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Evaluation of IL10, TGF-B and Specific IgE and IgG Levels during Sublingual Rye Grass Immunotherapy

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Abstract

Background: Sublingual Immunotherapy (SLIT) is a safe mechanism for treatment of some allergic disorders. This study investigated the effect of SLIT on specific IgG, IgE, Interlukin 10 (IL10) and Transforming Growth Factor beta (TGF-β) levels.

Material and methods: This randomized double blind trial was performed 2 months prior to the grass pollination till the end of the season for about 6 months. Patients (5-18 yrs old) with allergic rhinitis to rye grass pollen, randomly received grass pollen or placebo extract and specific IgG and IgE level were assessed. IL10 and TGF-β were also measured before and after treatment. Data were analyzed by SPSS software.

Results: Twenty of 24 patients completed the study. We did not find any significant difference in specific IgG and IgE levels before and after study between the two groups, however there was statistically significant elevation of IL10 (PV=0.003) and TGF-β (PV=0.006) levels after immunotherapy in the intervention group.

Conclusion: This study showed sublingual immunotherapy had significant effect on regulatory cytokines.

Keywords: Sublingual immunotherapy; Rye grass; Interleukin 10 (IL10); Transforming Growth Factor beta (TGF-β); Allergic rhinitis

Introduction

Allergen specific immunotherapy has been used in human as an effective treatment of allergic disorders [1-3]. Subcutaneous injection was known as a classic form of administration, but recently sublingual rout have been considered as an alternative method. It is now shown that Sublingual Immunotherapy (SLIT) is much safer than Subcutaneous Immunotherapy (SCIL), [2,4-7] because it is noninvasive and in several studies it was shown that it reduces both symptoms and medical requirements [2,8-10]. Some studies showed immunologic changes during SLIT such as increased Th1 to Th2 activities and increased T regulatory cytokine secretion [11-14], but other studies did not show significant effects [15-17]. Rye grass is the most common allergen in our area specially in children and youth and could affect activity and school works of sensitive patients [18].

In our study the effect of sublingual rye immunotherapy on specific IgE and IgG levels and IL10 and TGF B production was investigated.

Material and Method

This double blind, placebo-controlled trial was conducted in allergy clinic of Mousavi hospital in Zanjan City from March to August 2010. This Trial was registered in Iranian Registry of Clinical Trial. (IRCT No: 138812042967 N1) and approved by Ethic committee of Zanjan University of Medical Sciences. Thirty patients were invited to study and after obtaining a written consent, 24 subjects (5-18 years old) accepted to run into trial and randomly received sublingual immunotherapy or placebo. Patients with clinical history of significant grass pollen allergic rhinitis or rhino-conjunctivitis for 2 years or more and positive skin prick test (Stallergen France, wheal diameter >3 mm) to rye grass were included in this study. Patients who had moderate to severe asthma in accordance to GINA Guideline [19], multiple positive skin tests to other allergens and systemic or autoimmune disease were excluded from the study.

Rye grass extracts (Staloral 638, Stallergen, France) were instructed to spray under the tongue and kept about 1-3 minutes and then swallowed. Study started 8-10 weeks before grass pollen season with dose of 10 IR extract. During the build up phase, the dose was increased at alternate day. When the dose of 900 IR was achieved, it was continued 3 times a week as a maintenance therapy until the end of season. All patients were visited monthly and were in contact by phone call during study. Patients in placebo group received similar pattern of therapy. Blood sampling was done at the beginning and at the end of study. IL10 and TGF-β were evaluated in supernatants of cultured peripheral blood mononuclear cells after isolation by ficoll-hypaque. The quantitative determination was performed by Enzyme linked immunosorbant assay. (MT EAST, Dr Hook, Germany) specific IgG and IgE to Rye grass were also measured by enzyme-linked immunosorbant assay (Dr Hook Germany). Symptoms and medical score of patients were also measured in a parallel study [20].

The Kolmogorov-Smirnov test was used to evaluate the distribution of quantitative variables. Values were expressed as mean ± standard deviation, as appropriate. Comparisons were performed by chi-square test for categorical variables, independent or paired t-test for normally distributed, and Mann-Whitney or Wilcoxon test for non-normally distributed. P<0.05 was considered as statistically significant.

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Results

Twenty of 24 patients (10 patients as treatment and 10 patients as placebo group) completed the study. Mean age of treatment group and placebo group was similar; 8.13 ± 2.5 vs. 9.14 ± 6.4 (p=0.62). The female to male ratio were 8/2 and 7/3 in treatment and placebo groups respectively (p=0.61).

We did not find any significant changes in specific Rye grass IgG levels between treatment and placebo groups before and after immunotherapy. Specific IgE levels also were not changed statistically significant after treatment, between the two groups. At the beginning of study, IL10 and TGF β level was greater in control group, however after immunotherapy the amount of IL10 and TGF-β in treatment group was significantly increased whilst we found decreasing levels of both in control group after treatment. There was significantly greater amount of IL10 and TGF-β in treatment group in comparison to placebo after 6 months of immunotherapy (Figure 1) (Tables1-4).

Discussion

In this randomized clinical trial study, sublingual immunotherapy with rye grass did not significantly change specific IgG and IgE levels after 6 months. This may be due to the short course of our study. Several studies showed significant alternations of specific IgG and IgE after I-3 years of immunotherapy [21-23]. Although Dehlink et al. did not find any significant immunologic changes during a short period of 8 weeks [16],in the study of Marcucci et al. significant changes in specific IgE and IgG4 levels in a short period of therapy were shown [24].

