

● **Prevalence of allergies and benefit of specific immunotherapy (SIT)**

Twenty-five percent of the European population suffers from allergies (1). The 1999 European Allergy White Paper estimated the total costs for treating allergic diseases at 29 billion Euros (2). Allergic asthma alone accounted for 20 billion Euros.

With exception of avoidance of allergens, specific

Specific Immunotherapy with Allergoids: Effective, Safe, and Long-Lasting

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• increase of CD8⁺ T-cells, which regulate IgE response

the risk of adverse side effects. It was only with the development and application of allergoids, however, that so-called short-term therapy finally became feasible (14).

The development of allergoids pursued the therapeutic objective of producing allergen extracts with reduced potential for causing side-effect (i.e., with reduced allergenicity) – but with maintenance of immunological effectiveness (i.e., maintained immunogenicity). The allergic side-effects occurring in SIT are a consequence of the action of B-cell epitopes with relevant IgE antibodies. Most of the conformation-dependent B-cell epitopes are modified by chemical treatment of the native allergen with formaldehyde or glutaraldehyde (see Fig. 1) (15).



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immunotherapy (SIT) is the only form of treatment that can alter the natural course of allergic diseases (3). The ARIA Workshop Report (4) and the WHO Position Paper (3) have confirmed the effectiveness of SIT for prophylaxis and therapy of allergic rhinitis and allergic bronchial asthma in children and adults. From the cost-benefit standpoint, furthermore, SIT is economically superior to purely symptomatic therapy (5,6). Convincing evidence is also now available that SIT enhances the quality of life of allergy sufferers (7-9).

● **Immunological mechanisms in SIT**

Treatment of Type-I allergies by injection of the appropriate allergens has been practised for more than 90 years (10). Medical science, however, has not succeeded in completely elucidating the mechanism of action involved in SIT. Effector cells (mast cells and basophils) carrying IgE, in addition to responses by T-cells polarized to Th2, elicit allergy symptoms (11). The clinical improvement brought about by SIT evidently involves some or all of the following immune mechanisms:

• increase in allergen-specific IgG antibodies (primarily IgG₄, which apparently blocks the allergen as well as allergen presentation mediated by IgE)

• reduction of mast cells and eosinophils, as well as release of their mediators

• shift from a Th2 towards a Th1 cytokine pattern, with curtailment of IL-4 und IL-5 production



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• increase in IFN- γ ; and induction of anergy in peripheral T-cells mediated by IL-10 (12,13).

● **What are allergoids?**

The therapeutic success of SIT is evidently a function of the quantity of allergens administered (3). But high amounts of allergen increase the risk of IgE-related adverse reactions requiring slow increase of dosage, in conjunction with a great number of injections. Through introduction of depot preparations – e.g., those by adsorption to aluminium hydroxide – it became possible to reduce the number of injections and to reduce

● **How do allergoids work in vitro and in vivo?**

Histamine-release tests as well as IgE-inhibition testing have produced evidence of allergoid allergenicity significantly less than that of the native allergen: i.e., 0.1% of native allergen levels, and reduction by a factor of 100 ... 1,000, respectively (see Fig. 2) (16,17).

This evidence from *in vitro* studies has also been confirmed by skin tests performed on allergy patients. In prick tests conducted with timothy grass (*Phleum pratense*), it was necessary to increase dosage of allergoids by a factor of

90 to produce wheal sizes comparable to those from native allergens (18). Allergoidization enables an increase in cumulative dose of SIT by a factor of 2 ... 4.5, when compared to allergen depot preparations (19).

Allergoidization does not impair the sequence-dependent T-cell epitopes or, consequently, the therapeutic efficacy of the allergen extracts. In experiments conducted on animals, allergoids have accordingly induced IgG antibody titres comparable to those from native allergens (20-22). Reactivity measurements performed on peripheral mononuclear blood cells (PBMC) from allergy patients have shown that allergoids, similar to native allergen extracts, possess substantial T-cell stimulation capacity. In these tests, allergoids proved to be as effective as high doses of native allergens (23,24).

