

Allergoid preparations for allergen immunotherapy:

A brief overview

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Allergen immunotherapy (AIT) is now a well-established therapy for allergic diseases by modifying the natural course of disease and changing the Th2 reaction toward Th1. Thus, AIT is a disease-modifying and clinically effective therapy for the treatment of allergic diseases.^[1] The first successful human trial of subcutaneous immunotherapy (SCIT) is credited to Leonard Noon, a British physician who published his results in 1911.^[2] Over the last 50 years, numerous controlled studies, systematic reviews, and meta-analysis have shown the efficacy of SCIT in the treatment of allergic asthma and rhinitis.^[1] The efficacy of SCIT is a dose-dependent phenomenon; SCIT is ineffective at low doses while high doses of allergen extracts increase, to some extent, the risk of systemic reactions.^[3]

Attempts for modifications in AIT for the improvement in safety profile but maintaining the efficacy were being conducted in the world. The concept of allergoids was developed in the 1970s with the aim to improve the safety and efficacy of AIT.^[4] This was achieved by producing allergoids that have reduced allergenicity but retained immunogenicity.^[5] These properties allow allergoids to be used at high doses, with shorter up-dosing periods along with the improvements in safety and efficacy of SCIT. The allergoids have become a mainstay in AIT and have been used extensively in the European countries. Up to 50% of SCIT prescriptions in Europe are of allergoids. Allergoid preparations are available for house dust mites, grass pollen, and trees. In this editorial, we review the hypoallergenic principle described for allergoid preparations and their clinical utility.

Allergoids



The term “allergoid” was used by Marsh *et al.* “to denote an allergen derivative for which the residual allergenic reactivity relative to the native allergen has been significantly reduced,

while the original antigenic properties (both immunogenic and reactogenic) have been retained to a high degree.”^[6] The concept is that allergoids possess less reactive B-cell epitopes and thus reduced IgE binding (i.e., improved safety), while their T-cell epitopes and their immunogenic effect remain unaltered (i.e., retained efficacy).^[7]

Preparation and Composition of Allergoids



Allergoids are prepared by chemical modification of the allergen extracts using formaldehyde and/or glutaraldehyde. In the United States, formaldehyde was used to generate allergoids while the first European formulations were prepared with glutaraldehyde.^[4] Allergoids may also be produced using carbamylation.^[7] Carbamylated allergoids are primarily available for sublingual preparations. In addition, allergoids are then adsorbed to a carrier, such as aluminum hydroxide, tyrosine, or calcium phosphate to produce a depot preparation.^[7] The depot preparations facilitate slow release presentation of the allergen.^[8]

Allergenicity of Allergoids



The most characteristic feature of allergoids is that they are less allergenic (i.e., have a lower IgE reactivity) than natural allergen preparations.^[5] This property is ascribed to the reduced B-cell epitopes in allergoids.^[7] *In vitro* experiments have documented reduced allergenicity of allergoids on the enzyme allergosorbent inhibition test which showed 100–1000-fold reduced allergenicity and also on the more functional assay, the basophil activation test.^[5] In addition, allergoids have proved their reduced allergenicity on the skin prick tests.^[5] Based on this characteristic, the safety profile of allergoids seems to be better compared to the natural aqueous extracts.

Immunogenicity/antigenicity of Allergoid



The ability of allergoids to induce an immune response has been verified as allergoids have led to the induction of the immunomodulatory IgG4 antibodies in numerous clinical trials.^[5] The immunogenic potential of allergoids is well recognized.^[7] Based upon this characteristic, it is assured that the efficacy of the extracts is retained.