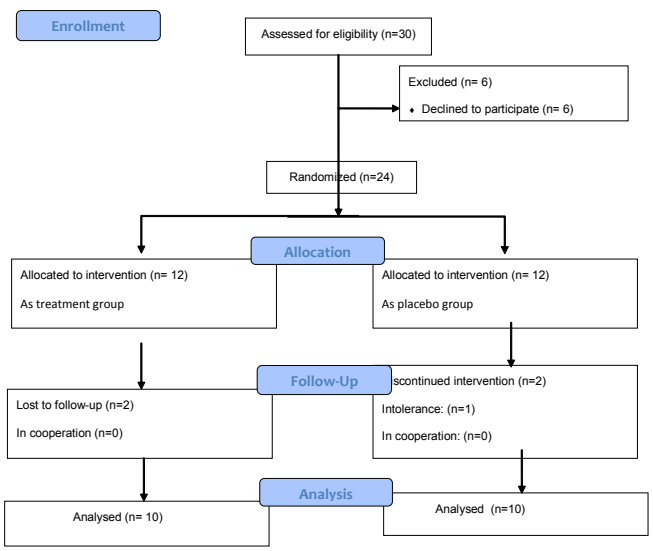

Figure 1: The Diagram of study.

IgG	Immunotherapy*	Control**	P Value
Baseline	139 ± 40	145 ± 16	0.679
After months	127 ± 24	135 ± 42	0.629

*Pv before and after immunotherapy in treatment group=0.479
**Pv before and after immunotherapy in control group=0.411

Table 1: Mean specific IgG (μg/ml) in the immunotherapy and placebo groups at the baseline and 6 months after treatment.

IgE	Immunotherapy*	Control**	P Value
Baseline	2.62 ± 0.27	1.26 ± 0.23	0.149
After 6 months	1.41 ± 0.61	1.47 ± 0.24	0.768

*Pv before and after immunotherapy in treatment group=0.176
**Pv before and after immunotherapy in control group=0.131

Table 2: Mean specific IgE (U/ml) in the immunotherapy and control groups at the baseline and 6 months after treatment.

IL10	Immunotherapy*	Control**	P Value
Baseline	188.9 ± 94.81	277 ± 121.59	0.086
After 6 months	314.9 ± 96.53	216 ± 96.6	0.035

*Pv before and after immunotherapy in treatment group= 0.003
**Pv before and after immunotherapy in control group=0.012

Table 3: Mean IL10 (pg/ml) amount in the immunotherapy and control groups at the baseline and 6 months after treatment.

TGF-β (pg/ml)	Immunotherapy*	Control**	P Value
Baseline	173.4 ± 73.15	284 ± 126.4	0.027
After 6 months	326.4 ± 126.7	250.4 ± 110.5	0.017

*Pv before and after immunotherapy in treatment group= 0.006
**Pv before and after immunotherapy in control group=0.182

Table 4: Mean TGF-β amount in the immunotherapy and control groups at the baseline and 6 months after treatment.

Assessment of total specific IgG level instead of IgG4 level could influence our results. In a similar study IgG4 levels were significantly raised after 6 months SLIT with grass pollen extracts [25]. However Mosges et al. showed that serum-specific IgG4 levels did not statistically differ in comparison to control after 9 months of SLIT in spite of significant reduction of symptom score, medical score and skin test titration [26]. We found similar results in a parallel study of our patients [20]. In study of Pfaar and Klimek allergen-specific IgE didn't change, although specific IgG4 and IgG1 increased with active treatment in the first and second study years compared with placebo [27].

One study also did not show any alternation of serum IgE/IgG4 ratios over time after 1 and 2 years SLIT [17]. Rossi et al. showed only high dose SLIT regimen results in an appreciable serum specific IgG4 increase [28]. We found increasing amount of IL10 and TGF-β levels in immunotherapy group, whereas significant reduction was observed in placebo group in comparison with baseline level and active treatment group. It implicated the induction of regulatory T cells by SLIT. Thus, SLIT could induce a systemic immunologic response. T regulatory cells induced by immunotherapy are type 1 cells producing high levels of IL10 and TGF-β. Both cytokines decrease the release of pro-inflammatory mediators and inhibit the production of Th2 cytokines. Savolainen et al. showed high-dose SLIT, induced activation of regulatory cytokine IL-10 and TGF-β associated with inhibitory effect on IL-5 expression [29]. Piconi et al. demonstrated that SLIT was associated with modulation of programmed cell death ligand 1 expression and IL-10 synthesis and favors the production of allergen-specific IgG4 [30]. In study of Ciprandi et al. there was negative relationship between TGF-β and eosinophilia in patients after SLIT and also higher levels of IgG and IgA in SLIT-treated patients [31].

Induction of T regulatory cells during SLIT seems to play a central role in inhibition of allergic inflammatory responses. Type 1 T regulatory cells produce increasing amounts of IL-10 and TGF-β associated with decreasing IgE and enhancement of IgG4 and IgA production, respectively [32]. Remarkably, this increase in IL10 was significant as early as 2-4 weeks during immunotherapy [33]. We found improvement of symptoms and medical score and also skin test reduction in patients during SLIT in our recent study [20]. Therefore, induction of T regulatory cells and production of IL-10 and TGF-β should be important mechanism for achieving effective treatment.

Conclusion

This study shows SLIT could change the immune profile of patients especially by induction of regulatory T cells after a short course of treatment. In addition, considering its convenience and safety administration, it is better to be recommended for treatment of children with poorly controlled allergic rhinitis.

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