Cultured dendritic cells react with allergoids and with allergens (25). Under *in vitro* conditions and under the influence of antigen-stimulated Th1 cells, dendritic cells can react with increased IL-12 production which in turn promotes a Th1 response and inhibits a Th2 response (26). This phenomenon elicits a shift in the cytokine profile of the stimulated Th cells toward Th1. Modification of the allergoids avoids presenta-

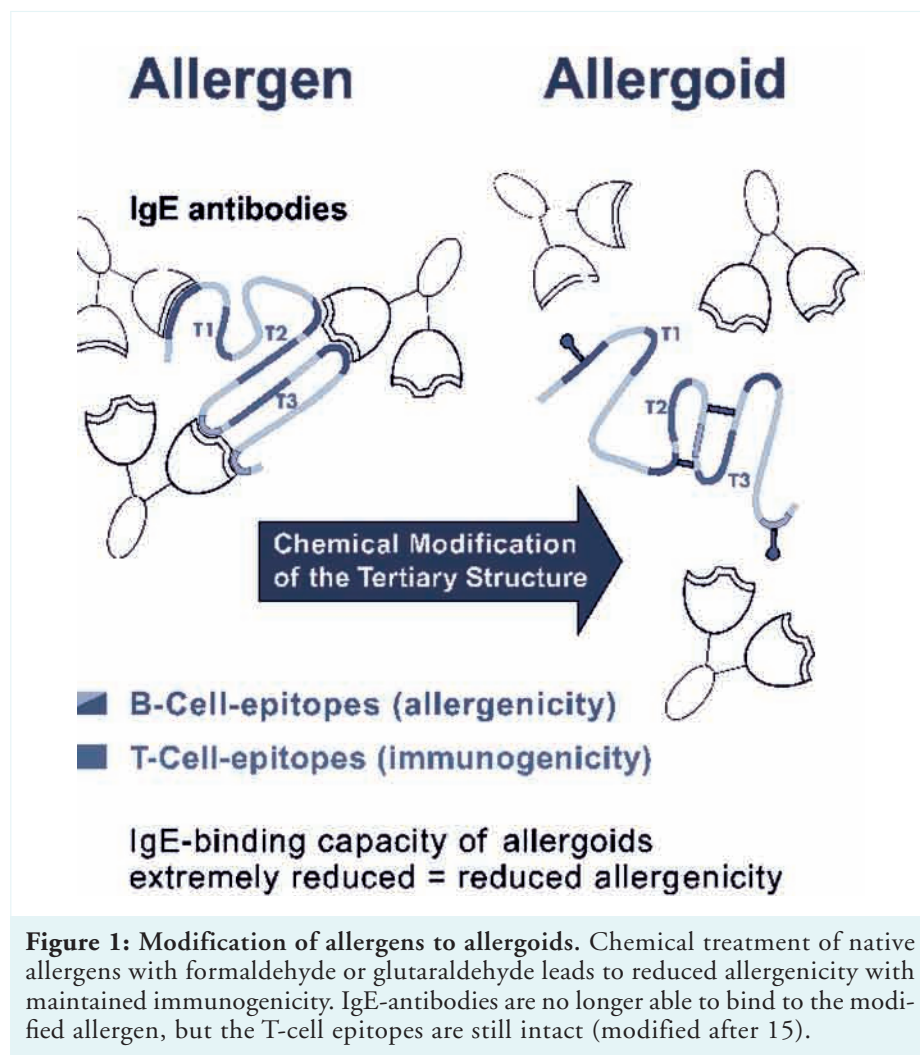


Figure 1: Modification of allergens to allergoids. Chemical treatment of native allergens with formaldehyde or glutaraldehyde leads to reduced allergenicity with maintained immunogenicity. IgE-antibodies are no longer able to bind to the modified allergen, but the T-cell epitopes are still intact (modified after 15).

tion by IgE-loaded B-lymphocytes, which primarily stimulate Th2 clones and promote the differentiation of naïve T-cells to Th2-cells (see Fig. 3) (13,26).

