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Efficacy of Sublingual Swallow Immunotherapy in Children with Rye Grass Pollen Allergic Rhinitis: A Double-blind Placebo-Controlled Study

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ABSTRACT

Specific local immunotherapy has been recently introduced as an alternative to classic subcutaneous immunotherapy in treatment of allergic rhinitis. In this study, the effects of sublingual immunotherapy (SLIT) on symptoms and medication score and skin prick test evaluation of patients with allergic rhinitis were investigated.

In this placebo controlled trial, twenty four patients aged 5-18 years old with grass pollen induced rhinitis and sensitive to rye grass by positive skin prick test received randomly sublingual extract of rye grass or placebo for 6 months. Symptom and medication scores and adverse effects of SLIT were assessed during treatment. Skin prick test induced wheal at the beginning and the end of therapy were also measured. Data were analyzed with SPSS software.

We found significant reduction of symptoms in intervention group from 21st week of immunotherapy ($p < 0.05$). Medication scores were also reduced after 16th week ($p < 0.05$), adverse effects were low and insignificant in both groups. Erythema induced diameter with skin prick test for grass and rye grass was significantly reduced in SLI group after immunotherapy.

This study indicates that SLIT in grass-pollen rhinitis is well tolerated, improves overall clinical symptoms, and reduces drug consumes. We recommend this therapy as a safe therapy in patients with allergic rhinitis.

Keywords: Allergen immunotherapy; Allergic rhinitis; Children; Sublingual

INTRODUCTION

Allergy is common problem in the world. It is a chronic condition and affect on patients' quality of life,

work productivity and expenditure.¹ Determination of environmental allergens, allergen avoidance and medication sometimes are beneficial and could control these disorders.

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However these therapeutic measures sometimes might be ineffective. Specific immunotherapy is identified as an effective treatment of allergy. It alters immunologic responses and reduces sensitization.¹⁻³ subcutaneous specific immunotherapy has been recognized as an effective treatment since a century ago. But, in recent decades sublingual immunotherapy have been investigated and determined as an alternative route.⁴⁻⁷ Several studies demonstrated the effectiveness of this treatment, but some other investigations did not show significant results.⁸⁻¹¹ There are limited data about SLIT in Asia especially in Iran. The aim of our study was to evaluate the effectiveness of SLIT on symptoms, medications and skin prick test results in children with documented allergic rhinitis to Rye grass pollen.

MATERIALS AND METHODS

This was a double blind, randomized parallel group, placebo-control trial. Thirty 5-18 years old patients suffering from grass pollen induced allergic rhinitis were invited to study. Patients with clinical history of significant grass pollen allergic rhinitis or rhinoconjunctivitis for 2 years or more duration and positive skin prick test (Stallergenes France, wheal diameter >3 mm) to rye grass were included in this study. Exclusion criteria were having moderate to severe asthma in accordance with GINA Guideline,¹² multiple positive skin tests to other allergens and systemic or organ autoimmune diseases.

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. Study was conducted in allergy clinic of Mousavi hospital in Zanjan City from March to August 2010. After giving writing consent 24 subjects were enrolled and randomly received Sublingual immunotherapy or placebo. The protocol of immunotherapy was on basis of the instruction of the company (Stallergenes, France) The extracts were 10, 100, 300 IR (Index of Reactivity) Rye grass spray (Staloral 638) or similar placebo. Extracts were instructed to spray under the tongue and keep it 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. Placebo preparation was identical to the extract in appearance, presentation and taste. All patients were visited monthly and were in contact by phone call during study. Symptoms of patients, medications and adverse effects of sublingual extracts were recorded daily and scored weekly.

Primary outcome measurements consisted of symptom and medication scores before and during treatment. Subjects rated their symptoms on scales from 0-3 (0= no symptoms; 1=symptoms <30 minutes; 2=symptoms more than 30 minutes and less than 3 hours; 3=symptoms more than 3 hours) for each symptoms.¹³ The symptoms were rhinorrhea, sneezing, itching of nose, red/itching eyes, cough, wheeze and dyspnea that recorded daily in their dairy cards.

Medical scores were also measured. The use of each type and dose of Antihistamines (Loratadine or cetirizine), inhaled β blockers (Salbutamol 100 μ g) or corticosteroids (fluticasone 125 μ g), Intranasal corticosteroids (fluticasone 50 μ g), eye drops (nephazoline or fluromethalon) were scored one.

Subjects kept diaries for 6 months to record nature and duration of symptoms and any dose of medications.

Averse events were recorded: Itching, soreness and swelling in oropharynx area were recorded as adverse events and scored one for each symptom.

