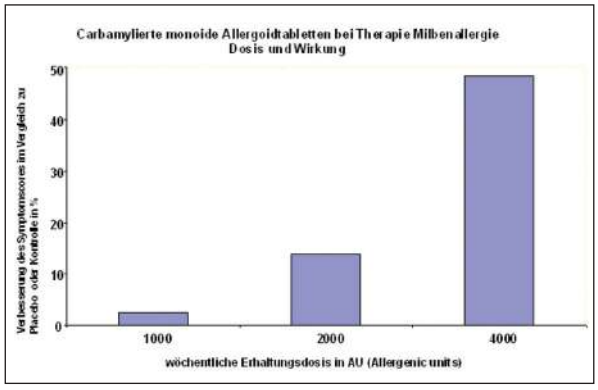


Figure 2. Dose and effect in the treatment of dust mite allergies.

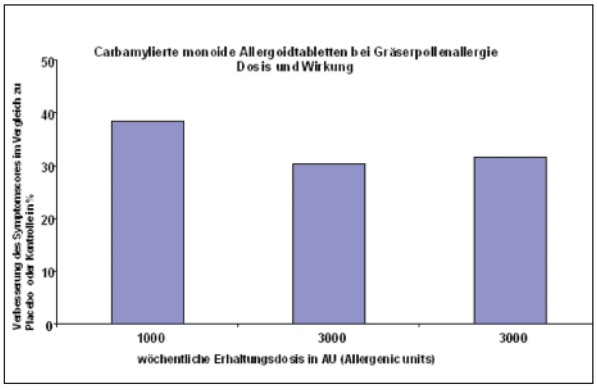
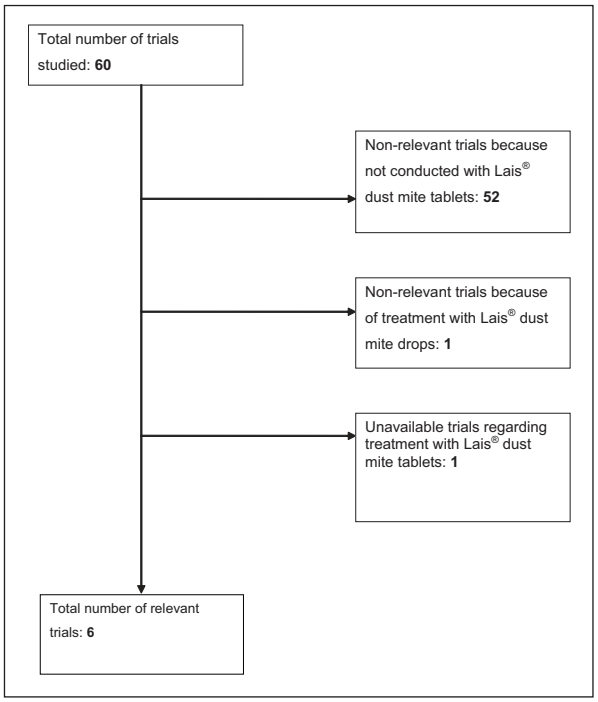
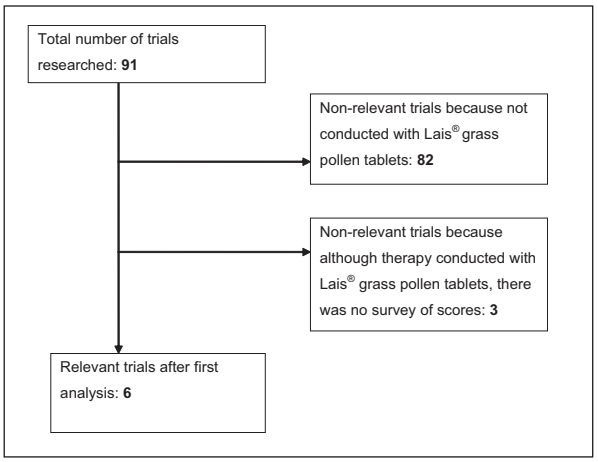


Figure 3. Dose and effect in the treatment of grass pollen allergies.



Appendix 1. Treatment trials for dust mite–induced allergic rhinoconjunctivitis.



Appendix 2. Treatment trials for grass pollen–induced allergic rhinoconjunctivitis.

Discussion

In regard to the effectiveness of the medication, studies investigating the efficacy, tolerability, and safety of SLIT with carbamylated monomeric allergoid tablets all show predominantly positive results in terms of a decrease in the rhinoconjunctivitis symptoms and the reduced use of allergy PRN medication in comparison to placebo groups.

The 34% average improvement in symptom score in the treatment of grass pollen allergies as compared to the placebo group corresponds very well with the results obtained from placebo-controlled, double-blind tests of sublingual tablets from other manufacturers. In their study of SLIT for grass pollen allergies, Dahl et al. noted a 30% decrease in symptoms in comparison to the placebo group ($p < 0.0001$) and an average decrease in the use of allergy medication of 38% ($p < 0.0001$) (16). A further study by Malling et al. of SLIT for grass pollen allergies likewise showed a symptom score improvement in comparison to the placebo group (17). The symptom score improved by 27.4%. The medication score decreased by 46.1% at the same dosage strength of 300 IR (index of reactivity). Durham et al. achieved improvements in symptom score of 22 to 44% compared to treatment with placebos (18).