● **Have allergoids proven their clinical efficacy?**

Allergovit® is a high-dose depot allergoid modified with formaldehyde that is adsorbed on aluminium hydroxide. It is available on the European market for pre-seasonal immunotherapy (7 injections during 6 weeks to achieve maintenance dose). Different aspects of clinical efficacy of allergoids were studied in several clinical trials. The most important parameters which have to be positively influenced by a successful SIT preparation are the symptom-, the medication- and the combined symptom-medication scores for rhino-conjunctivitis and/or allergic asthma (GINA I and II). With regard to this Allergovit® has proven its efficacy in double-blind, placebo-controlled (DBPC) trials (27,28,29). It also beneficially influences the antibody titres for specific IgE, IgG and IgG₄ (19,29). The inflammatory cytokines IL-1 and IL-8 are diminished in the

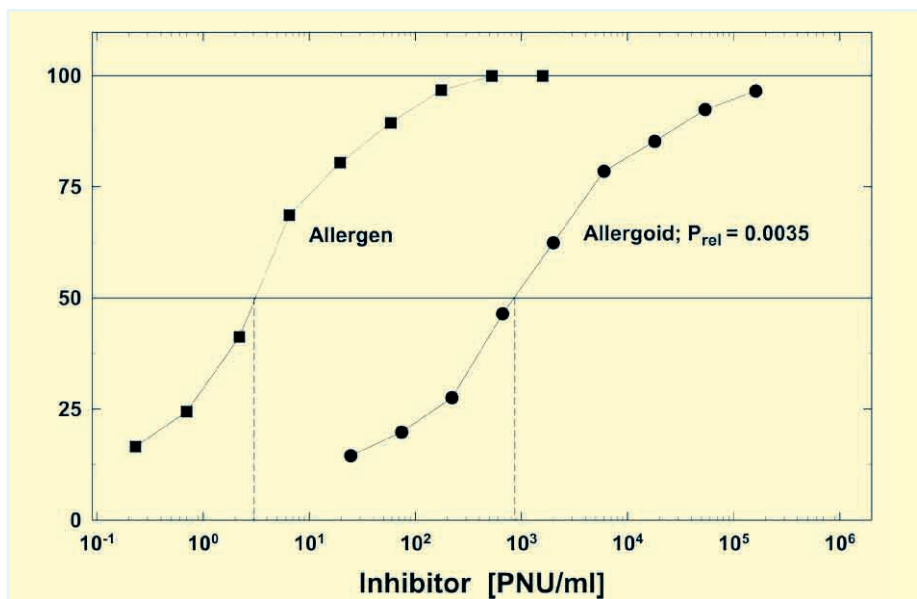


Figure 2: Evidence of reduction in allergenicity of allergoids by RAST-inhibition tests. The IgE-binding to solid-phase-bound 6-grass-extract is inhibited by soluble 6-grass-allergen and -allergoid. The inhibition by the allergoid is only possible with substantially larger amounts of protein (B. Weber, Allergopharma,1996).