Secondary variable of our trial was reduction of wheal diameter to rye grass based on skin prick test after 6 months immunotherapy.

Data were analyzed by SPSS software. Symptoms and medical scores and adverse events compared weekly and skin test evaluation at the beginning and the end of study was done. Data were parametric distribution and Median $\pm$ standard deviation were measured and analyzed by student t tests.

RESULTS

20 of 24 patients completed the study. Two patients in treatment group and 2 patients in placebo group withdrew because of noncompliance and no adherence (Figure 1). Mean age of treatment group and placebo group was similar; 8.13 $\pm$ 2.5 vs. 9.14 $\pm$ 6.4 ($p=0.62$). The female to male ratio were 8/2 and 7/3 in treatment and placebo group respectively.

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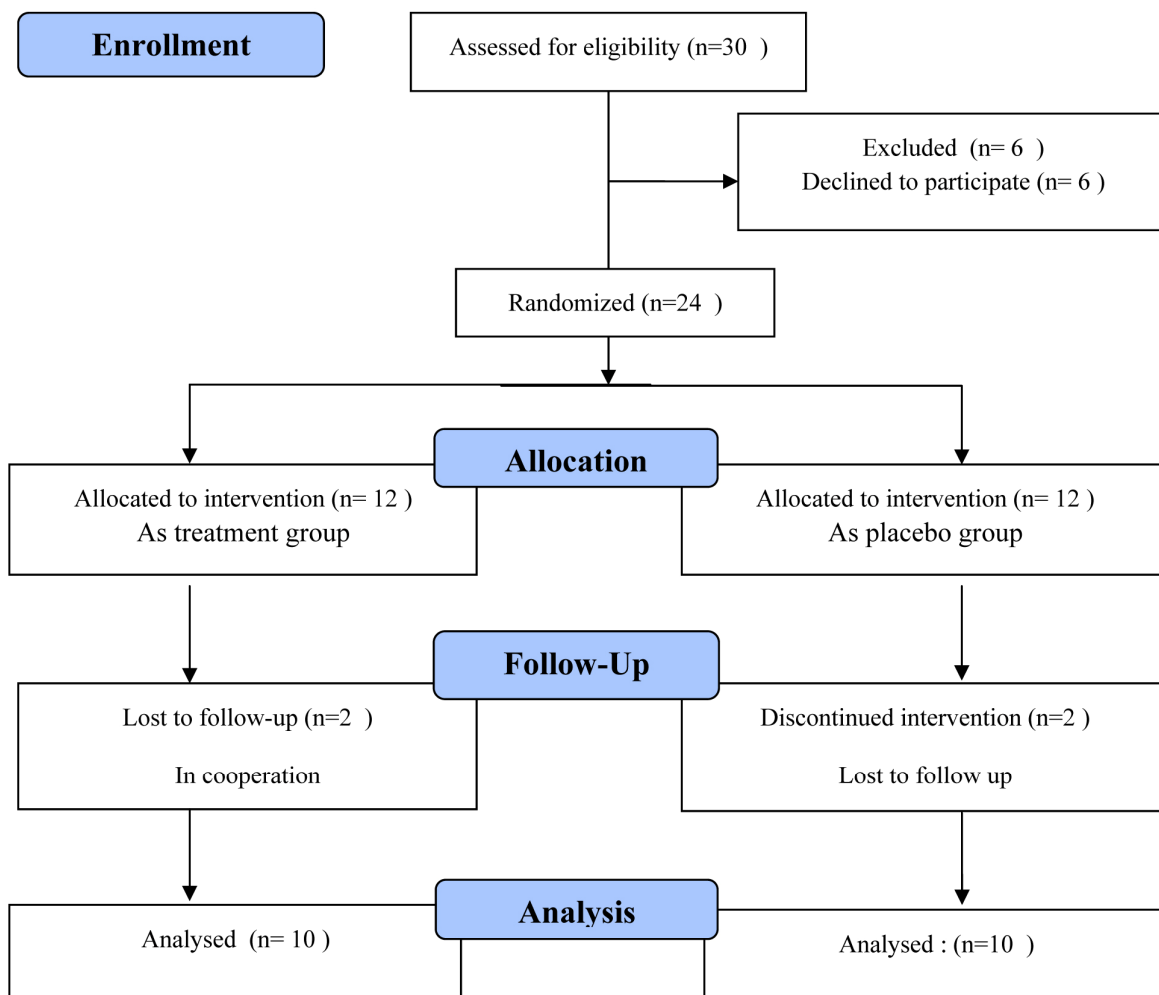


