Immunotherapy and Immunomodulation

Efficacy of Long-term Sublingual Immunotherapy as an Adjunct to Pharmacotherapy in House Dust Mite-Allergic Children With Asthma

PURPOSE OF THE STUDY. To evaluate the effect of 3 years of dust mite sublingual immunotherapy (SLIT) on clinical and laboratory outcome measurements.

STUDY POPULATION. This was a prospective study of 90 children aged 4 to 16 years who were followed for 4 years from the time of enrollment. Inclusion criteria were mild-to-moderate persistent asthma requiring an inhaled steroid, monosensitization to dust mite, and no previous history of immunotherapy.

METHODS. Participants were randomly assigned to treatment for 3 years with dust mite SLIT plus standard pharmacotherapy or pharmacotherapy alone. The prescribed SLIT solution consisted of 50% Dermatophagoides pteronyssinus and 50% Dermatophagoides farinae. Doses were increased gradually to a maintenance dose, which was taken 2 times per week. All participants were initially started on 800 µg/day of inhaled budesonide. Follow-up visits were performed every 2 to 3 months, at which times the inhaled corticosteroid (ICS) dose was decreased until either it was discontinued or the minimum dose allowing for control of symptoms was reached. Pulmonary-function testing was performed at each visit. Skin-prick testing to 15 aeroallergens and a serum total immunoglobulin E measurement were performed annually.

RESULTS. A total of 90 children were randomly assigned: 62 to SLIT plus pharmacotherapy and 28 to pharmacotherapy alone. There were 19 drop-outs (31%) in the SLIT group after 3 years compared with 5 (18%) in the pharmacotherapy group. The number of months per year in which the children required ICS, as well as mean dose per day of budesonide, was significantly lower in the SLIT group compared with pharmacotherapy group during all 3 years. By the end of the 3 years, 52.4% in the SLIT group versus 9.1% in the pharmacotherapy group were able to successfully discontinue ICSs for at least 6 months. Both forced expiratory volume in 1 second and forced expiratory flow, midexpiratory phase, were significantly increased from baseline in the SLIT group after 3 years, whereas the pharmacotherapy controls showed no change. Total immunoglobulin E levels were significantly decreased only in the SLIT group after 3 years. Finally, there were no serious adverse reactions during the study.

CONCLUSIONS. Three years of SLIT as an adjunct to pharmacotherapy in house dust mite–allergic children with asthma resulted in a reduction of the necessity for ICS usage along with improvement in lung functions.

REVIEWER COMMENTS. This study adds to the body of work defining SLIT as a modality that is capable of providing clear but modest benefit in the treatment of allergic airway disease. The primary focus was on evaluating the steroid-sparing effect of SLIT. Unfortunately, symptom scores and rescue-medication usage were not reported. There was a 31% drop-out rate after 3 years among the SLIT group, compared with 18% among the pharmacotherapy group. So, although there may be some compliance advantage in SLIT over injection immunotherapy, there are clearly still some adherence challenges. This study demonstrates that the addition of SLIT to standard pharmacotherapy can provide a significant decreases in ICS usage and modest increases in lung function over the course of 3 years of treatment.

Cutting Edge: Immunosuppressant as Adjuvant for Tolerogenic Immunization

PURPOSE OF THE STUDY. Immunosuppressive agents are used frequently for the treatment of allergy, autoimmune disease, and transplant rejection but are thought to provide only temporary benefit. The authors of this study sought to determine if dexamethasone, a glucocorticoid with potent immunosuppressive properties, could promote long-term antigen-specific tolerance when administered with a peptide immunogen.

METHODS. The authors used a model of delayed-type hypersensitivity (DTH) to hen ovalbumin by subcutaneously injecting ovalbumin twice during a 2-week interval into BALB/c mice. Mice with established DTH to ovalbumin were then immunized with an ovalbumin-derived MHCII-restricted peptide in the presence or absence of dexamethasone. All mice were retested for DTH at 2-week and 4- to 5-month time points after completion of immunization by injecting ovalbumin into the footpad and measuring the increase in footpad thickness. Blood-derived CD4+/CD25+Foxp3+ regulatory T cells (Tregs) were quantitated by labeling peripheral white blood cells with carboxyfluorescein diacetate succinimidyl ester (CFSE), stimulating the cultures with ovalbumin peptide, and analyzing for CFSE dilution (indicating cell division). Dendritic cells (DCs) in draining lymph
nodes (LN s) were assessed for maturity by staining for CD11c, CD83, and CD86, as well as interleukin 10 (IL-10) in some experiments. Transgenic mice containing large numbers of ovalbumin-specific CD4\(^+\) T cells were studied also. A similar set of experiments was performed with nonobese-diabetic mice, a mouse model of autoimmune diabetes, by using dexamethasone and an insulin-derived MHCII-restricted peptide. Primary outcomes measured were median time to development of diabetes (as defined by glycosuria) and measurement of Treg numbers and antigen-specific proliferation.

