

EFFICACY OF LOW DOSE SUBLINGUAL IMMUNOTHERAPY IN CHILDHOOD ASTHMA

Ariyanto Harsono

ABSTRACT

Background: Evidences begin to accumulate that high dose sublingual immunotherapy is as effective as subcutaneous immunotherapy. Since the capacity of sub lingual area is similar whether the dose is high or low, the efficacy of low dose SLIT may be important to be studied. **Objective:** To investigate the efficacy of low dose sublingual immunotherapy in childhood asthma. **Methods:** Parents signed informed consent after receiving information of the study prior to enrollment. Patients were moderate asthma aged 6-14 years with disease onset of less than 2 years and PEFr variability of more than 15%. Patients were randomly allocated into Group A receiving subcutaneous immunotherapy, Group B receiving low doses sublingual immunotherapy and Group C receiving conventional asthma therapy. Randomization was stratified into two strata according to age, 6-11 years or more than 11 years. Within each stratum, patients were randomized in block of three in each group using systematic random sampling. At the end of three month, lung function tests were performed again. The primary outcome was PEFr variability at the end of the study. Ethical clearance was approved by Ethical Committee of Dr. Soetomo Hospital Surabaya. **Results:** Distribution of variants as represented by sex, age eosinophil count and total IgE concentration were normal in the three groups. PEFr variability decreased significantly from 16.97 ± 0.81 to 8.50 ± 5.08 and 17.0 ± 0.87 to 8.40 ± 4.72 in group receiving SIT and SLIT respectively ($p < 0.05$), but decreased not significantly from 17.00 ± 0.83 to 10.82 ± 0.541 in control group ($p > 0.05$). **Conclusion:** Low dose SLIT is as efficacious as SIT in the treatment of mild asthma in children

Keywords: childhood asthma, sublingual immunotherapy, subcutaneous immunotherapy, efficacy.

Abbreviations used:

PEFR: Peak Expiratory Flow Rate
SIT: Sub cutaneous immunotherapy.
SLIT: Sub lingual immunotherapy

INTRODUCTION

Immunotherapy is applied to asthmatic patients who are sensitive to inhalant allergen. In patients sensitive to house dust, house dust extract is used accordingly. The World Health Organization and various allergy, asthma and immunology throughout the world met on January 1997, in Geneva to write guidelines for allergen immunotherapy. The editor and panel members reached a consensus about the information to include in the WHO position paper "Allergen immunotherapy as a therapeutic vaccines for allergic diseases" (Bousquet, 1998). Meta analysis indicate the efficacy of subcutaneous immunotherapy in the management of asthma (Finogold, 2000). In recent year, sublingual immunotherapy with high doses of house dust extract shows as effective as subcutaneous immunotherapy (Frew, 1999). The safety profile, assessed in clinical trials and post marketing surveillance studies is

satisfactory. Sublingual immunotherapy is now accepted by the World Health Organization as a valid alternative to the subcutaneous route also in children. Although the long lasting efficacy has been recently documented for the sublingual route, several point still need to be elucidated, including optimal dosage (Conanica, 2003). We conducted a study to determine whether low dose of sublingual immunotherapy is as effective as subcutaneous immunotherapy.

METHODS

Patients

Between January, 2003 and Augustus, 2003, we recruited patients aged 6-14 years who had had symptoms of moderate Asthma with the onset of less than 2 years. Moderate Asthma was defined by wheeze, cough, dyspnoea or chest tightening at least once per week, but not as often as daily, had reversible airway obstruction, defined as PEFr variability of more than 15% between the two highest and two lowest peak expiratory flow rates during 14 days. PEFr Variability $> 15\%$ without bronchodilator, calculated out of 14 days period after discarding the first three days values, was formulated as :

*Department of Child Health
Airlangga University School of Medicine
Dr Soetomo Teaching Hospital, Surabaya*

$$\text{PEFR Variability} = \frac{(A1+A2)-(B1+B2)}{(A1+A2)} \times 100\%$$

A1 = highest PEFR
 A2 = second highest PEFR
 B1 = lowest PEFR
 B2 = second lowest PEFR

Exclusion criteria were symptoms of Asthma or Asthma treatment for more than 2 years before entry to the study, more than 30 days of treatment with glucocorticoid, or more than one depot glucocorticoid injection per year, a decision by a treating physician that delay of inhaled glucocorticoid treatment was inappropriate, or another clinically significant disease. Patients or their parents gave written informed consent, and local institutional review boards approved the study.