Clinical efficacy – historical overview	Study No.
Allergoids achieve higher IgG antibody titres and are clinically more effective than usual native allergens used at that respective time.	36,37,38
The efficacy of aqueous allergoids is confirmed in DBPC trials.	36,39,40
Allergoid aluminium hydroxide adsorbates and allergen depots are comparable with respect to efficacy and safety.	19,41,42,43
Allergoids cause beneficial variations in the antibody titres for specific IgE, IgG and IgG ₄ .	19
Compared to adsorption on tyrosine adsorption to aluminium hydroxide revealed appreciable advantages with respect to symptom and medication score, the patient's assessed impressions of her own condition of health and development of the specific IgE antibody titre; fewer local and systemic side-effects occurred.	44
After two years of therapy in children, pre-seasonal immunotherapy proved clearly superior to symptomatic treatment with respect to the clinical parameters investigated: consumption of medication, course of symptoms, and results of skin tests. The pulmonary symptoms of all children with asthma were "improved" or "much improved".	33
Several studies prove clinical safety and efficacy of Allergovit®. One study (48) evidenced therapeutic success of 85%, as long as three years after completion of a three-year course of SIT.	33,45,46,47,48
Pre-seasonally-administered allergoid depot (7 injections) and perennially administered allergen depot demonstrated comparable results during the course of three years of immunotherapy.	49
DBPC studies show that Allergovit® induces the immunological processes relevant for successful SIT (eg. changes in serum concentrations of specific IgE and IgG; inflammatory cytokines IL-1β and IL-8 are diminished in the target organ, the nasal mucosae).	31,46,47,50
Pollen-associated apple allergy is improved after two years of Allergovit® birch immunotherapy.	32
A DBPC trial in patients allergic to grass pollen, including asthmatics, demonstrated that Allergovit® achieves clear improvement in symptom-medication score (SMS) assessment after one year of treatment. After a second year of therapy a total of 83% of the patients showed appreciable relief from symptoms.	27, 28
In a 2-year DBPC trial in grass pollen allergic patients a difference in SMS of 48.4% in favour of Allergovit Grasses was revealed. The rhinitis quality of life (RQLQ) showed a significant advantage for the active group. A third year of treatment even increased the positive effects in SMS and RQLQ.	29, 30
Six years after cessation of a three-year therapy children who had received Allergovit® demonstrated symptom and medication scores that were significantly lower than the group that had undergone purely symptomatic therapy. 67% of the formerly verum-treated patients no longer demonstrated symptoms of asthma. The development of new sensitizations was lower than that experienced by the patients who had received purely symptomatic therapy. This effect even lasts for 12 years after cessation of SIT.	34,35

Table 1: Clinical studies with allergoids/Allergovit®

nasal mucosa showing an immunological efficacy in the target organ (31). Pollen-associated food allergy

to apples was shown to be improved in 60% of patients after two years of allergoid depot treatment (32).

Since the WHO recommends the commencement of SIT as early as possible during the course of development of allergic disease, the preparations administered must be safe and effective for children as well. Three Allergovit® studies were especially carried out in children (33,34,35). Even 12 years after cessation of the three-year course of SIT the development of new sensitizations was lower than that experienced by the patients who had received purely symptomatic therapy. Also the symptom and medication scores in the children who had received pre-seasonal Allergovit® therapy were significantly lower (34,35). This shows the long-term efficacy of the allergoid treatment.

The following table gives an overview on the studies proving immunological and clinical efficacy and safety of Allergovit®. The historical development of the clinical allergoid research is described (see Tab. 1).

	native allergens	allergoids
IgE-binding capacity (allergenicity)	IgE binds to conformation epitopes of allergens	conformation epitopes mainly destroyed → only reduced IgE-binding possible
Antigen presentation	small allergen doses: antigen presentation via B-lymphocytes → induction of Th2-like cytokine pattern high allergen doses: antigen presentation via dendritic cells and macrophages → induction of Th0/Th1-like cytokine pattern	antigen presentation via dendritic cells and macrophages → induction of Th0/Th1-like cytokine pattern
T-cell activation (immunogenicity)	sequence epitopes induce T-cell activation	sequence epitopes induce T-cell activation
Adverse side effects	risk of IgE-mediated adverse side-effects during SIT	reduced risk of adverse side-effects during SIT because of reduced IgE-binding capacity less side effects per patient less side effects with delayed onset
Clinical efficacy	clinical efficacy proven	clinical efficacy proven rapid dose increase and application of higher doses of allergens possible

