



Comparative analysis of sublingual immunotherapy medicines for adherence and clinical outcomes

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Abstract

Objective Sublingual immunotherapy (SLIT) has been considered as an effective and safe alternative to the subcutaneous route. However, different modalities and administration methods may lead to significant changes in their adherence and clinical outcomes. The purpose of this study was to compare the adherence, efficacy, and side effects of SLIT medicines: SLITone[®], Lais[®], and Staloral[®].

Subjects and methods Eighty-two patients suffering from AR symptoms and sensitized only to house dust mite allergens were included. The patients were treated with SLITone[®], Lais[®], or Staloral[®]. Treatment outcomes related to efficacy, dropout rate, and adverse events were evaluated. The visual analogue scale (VAS) including sneezing, rhinorrhea, nasal obstruction, and itching was scored from 0 (normal) to 10 (severe), before and after SLIT. Dropout rate was defined as the number of patients who discontinue SLIT of oneself compared to the number of patients who receive SLIT.

Results All of the nasal symptoms and total symptom scores were significantly decreased in SLITone[®], Lais[®], and Staloral[®]. Furthermore, there were significant difference in the improvement of rhinorrhea and TNSS between SLITone[®] and Staloral[®] group ($p=0.011$ and $p=0.001$, respectively). Four patients out of 26 in SLITone[®] group, 4 patients out of 30 in Lais[®] group, and 11 patients out of 26 in Staloral[®] group have stopped SLIT of themselves. The dropout rate was significantly higher in the Staloral[®] group than other two groups ($p=0.024$). Only one patient complained adverse reaction such as swelling of mouth floor in the Staloral[®] group.

Conclusion Although all three SLIT medicines are effective in improving AR symptoms, the adherence to SLIT assessed in accordance with dropout rate was the lowest in the Staloral[®].

Keywords Sublingual immunotherapy · Rhinitis · Allergic · Medication adherence · Treatment outcome · Drug-related side effects · Adverse reactions

Introduction

Allergic disease is a condition caused by allergen-induced unfavorable immune responses and contains various manifestations in different organs [1]. Allergic rhinitis (AR) is

characterized by sneezing, nasal obstruction, rhinorrhea and itching of the nose [2]. It is the most common type of allergic disease and significantly affects daily activity, work efficiency, learning, sleep, and quality of life [1, 2]. Although treatment of AR is based on symptom management through allergen avoidance and pharmacotherapy including oral H₁ antihistamine and intranasal corticosteroids, symptomatic drugs cannot eradicate and modify the natural course of AR [3–5].

Immunotherapy treats allergic diseases by changing the response to allergen exposure through immunological tolerance mechanism [6, 7]. Allergen-specific products are used for immunotherapy and manufactured from major allergen such as pollens and house dust mite cultures [6]. There are many routes to induce immunological tolerance to allergen. Subcutaneous allergen immunotherapy (SCIT) was first

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introduced in 1911 and has been shown to be highly effective, particularly for seasonal pollinosis but also for perennial disease in patients with house dust mite allergy [8, 9]. However, SCIT has some limitation such as the requirements for frequent hospital visits, injection site pain, and the risk of rare serious adverse drug reactions such as anaphylaxis [10]. Therefore, sublingual allergen immunotherapy (SLIT) was developed to overcome these drawbacks.

SLIT has been considered as an effective and safe alternative to the subcutaneous route, in which the allergen is administrated by holding antigen drops or tablets under the tongue using mouth floor mucosal immune system [11]. Furthermore, there are different modalities and administration methods for delivering SLIT. SLIT may deliver allergenic proteins in liquid preparations or tablet forms with and without a variable escalation phase. However, there are no reports of studies directly comparing the efficacy and safety for the treatment of AR according to the various SLIT medicines. This study was designed to compare the efficacy, adherence, and side effects of various SLIT medicines: SLITone[®], Lais[®], and Staloral[®].

Subjects and methods

Subjects

SLIT medicines were applied to the patients who were diagnosed with AR and a sensitization to house dust mite (HDM) including *Dermatophagoides pteronyssinus* (DP) and *Dermatophagoides farina* (DF). Sensitization to DP and DF was defined as a mean wheal diameter for DP and DF that was greater than or equal to that of histamine in the absence of any reaction to saline in a skin-prick test. Exclusion criteria were pregnant or lactating women, subjects with immunologic or hematological disease, and subjects who receive chronic corticosteroid or beta-blocking treatments.