Study Protocol

Parents signed informed consent after receiving information of the study prior to enrollment. Patients were randomly allocated into Group A receiving subcutaneous immunotherapy, Group B receiving low dose sublingual immunotherapy and Group C receiving conventional asthma therapy. Randomization was stratified into two strata according to age, 6-11 years or more than 11 years. Within each stratum, patients were randomized in block of three in each group using systematic random sampling. Specific subcutaneous immunotherapy was house dust extract with the doses of 0.1 ml, 0.15 ml, 0.22 ml, 0.32 ml, 0.48 ml, 0.72 ml, 1 ml of 0.05 mg/ml solution once, continued with 0.1 ml, 0.15 ml, 0.22 ml, 0.32 ml, 0.48 ml, 0.72 ml, 1 ml of 0.5 mg/ml solution with the interval of 1 week, continued with maintenance dose of 0.1 ml of 5mg/ml solution three weeks interval. Low doses Sublingual immunotherapy was Novocare sublingual extract with the doses of 2 drops, 4 drops, 6 drops, 8 drops, 10 drops,

12 drops, 14 drops of first strength solution, continued with 2 drops, 4 drops, 6 drops, 8 drops, 10 drops, 12 drops, 17 drops of second strength solution with the interval of 1 week, continued with 2 drops of third strength solution with the interval of 3 weeks. At the end of three month, lung function tests were performed again. The primary outcome was PEFR variability at the end of the study. Ethical clearance was approved by Ethical Committee of Dr. Soetomo Hospital Surabaya.

Sample Size

To meet normal distribution, sample size was determined 30 patients in each group.

Statistical Analysis

The Wilcoxon signed rank test was applied to analyze the data comparing results of PEFR variability at baseline and at post treatment. To analyze the data between group A, B, and C, the Mann-Whitney U Test was used. Differences were considered to be at the $p < 0.05$ levels

RESULTS

Distribution of sex, age, eosinophil count and total IgE concentration were normal in the three groups, $p=0.870$, 0.964 , 0.593 , 0.478 respectively (Figure 1).