Table 2: Characteristics of allergens and allergoids

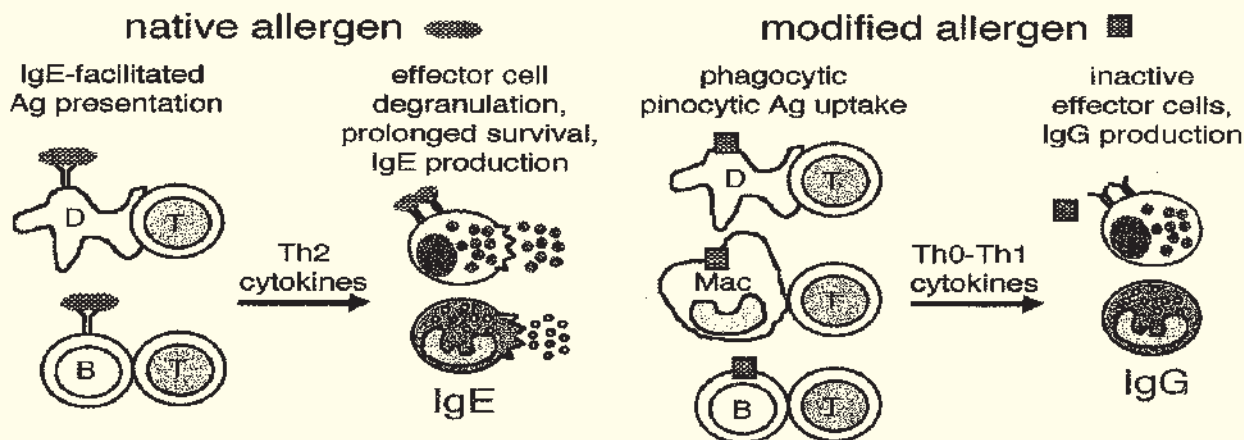


Figure 3: Difference in antigen presentation and immune response by native and modified allergens. Native allergens can degranulate mast cells and basophils and utilize an IgE-mediated antigen presentation, which leads to increased Th2 cytokine and IgE production. In contrast, modified allergens lacking IgE-binding sites utilize phagocytic or pinocytic antigen-uptake mechanisms by dendritic cells (D) and monocytes/macrophages (Mac), generating a balanced Th0/Th1-like cytokine pattern by T cells, and resulting in normalized isotype production by memory B cells. Ag: allergen (13).

● Are allergoids cost effective?

Schädlich et al. have described the cost effectiveness of therapy with allergoids. In this study, which compared allergoid with symptomatic therapy, allergoid treatment reached the break-even point for cumulative costs as soon as 6 ...7 years after initiation of therapy (5).

● Are allergoids safe?

We compared the incidence of serious, non-fatal systemic reactions during hyposensitization treatment course either with an allergoid (Allergovit®) or with an unmodified semi-depot preparation (Novo-Helisen® Depot) for the years 1996 ... 2000. With Allergovit® every 7500th patient had the risk to develop a serious systemic reaction whereas every 5000th patient was concerned with the unmodified preparation (51). This is in accordance with studies of Lüderitz-Püchel et al. who have evaluated the adverse side effects from specific immunotherapy that were reported to the Paul- Ehrlich-Institute in Germany between 1991 and 2000 (52). The incidence of serious, non-fatal systemic reactions to allergoids was 0.0005 ... 0.01% per injection, which is slightly better than the rate for unmodified allergens. Allergoids are furthermore more rarely responsible for serious adverse side-effects that may appear with delayed onset. These findings also concur with the results of various clinical studies on allergoids in which the observed side-effects consist primarily of local reactions. Even if these effects are only secondary effects of

the immunotherapy they are nevertheless indicators of the desired immunological effect (perhaps mediated by T-cells). The literature only rarely describes adverse effects in the form of slight general reactions or serious systemic side-effects (27,33,44,46,49).

In conclusion, allergoids and native allergens show the characteristics given in Tab. 2.

● Summary

Allergoids are allergen extracts with reduced allergenicity but with intact immunogenicity. They enable rapid achievement of high allergen dosage and, consequently, the application of fewer injections in the initial phase, without an increase in the rate of adverse side-effects. Numerous clinical studies have attested to the safety and effectiveness of SIT with allergoids. The necessity for fewer injections – which can also be administered shortly before periods of high pollen count – enhances the likelihood of patient compliance. Administration of only 7 injections in the case of Allergovit® can achieve appreciable therapeutic benefits for both adults and children with allergic rhinitis and/or allergic asthma. SIT with allergoids not only offers confirmed long-time effects, but may also prevent the development of new sensitization.

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