For the treatment of dust mite allergies, two studies showed an average symptom score improvement of 22% compared to the placebo and control groups. A 20% improvement in symptom score was demonstrated in a study conducted by the manufacturer Stallergenes (19). This result turned out to be highly significant compared to treatment with placebos ($p \leq 0.0136$). This was particularly the case for the symptoms of nasal obstruction and nasal itching, showing median values of 40% and 32% respectively.

For the treatment of dust mite allergies with carbamylated monomeric allergoid tablets, symptom scores showed improvement compared to placebo and control groups in connection with weekly maintenance dose increases. This tendency was based upon the results of three trials (10–12). For the treatment of grass pollen allergies, this effect could not be verified for tests using carbamylated monomeric allergoid tablets. This correlation could be shown for grass pollen allergy, however, using a sublingual tablet from another manufacturer (20). Significant symptom score reductions were obtained in connection with higher allergen dosages ($p = 0.0005$).

The adverse drug reactions that occurred during treatment were almost exclusively local irritations such as itching of the oral and nasal mucosa and swelling of the nasal mucosa. No severe systemic reactions were noted. None of the reported side effects required discontinuation of the allergoid tablets. In other trials of rhinoconjunctivitis treatment with sublingual tab-

Appendix 3. Published trials of the treatment of dust mite–induced allergic rhinoconjunctivitis.

Author	Method	Study participants		Duration	Intervention	Outcomes	
		Allergoid tablets	Placebo, control			Relative improvement in symptom score	Relative improvement in medications score
L Cosmi (2006)	Open, parallel group design	11	9	2 yrs	SLIT vs. control	2.44% *($p < 0.05$)*	39.51% *($p < 0.05$)*
M La Rosa (1996)	Randomized trial, parallel group design	30	21 SCIT	19 mos	SLIT vs. SCIT	n.s.	n.s.
M Marogna (2007)	Retrospective trial	53	12	1–4 yrs	SLIT vs. control	*$p < 0.001$*	*$p < 0.001$*
ML Pacor (1995)	Open observational study	14		2 yrs	SLIT	n.s.	n.s.
G Passalacqua (1998)	Double-blind, placebo-controlled trial	10	9	23 mos	SLIT vs. placebo	48.4% *($p < 0.0002$)*	n.s.
G Passalacqua (2006)	Double-blind, placebo-controlled trial	28	28	3 yrs	SLIT vs. placebo	13.9% *($p < 0.05$)*	7.83% *($p = 0.036$)*

Note: *n.s. = not specified*

Appendix 4. Published trials of the treatment of grass pollen–induced allergic rhinoconjunctivitis.

Author	Method	Study participants		Duration	Intervention	Outcomes	
		Allergoid tablets	Placebo, control			Relative improvement in symptom score	Relative improvement in medications score
V Bordignon (1994)	Double-blind, placebo-controlled trial	30	30	3 yrs	SLIT vs. placebo	38.5% *($p < 0.05$)*	74.60% *($p < 0.001$)*
C Caffarelli (2000)	Double-blind, placebo-controlled trial	24	20	1 yr	SLIT vs. placebo	31.66% *($p < 0.01$)*	n.s.
G Cavagni (1996)	Double-blind, placebo-controlled trial	24	20	2 yrs	SLIT vs. placebo	30.45% *($p < 0.01$)*	22.63% *($p<0.05$)*
C Lombardi (2001)	Open controlled trial	26	25	3 yrs	SLIT vs. control	Rhinitis: 17.27% *($p=0.01$)* Asthma: 60.47% *($p=0.01$)*	Rhinitis: 55.55% *($p = 0.01$)* Asthma: 68.43% *($p = 0.01$)*
ML Pacor (1996)	Observational study	34		2 yrs	SLIT	*$p<0.001$*	n.s.
AG Palma-Carlos (2006)	Double-blind, placebo-controlled trial	17	16	2 yrs	SLIT vs. Placebo	*$p<0.03$*	*$p<0.02$*

Note: *n.s. = not specified*

lets, local side effects were also almost exclusively all that occurred (16, 17). In a trial by Malling et al., mild systemic side effects such as mild rhinitis and urticaria were observed (17). The occurrence of systemic side effects has been connected with carbamylated allergoid tablet treatment, but in the cases examined here the side effects could not be clearly attributed to the allergoid therapy (11).

These results suggest that side effects seldom occur during treatment with SLIT using carbamylated monomeric allergoid tablets. Severe side effects in particular do not occur. These results speak for the safety of SLIT using carbamylated allergoid tablets.

Conclusion

For a further evaluation of the clinical efficacy of SLIT with allergoid tablets, further randomized trials are necessary that would sufficiently characterize the patients (rhinoconjunctivitis and/or asthma), define the planned treatment goals and fixed allergen dosages more precisely, and measure allergen exposure (10). The results of the studies evaluated here suggest that SLIT using carbamylated monomeric allergoid tablets is an effective, well-tolerated, and, in its application, safe treatment for dust mite– and grass pollen–induced allergic rhinoconjunctivitis.

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