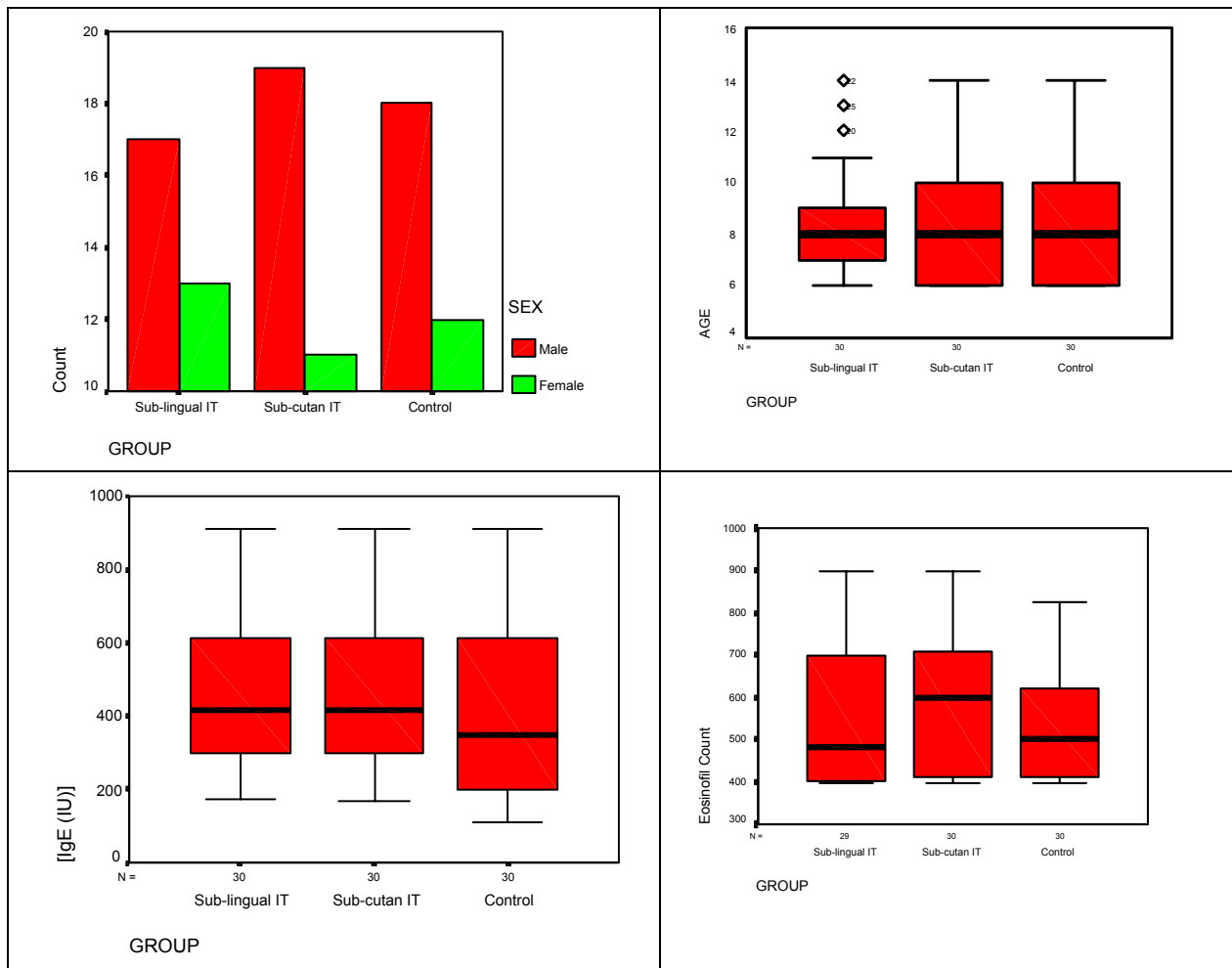


Figure 1. Homogeneity of variants between groups

PEFR variability decreased from 16.97 ± 0.81 to 8.50 ± 5.08 in group receiving SIT ($p < 0.05$), and from 17.0 ± 0.87 to 8.40 ± 4.72 in group receiving SLIT

($p < 0.05$), but decreased not significantly from 17.00 ± 0.83 to 10.82 ± 0.541 in control group ($p > 0.05$) (Figure 2).

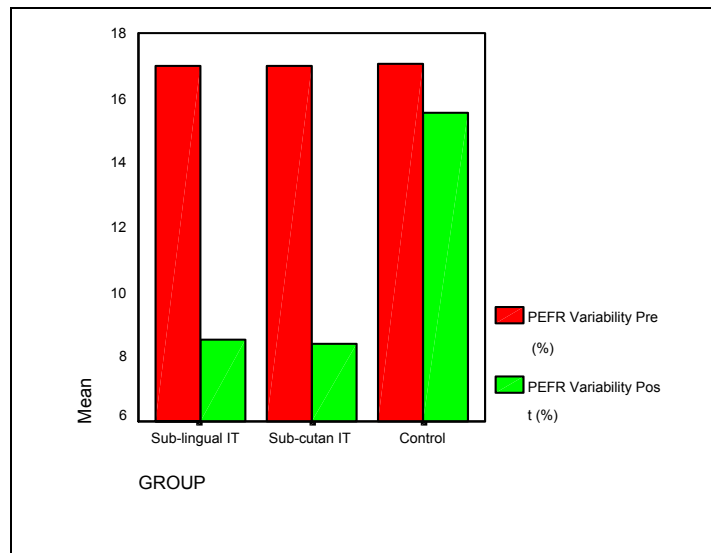


Figure 2. PEFR variability pre and post treatment.

No medication adverse effects were observed in the three groups.

DISCUSSION

This study compared the efficacy of sublingual immunotherapy versus subcutaneous immunotherapy with house dust extract in children with mild asthma treated with conventional treatment. The control group was children with mild asthma treated with conventional treatment. The major outcome, indicating efficacy of treatment, was PEFR variability. The results of this study showed a clinical benefit of sublingual immunotherapy with low doses of allergen in the term PEFR variability parameter. A significant improvement was also observed in SIT group compared with control group.

Low dose regimens for desensitization have been widely used by mainstream allergists, although their effectiveness is disputed. In the last few years, there has a resurgence of interest in the possibility of achieving desensitization by giving highdoses of allergen topically. Most studies of human SLIT have been small but show fairly consistent benefits on symptom scores, with few systemic side effects. (Frew, 2001, Frew, 2003).