Immunotherapy

The patients were treated with SLITone[®] (ALK-Abello, Horsholm, Denmark), Lais[®] (Lofarma SpA, Milan, Italy), or Staloral[®] (Stallergenes, Antony, France) between January 2000 and December 2015. SLITone[®] is a biologically standardized allergenic extract presented in a single-dose container containing 0.2 ml of extractable volume [12]. SLITone[®] was directly initiated by the administration of single-dose containers directly under the tongue. Lais[®] is soluble tablet of monomeric carbamylated allergoid [13]. The patient took during the first 4 days progressive quantities of tablets (300–600–900–1200 AU) and continued with 1000 AU tablets taken two times a week at maintenance phase. The Staloral[®] is a liquid solution in a vial endowed with a

dosage pump [14]. The HDM extracts were used in the form of drops. During escalation phase in the initial treatment, the patient took daily increasing doses of 1–10 presses of 10 IR/mL solutions from days 1–6 and 1–8 presses of 300 IR/mL solutions from days 7–11. After reaching the maintenance dose, the patient took the allergen extract (8 presses of 300 IR/mL solution) 3 days/week during the maintenance phase. The drops or tablets had to be maintained under the tongue for 2–3 min before being swallowed.

Data analysis

All of the patients were asked to complete questionnaires for the symptoms before and 2 years after SLIT. A total of four nasal symptoms were assessed including sneezing, rhinorrhea, nasal obstruction, and itching. Symptoms were scored using a visual analogue scale (VAS) ranging with a range of 0–4, 0 being no symptoms and 10 being worst severe symptoms. The total nasal symptom score (TNSS) was defined as the sum of all the nasal symptom scores. The adherence to SLIT was assessed in accordance with dropout rate which was defined as the number of patients who discontinued SLIT of oneself compared to the number of patients who enrolled in SLIT. The adverse events related to SLIT during whole period were recorded by patients.

Data were presented as mean $\pm$ standard error of the mean. Statistical significance was assessed by one-way repeated analysis of variance (ANOVA) and Kruskal–Wallis test using the SPSS software version 20.0 (SPSS Inc., Chicago, IL, <http://www.spss.com>). A p value < 0.05 was considered to indicate statistical significance.

Ethics statement

This study protocol was approved by the Institutional Review Board of Pusan National University Hospital (PNUHIRB 1804-013-066). However, written informed consent was not obtained from each parent prior to the patient's participation in the study because of retrospective chart reviews.

Results

Study population

A total of 82 patients were enrolled in the study, including 61 males and 21 females from 5 to 62 years of age, with mean age of 19.7 years. Among 82 patients, 26 patients were treated with SLITone[®], 30 patients were treated with Lais[®], and 26 patients were treated with Staloral[®].

Mean age was 16.4 years, 28.3 years, and 13.0 years in SLITone[®], Lais[®], and Staloral[®] group, respectively. The percentage of male was 73.1% in SLITone[®] group, 73.3%

in Lais[®] group, and 76.9% in Staloral[®] group, respectively. The mean treatment duration was 26.8 months in SLITone[®] group, 28.9 months in Lais[®] group, and 24.6 months in Staloral[®] group, respectively. The percentage of comorbid diseases such as atopic dermatitis or asthma and family history of AR was 7.7% and 19.2%, 13.3% and 23.3%, and 15.4% and 30.8% in the SLITone[®], Lais[®], and Staloral[®] group, respectively. However, there were no significant differences in age, sex, treatment duration, comorbid disease, and family history of AR among the groups (Table 1).

Table 1 Demographic and clinical characteristics

Parameters	SLITone	Lais	Staloral	<i>p</i> value
Sex (M/F)	19/7	22/8	20/6	1.000
Age (years)	16.4 ± 11.5	28.3 ± 10.9	13.0 ± 9.0	0.052
Tx duration (months)	26.8 ± 13.8	28.9 ± 10.7	24.6 ± 11.1	0.396
Comorbid disease	2 (7.7)	4 (13.3)	4 (15.4)	0.766
Family history of AR	5 (19.2)	7 (23.3)	8 (30.8)	0.589

Data are expressed as the number (percentage) except age, treatment duration (mean ± standard error of the mean)