Figure 1. The diagram of study

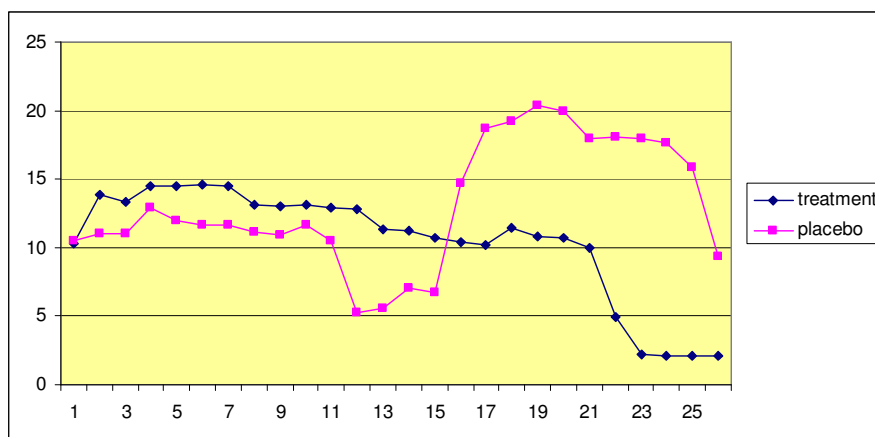


Figure 2. Symptom scores during 26 weeks in treatment and placebo groups

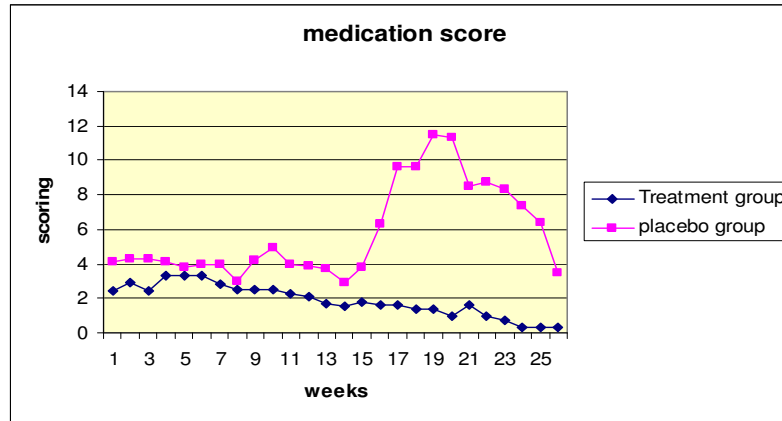


Figure 3. Medication scores in immunotherapy and control groups

The symptom scores in treatment group and placebo were similar at the beginning of study until 21st week, after that significant reduction was seen in treatment group up to the end study (Figure 2).

The comparison of medical scores between two groups showed significant reduction in treatment group from week 15th of immunotherapy (Figure 3).

The adverse effects which were recorded were similar in immunotherapy and placebo group. However, from week 19th up to week 22nd these were significantly lower in treatment group (Figure 4)

Skin prick test to Rye grass and grass were similar in two groups before therapy. But after 6 months, Wheal diameters that induced by rye grass and grass extract were shown significant reduction (Table 1).

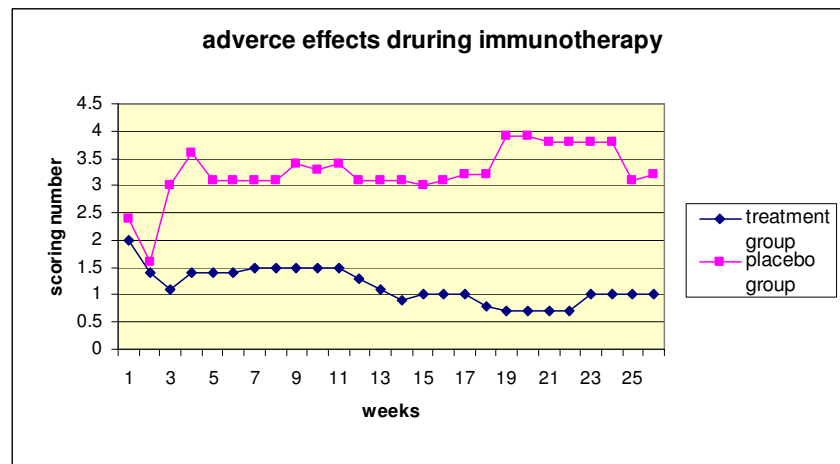


Figure 4. Adverse effects reported in immunotherapy and control groups.