The theoretical basis for sublingual immunotherapy rests on two concepts. First: it is proposed that allergens given through the mucosal surface are handed differently from allergens given parenterally, leading to a special immunologic tolerance. Second: it is proposed

that giving the allergen directly to the target organ may lead to downregulation of local effector responses. Clearly, both mechanisms could apply when the allergen is given directly to the target organ, eg, nasal immunotherapy, whereas indirect routes, including SLIT, rely on the first of these propositions. From a theoretic perspective, the mucosal surface has to deal with regular exposure to a wide range of innocuous material, and its default response is set to nonresponse (Holt, 1989). This contrasts with the internal immune defenses, which are not normally exposed to foreign material because of the barrier epithelial defences. Anything that reaches the internal defences must have breached the external barriers and can therefore be considered dangerous, whereas most material seen at the surface may not be going anywhere and can be ignored. The more complex question regards what determines that some foreign material will elicit an immune response at the mucosal surface, despite being incapable of invasion, and furthermore why some materials elicit allergic-type responses while others drive more conservative, IgG responses. This issue lies at the heart of what makes an allergen allergenic and also determines whether we may be able to achieve desensitization by mean of the topical route. Experimental support for this theory is available. It has been shown that locally administered allergen is taken up by mucosal dendritic cells, and at least in nonsensitized mice, the allergen is then presented to T cells together with IL-12, thereby biasing the reponse toward a Th1 profile and away from the pro-IgE Th2 profile (van-Willem, 1994). It is less clear whether this mechanism can suppress established allergic responses, which is the situation that we would wish to achieve

with SLIT. It is clear, however, when allergen is given by the sublingual route to allergic human subjects, that the allergen is retained in the buccal region much longer than if the allergen is simply placed in the mouth and then swallowed, suggesting that allergens are indeed taken up locally after sublingual administration (Bagnasco, 1997). In contrast to animal models, the immunologic response to SLIT in human studies has been relatively modest. Some changes have been found in skin sensitivity, but most studies have not found any change in systemic parameters, such as specific IgE, specific IgG, or T cell-cytokine balance (La Rosa, 1999). A study using *Parietaria judaica* allergen administered sublingually in patients with allergic *rhinoconjunctivitis* showed a significantly increase in specific IgG4 in treated group (Tari, 1990).

Giving the allergen by mouth rather than by injection should increase compliance of the patients to follow the treatment procedure, decrease the cost of SIT by reducing the need for medical and nursing time, as well as cost of consumables, such as syringes and needles.

CONCLUSION

Low dose SLIT is as efficacious as SIT in the treatment of mild asthma in children

REFERENCES

- Bousquet J, Lockey R, Malling HJ, 1998. WHO panel members. Allergen immunotherapy: Therapeutic vaccines for allergic diseases, A WHO position paper. J Allergy Clin Immunol, 102:658-62.
- Bagnasco M, Mariani G, Passalacqua G, 1997. Absorption and distribution kinetics of the major *Parietaria judaica* allergen (Par j 1) administered by non-injectable route to healthy human being. J Allergy Clin Immunol, 1997, 100: 122-9
- Conanica GW, Passalacqua G, 2003. Non injection routes of immunotherapy. J Allergy Clin Immunol, 111: 437-48.
- Finegold I, 2001. Analyzing meta-analyses of specific immunotherapy in the treatment of asthma. Ann Allergy Asthma Immunol, 87:33-37,
- Frew AJ, White PJ, Smith HE, 1999. Sublingual Immunotherapy. J Allergy Clin Immunol, 104:267-70.
- Frew AJ, Smith HE, 2001. Sublingual immunotherapy. Allergy Clin Immunol, 104: 441-444.
- Frew AJ, 2003. Immunotherapy of Allergic disease. J Allergy Clin Immunol, 111: S172-179.
- Holt PG, McMenamin C, 1989. Defence against allergic sensitization in healthy lung: the role of inhalation tolerance. Clin Exp Allergy, 19: 55-62.
- La Rosa M, Ranno C, Andre C, Crart F, Tosca MA, Canonica GW, 1999. Double-blind placebo-controlled evaluation of sublingual-swallowed immunotherapy with standardized *Parietaria judaica* extract in children with rhinoconjunctivitis. J Allergy Clin Immunol, 104:425-32.
- Tari MG, Mancino M, Monti G, 1990. Efficacy of sublingual immunotherapy in patients with rhinitis and asthma due to house dust mite. A double-blind study. Allergol Immunopathol, 18: 277-84.
- Van-Willem EJ, van Hoogstraam IM, Breve J, Scheper RJ, Krat G, 1994. Dendritic Cells of the oral mucosa and the induction of oral tolerance. Immunology, 83: 128-32.