

Editorial

Local immunotherapy is not documented for clinical use

The immunologic events leading to sensitization and subsequently to allergic reactions in the respiratory tract take place in the mucosa and regional lymph nodes. It would therefore seem to be logical to employ local rather than systemic treatment for immunotherapy (IT) of asthma and allergic rhinitis. Local IT in the most important organ, i.e., bronchial provocation with increasing doses of allergen, is not feasible for safety reasons, although a controlled study has been reported (5). Nasal IT with pollen extracts has, however, been tried in several studies for treatment of allergic rhinitis (1, 2, 6, 10–13, 17, 25, 26). The treatment undoubtedly reduces nasal sensitivity, and it is associated with some reduction of clinical symptoms during the pollen season, although the long-term efficacy has not been determined. Unfortunately, the treatment also induces clinical symptoms of the same type that the treatment is intended to prevent. Thus, the period with allergic rhinitis is prolonged beyond the pollen season. It could be said that the treatment results in perennial moderate symptoms caused by the treatment, rather than severe symptoms during a limited period, i.e., the pollen season. Furthermore, long-term follow-up studies have not been done to determine whether the treatment effects are lasting.

Two lines of research have been applied to avoid eliciting local symptoms by nasal IT. One way is to modify the allergen preparations chemically in order to reduce their allergenicity, while retaining immunogenicity. Clinical trials of local IT have been performed with modified extracts (6, 12, 13). The results are promising and indicate that the principle is correct. Unfortunately, however, it is not possible to ascertain whether all epitopes are retained in modified extracts, perhaps because of difficulty in standardizing their production.

The second way to avoid eliciting local reactions during local IT is to employ alternative routes for administration of the allergen preparation intended to stimulate mucosal immunity. Theoretically, induction of mucosal immunity on one site is transferred also to other sites. Oral IT is an obvious alternative, as this route would provide an intense mucosal stim-

ulation. There are controlled studies showing that administration of large doses of birch pollen extract in enteric-coated capsules reduces clinical symptoms during the pollen season, as well as conjunctival and nasal sensitivity, as assessed by challenge tests (3, 4, 7, 15, 16, 20, 21). The treatment also increases IgG antibody levels against the allergen and eliminates the seasonal increase in IgE antibodies (21). Unfortunately, the amount of allergen extract needed for this treatment is 100–300 times higher than for conventional IT. Until large amounts of recombinant allergens are available, oral IT does not appear to be feasible. Furthermore, the efficacy seems to be limited to a few allergens, e.g., birch pollen and *Artemisia* (8, 14). For grass pollen, oral IT is not effective, as indicated by several (7, 22), but not all (23), controlled studies, because the predominant allergens in grass pollen are rapidly destroyed by duodenal juice (9) and thus would be inactivated before they could stimulate the immune system. The study claiming efficacy (23) was not truly blinded; the authors admitted when the study was presented orally that patients receiving active therapy had experienced itching in the mouth. In conclusion, oral IT with conventional allergens that would be effective is not economically feasible. Allergens that would be economically possible to use, e.g., grass pollen, are not effective, as they are destroyed rapidly by intestinal juices.

Sublingual IT has also been tried in several studies, some of which have been controlled (19, 24). The theory behind this treatment is not clear, although it has been suggested that it would be a particularly effective route for stimulation of local immunity, or, alternatively, that low dose tolerance would be induced. Most immunologists would reject either possibility. Unfortunately, the studies claiming efficacy had several flaws in the design, including inadequately defined patients, lack of objective verification of effect, and short observation time. Furthermore, incorrect statistical methods were usually employed, e.g., assuming a normal distribution of the results, which rarely occurs. Although a double-blind design has been employed in some

studies, no evidence was given that the design actually worked. This is important, because it was observed in studies of oral IT with birch pollen (4) and grass (23) (see above) extracts that both patients and doctors could correctly guess, from side-effects, who had received active substance and who had received placebo.

In this issue of *Allergy*, yet another study of sublingual IT is reported (18). Unfortunately, it does not clarify the issue of efficacy because most of the above critique applies to the study. Nothing is said about the severity of disease in the patients, the assessment is exclusively subjective, and immune responses were not studied, nor was the claimed efficacy supported by increased tolerance to the allergen in provocation tests. From the rescue medication that was used in the study, it would appear that most patients had only mild disease. It is therefore doubtful whether they were candidates for IT in the first place. Several of them had also been subject to parenteral IT. The data were treated as normally distributed. This is surprising, because in most studies there are patients who respond very well and others who do not respond at all. At best, there is a normal distribution among the responders when nonresponders have been excluded.

In conclusion, local IT for severe allergic rhinitis and possibly allergic asthma remains an interesting possibility. The most promising treatments so far include the use of modified allergen preparations with reduced allergenicity but maintained immunogenicity, and oral IT with large quantities in enteric-coated vehicles to avoid premature degradation in the stomach. Both these treatments rest on a reasonably sound theoretic basis. Sublingual IT has not been documented clinically, and it is not clear why small amounts of allergens applied under the tongue would be effective. More conclusive data are required before sublingual, and particularly low-dose, therapy can be considered for routine treatment of allergic disorders.

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