Table 1. Wheal diameter (mm) induced by Rye grass and grass based on skin prick test before and after immunotherapy

Topics	Immunotherapy (SD)	Placebo (SD)	P value
Rye Grass at the baseline	5.6 (1.71)	6.6 (2.12)	0.26
Grass At the baseline	5.4 (3.06)	6.7 (3.4)	0.38
Rye grass after 6 months	2.3 (1.57)	5 (1.88)	0.003
Grass after 6 months	3.2 (3.01)	5.9 (2.8)	0.03

DISCUSSION

SLIT seems to have better safety and achieve higher compliance than subcutaneous regular immunotherapy and could give the favorable outcomes.^{14,15}

Sublingual space is suitable for allergen delivery. When antigen is kept in sublingual space, it rapidly binds and contacts with the oral mucosa leading to inducing some immunologic responses. It stimulates allergen-specific B lymphocytes to increase IgA and IgM production, which could boost the barrier function against antigen penetration at the mucosal surfaces. It alters the function of T cells increasing the ratio of TH1 to TH2 lymphocytes and increasing the number of suppressor T cells. Reduction in recruitment and activation of proinflammatory cells have been demonstrated.^{7,16}

According to our trial SLIT reduced the symptoms and medical scores of patients 3-4 months after therapy. Our study was designed similar to study of clavel et al and gave the same results. Our study is in accordance with Trails of ARIA-GA2 Statement.^{17,18}

There were several studies to show similar results.^{10,19} However other studies did not demonstrate clinical improvement after SLIT.^{9,20}

Patients in our study were in childhood or teenage life-time. It is expected that immunotherapy to be more efficacious, when started at younger ages and several independent studies have suggested that SLIT in children with rhinoconjunctivitis to either grass pollen or half dust mite (HDM) in addition to clinical improvement of patients, could prevent asthma as well as new sensitization.^{7,21-23} Agostinis and coworkers showed the effectiveness of immunotherapy in very younger ages and increased acceptance of immunotherapy in children younger than 5 years.²⁴ Although, The up dosing phase of our study was very longer because of every alternate increasing doses of allergens and it took about 8 weeks. However we could achieve good clinical outcome and reduction of skin tests in treatment group. In several studies duration of treatment varied from 2 months to 5 years.^{7,21,25} It should be emphasized several rush and ultra rush protocols for SLIT have demonstrated that it can induce a decrease in skin reactivity and readily detectable clinical benefits within weeks or even days.^{14,26} This type of therapy could prove the possible rapid relief of allergic symptoms, without concerning about serious side effects that could appear with injectable route of

immunotherapy. Minor side effects consisting of itching and swelling of oral mucosa were reported but were rarely significant.^{7,19} In our study any problem in oropharyngeal area was considered as side effects of sublingual administration and reduction of these symptoms in treatment group showed that this seems better to be considered as manifestation of allergic process in oral cavity rather than adverse effects.

Recently the role of toll like receptors was also investigated and one study demonstrated that SLIT of grass pollen together with monophosphoryl lipid A (as adjuvant) therapy leads to faster response and better tolerance of immunotherapy.²⁷

CONCLUSION

We found that SLIT is a safe and effective route of therapy of allergic rhinitis. It was tolerable and even high doses of allergen could be administered at home. However, further investigation for activation of the innate immune system through Toll-like receptor agonists with specific allergens appears to improve the immunologic responses and clinical outcomes in patients with allergic diseases.

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REFERENCES

1. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008; 63 (Suppl 86):8-160.
2. Akdis C, Blaser K. Mechanisms of allergen-specific immunotherapy. *Allergy* 2000; 55(6):522-30.
3. Nelson H. Advances in upper airway diseases and allergen immunotherapy. *J Allergy Clin Immunol* 2003; 111(3 Suppl):793-8.
4. Cox L, Calderon MA. Subcutaneous specific immunotherapy for seasonal allergic rhinitis: a review of