Efficacy of Allergoids



The efficacy of allergoids have been documented for house dust mites, grass pollen, and birch pollen.^[5]

In a randomized clinical trial conducted in children with mild persistent asthma, the house dust mite allergoid demonstrated a steroid-sparing effect with a significant reduction in the dose of inhaled corticosteroids needed for asthma control and improved the lung function after 2 years of therapy.^[9] The mean daily dose of fluticasone propionate in the immunotherapy group decreased from 330.3 µg in the baseline period to 151.5 µg, whereas in the control group, the dose decreased from 290.6 to 206.3 µg. In addition, immunotherapy with the allergoid resulted in significant improvements in the morning peak expiratory flow ($P = 0.0315$) as compared to the control group.^[9] The house dust

mite allergoid has also shown improvements in quality of life,^[10] cost-savings as compared to conventional pharmacotherapy,^[11] better compliance as compared to unmodified allergen extracts,^[12] and improvements in patient-perceived symptoms.^[13]

Grass pollen allergoid has demonstrated efficacy in nasal and bronchial allergy in the first pollen season and the maintenance of efficacy in the second and third pollen seasons.^[5] The grass pollen allergoid has also shown a disease-modifying effect. In a prospective controlled study with 12-year follow-up data, there was a significant reduction ($P < 0.05$) in the number of patients developing new sensitizations as compared to the control group. In addition, there was a trend of lower seasonal asthma in the posttreatment years (12-year follow-up) as compared to the control group.^[14] This study also demonstrated that the total hay fever symptom score ($P < 0.03$), use of medication ($P < 0.05$), and combined symptom and medication score ($P < 0.03$) remained lower in patients treated with grass pollen allergoid when compared with the control group.^[14]

Safety of Allergoids



The advantageous safety profile of allergoids allows for usage of allergoids in a clinically effective dose and without increasing the risk of adverse events. In general, the allergoid preparations show rare incidences of “severe systemic side effects.” The German Regulatory Authorities (Paul Ehrlich Institute) has published the rates of 0.0005%–0.01% per injection.^[5]

In a recently published prospective, longitudinal, web-based survey of “real-life” respiratory AIT in 4316 patients, the safety profile of allergoids was significantly better as compared to natural allergen extracts ($P = 0.001$). Patients receiving allergoids in SCIT had a significantly lesser chance of developing a systemic reaction in comparison to the natural extracts.^[15]

The main reason for allergoids preparations not to be used earlier was due to few side effects reported with the allergoids allergen extracts, mainly due to additives such as aluminum hydroxide, aldehydes, and phenol. Now, the clinically effective dose schedule for additives is regulated and is practically safe. Therefore, it is recommended that the composition of the adjuvants and residual products such as aldehydes and aluminum hydroxide should be in the permissible limits as per the European Pharmacopoeia. Thus, the use of aluminum hydroxide as adjuvant in products for specific immunotherapy is regulated in the European Pharmacopoeia. Now, no safety concerns have resulted from the use of aluminum hydroxide in AIT using allergoid preparations.^[16]

Dosing Schedule of Allergoids



Immunotherapy involves an up-dosing phase and a maintenance phase. The up-dosing phase of natural AIT extracts can extend up to 4–6 months (16–24 weeks). In contrast, the up-dosing of allergoids can be completed in 4–8 weeks.^{[9],[17]} Furthermore, the maintenance dose of allergoids can be given at an interval of 4–8 weeks, thereby improving patient and physician acceptability.

Preference for Allergoids



In a large real-world survey, approximately 50% of the prescriptions in AIT (SCIT) were for

allergoid SCIT.^[15]

Summary

Allergoids are now the preferred form of SCIT in Europe, by demonstrating by improving the safety and efficacy of AIT. The features, effects, and clinical implications of allergoids are produced in [\[Table 1\]](#).

Feature of allergoids	Effect	Clinical implications
Reduced allergenicity (reduced B-cell epitopes)	Improved safety profile	Reduced risk of systemic adverse events
Retained immunogenicity	Efficacy retained	Efficacy proven in clinical trials
Depot preparations	Significantly shortened up-dosing phase	Better patient and physician acceptance Better compliance

Table 1: Features, effects and clinical implications of allergoids

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