RESULTS. Treatment with dexamethasone induced long-term desensitization (as long as 4–5 months) in mice with preestablished DTH to hen ovalbumin as evidenced by a decrease in foot-pad swelling after ovalbumin challenge. This finding was accompanied by an expansion of CD4\(^+\)CD25\(^+\)Foxp3\(^+\) Tregs, which largely had specificity for ovalbumin. Dexamethasone, in the presence of ovalbumin, seemed to block DC maturation in draining LNs and facilitated differentiation of IL-10\(^+\) DCs. Furthermore, treatment of nonobese-diabetic mice with dexamethasone hindered development of spontaneous diabetes and was associated with the development of long-term antigen-specific persistent Tregs.

CONCLUSIONS. Dexamethasone, when applied together with peptide, can promote long-term tolerance. The underlying mechanism may involve dexamethasone’s effect on inhibiting DC maturation and promoting development of persistent antigen-specific Tregs.

REVIEWER COMMENTS. Development of long-term tolerance, as opposed to transient desensitization, is the end goal of immunotherapy protocols, and this study suggests that glucocorticoids may be effective adjuvants in achieving this goal. The authors of this article speculated that other small-molecule immunosuppressant drugs, including cyclosporine and FK506, may also be effective for this purpose, but there is some evidence that these agents may actually promote development of allergic disease in children after solid organ transplantation.

Probiotics Have a Different Immunomodulatory Potential In Vitro Versus Ex Vivo on Oral Administration in Children With Food Allergy


PURPOSE OF THE STUDY. Previous studies have suggested that administration of probiotics in vitro can stimulate regulatory and T helper type 1 (Th1) immune responses. The authors studied both the in vitro immunologic effects of probiotics and the ex vivo immuneologic effects after oral administration of probiotics in children with food allergy, a Th2-mediated disease.

STUDY POPULATION. Thirteen food-allergic children aged 0.5 to 2.8 years were enrolled from the Department of Pediatric Dermatology and Allergology at Wilhelmina Children’s Hospital (University Medical Center, Utrecht, Netherlands).

METHODS. Probiotics (n = 7) or placebo (n = 6) were orally administered during 3 months. At baseline and after 1 and 3 months, peripheral blood mononuclear cells were stimulated with crude peanut extract, anti-CD3, or anti-CD40 and interleukin 4 (IL-4) in the presence (in vitro response) or absence (ex vivo response) of probiotics. The proliferation and production of interferon \(\gamma\), IL-5, IL-13, IL-10, tumor necrosis factor \(\alpha\) (TNF-\(\alpha\)), IL-6, and immunoglobulin E (IgE) were analyzed. Sensitization to peanut, cow’s milk, and hen’s egg was determined before and after treatment.

RESULTS. The in vitro addition of probiotics to peripheral blood mononuclear cell cultures resulted in enhanced proliferation and production of interferon \(\gamma\), IL-10, and TNF-\(\alpha\). After oral treatment, proliferation in the presence of probiotics increased, whereas in vitro IgE production decreased in the probiotics group compared with baseline. The ex vivo production of IL-10, TNF-\(\alpha\), and IL-6 tended to decrease. Th1 and Th2 cytokines were not altered. Sensitization remained unchanged.

CONCLUSIONS. Probiotics enhanced the production of Th1 and regulatory cytokines in vitro. Oral administration of probiotics resulted in a slightly decreased ex vivo production of IL-10, TNF-\(\alpha\), and IL-6, which indicates that probiotics have a different potential to modulate the immune response in vitro versus ex vivo.

REVIEWER COMMENTS. There is great interest in the potential for probiotics to divert the immune systems from the Th2 (allergic) profile. Although many studies have investigated the effects of probiotics in vitro, few have examined the effects in atopic children. This study, with a limited number of patients, demonstrates that results obtained in vitro may not reflect the effects of probiotics when they are ingested and exposed to the intestinal mucosa, thus suggesting that additional in vivo studies are necessary to better understand the mechanism of action and optimize the therapeutic potential of probiotics in atopic children.

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