- treatment practices in the US and Europe. *Curr Med Res Opin* 2010; 26(12):2723-33.
5. Ebner C, Siemann U, Bohle B, Willheim M, Wiedermann U, Schenk S, et al. Immunological changes during specific immunotherapy of grass pollen allergy: reduced lymphoproliferative responses to allergen and shift from TH2 to TH1 in T-cell clones specific for Phl p 1, a major grass pollen allergen. *Clin Exp Allergy* 1997; 27(9):1007-15.
 6. Larché M, Akdis CA, Valenta R. Immunological mechanisms of allergen-specific immunotherapy. *Nature Reviews Immunology* 2006; 6(10):761-71.
 7. Leatherman BD, Owen S, Parker M, Chadwick S, Fornadley JA, Colson D, et al. Sublingual Immunotherapy: Past, present, paradigm for the future? A review of the literature. *Otolaryngol Head Neck Surg* 2007; 136(3 Suppl):1-20.
 8. Rolinck-Werninghaus C, Kopp M, Liebke C, Lange J, Wahn U, Niggemann B, et al. Lack of detectable alterations in immune responses during sublingual immunotherapy in children with seasonal allergic rhinoconjunctivitis to grass pollen. *Int Arch Allergy Immunol* 2005; 136(2):134-41.
 9. Bufe A, Ziegler-Kirbach E, Stoeckmann E, Heidemann P, Gehlhar K, Holland-Letz T, et al. Efficacy of sublingual swallow immunotherapy in children with severe grass pollen allergic symptoms: a double-blind placebo-controlled study. *Allergy* 2004; 59(5):498-504.
 10. Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006; 118(2):434-40.
 11. Incorvaia C, Fuiano N, Leo G. Sublingual immunotherapy for treating respiratory allergy: a review on its effectiveness and suitability. *Clin Ter* 2010; 161(6):543-7.
 12. Bethesda M. Guidelines for the diagnosis and management of asthma: National Institute of Health, US Department of Health and Human Services: National Heart and Blood Institute. 2007
 13. Marshall P, Valenta R. Allergic Rhinitis. *N Engl J Med* 2005; 353(18):1934-44.
 14. Mösges R, Graute V, Christ H, Sieber HJ, Wahn U, Niggemann B. Safety of ultra-rush titration of sublingual immunotherapy in asthmatic children with tree-pollen allergy. *Pediatr Allergy Immunol* 2010; 21(8):1135-8.
 15. Passalacqua G, Guerra L, Pasquali M, Lombardi C, Canonica GW. Efficacy and safety of sublingual immunotherapy. *Ann Allergy Asthma Immunol* 2004; 93(1):3-12.
 16. Moingeon P, Batard T, Fadel R, Frati F, Sieber J, Van Overtvelt L. Immune mechanisms of allergen-specific sublingual immunotherapy. *Allergy* 2006; 61(2):151-65.
 17. Clavel R, Bousquet J, André C. Clinical efficacy of sublingual-swallow immunotherapy: a double-blind, placebo-controlled trial of a standardized five-grass-pollen extract in rhinitis. *Allergy* 1998; 53(5):493-8.
 18. Bousquet J, Schünemann HJ, Bousquet PJ, Bachert C, Canonica GW, Casale TB, et al. How to design and evaluate randomized controlled trials in immunotherapy for allergic rhinitis: an ARIA-GA(2) LEN statement. *Allergy* 2011; 66(6):765-74.
 19. Wilson DR, Lima MT, Durham SR. Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. *Allergy* 2005; 60(1):4-12.
 20. Lima MT, Wilson D, Pitkin L, Roberts A, Nouri-Aria K, Jacobson M, et al. Grass pollen sublingual immunotherapy for seasonal rhinoconjunctivitis: a randomized controlled trial. *Clin Exp Allergy* 2002; 32(4):507-14.
 21. Pradaliere A, Basset D, Claudel A, Couturier P, Wessel F, Galvain S, et al. Sublingual-swallow immunotherapy (SLIT) with a standardized five-grass-pollen extract (drops and sublingual tablets) versus placebo in seasonal rhinitis. *Allergy* 1999; 54(8):819-28.
 22. Bufe A, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L, et al. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol* 2009; 123(1):167-73.
 23. Wüthrich B, Bucher Ch, Jörg W, Bircher A, Eng P, Schneider Y, et al. Double-blind, placebo-controlled study with sublingual immunotherapy in children with seasonal allergic rhinitis to grass pollen. *J Invest Allergol Clin Immunol* 2003; 13(3):145-8.
 24. Agostinis F, Tellarini L, Canonica GW, Falagiani P, Passalacqua G. Safety of sublingual immunotherapy with a monomeric allergoid in very young children. *Allergy* 2005; 60(1):133.
 25. Casanovas M, Guerra F, Moreno C, Miguel R, Marañón F, Daza JC. Double blind, placebo-controlled clinical trial of preseasonal treatment with allergenic extracts of Olea europea pollen administered sublingually. *J Invest Allergol Clin Immunol* 1994; 4(6):305-14.

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26. Bousquet J. Sublingual immunotherapy: from proven prevention to putative rapid relief of allergic symptoms. *allergy* 2005; 60(1):1-3.
27. Pfaar O, Barth C, Jaschke C, Hörmann K, Klimek L. Sublingual Allergen-Specific Immunotherapy Adjuvanted with Monophosphoryl Lipid A: A Phase I/IIa Study. *Int Arch Allergy Immunol* 2011; 154(4):336-4.