AR allergic rhinitis, *F* female, *M* male, *Tx* treatment

Efficacy

All of the nasal symptoms, including sneezing (all $p < 0.01$), rhinorrhea (all $p < 0.001$), nasal obstruction (all $p < 0.001$), and itching (all $p < 0.05$) were significantly decreased in the SLITone[®], Lais[®], and Staloral[®] group (Fig. 1). The initial TNSS were 22.1, 24.0, and 13.2, and they significantly decreased to 6.8, 11.1, and 4.3 after follow-up in the SLITone[®], Lais[®], and Staloral[®] group, respectively (all $p < 0.001$) (Fig. 2). Furthermore, there was significant difference in the improvement of rhinorrhea and TNSS between SLITone[®] and Staloral[®] group ($p = 0.011$ and $p = 0.001$, respectively). However, there were no significant differences in sneezing, nasal obstruction, and itching among three groups (Table 2).

Adherence

The dropout rate was calculated and substituted for adherence in this study. Among the 82 enrolled patients, 19 patients stopped SLIT of themselves and dropout rate was 23.2%. Four patients in the SLITone[®] group, 4 patients in the Lais[®] group, and 11 patients in the Staloral[®] group dropped out. Therefore, the dropout rate was 15.4%, 13.3%, and 42.3% in the SLITone[®], Lais[®], and Staloral[®] group, respectively. The dropout rate was significantly higher in

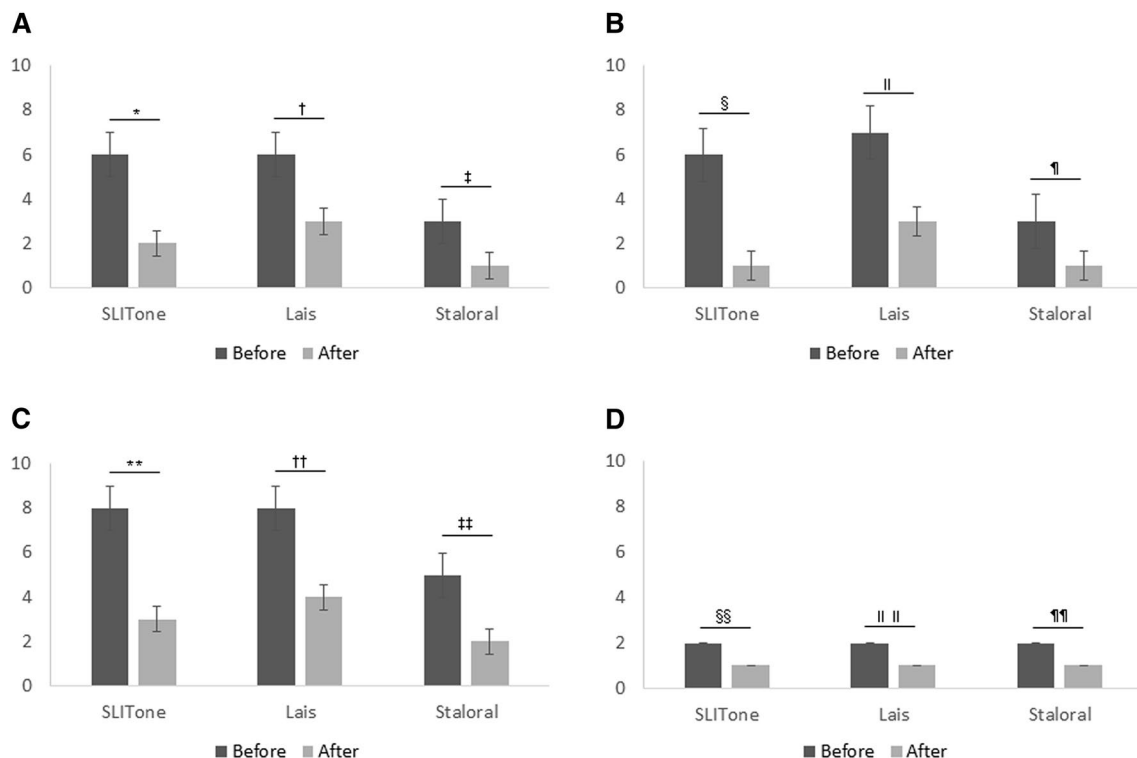


Fig. 1 Effect of sublingual immunotherapy on allergic rhinitis symptom. SLITone[®], Lais[®], and Staloral[®] significantly decreased sneezing (a), rhinorrhea (b), nasal obstruction (c), and itching (d). *, †, §, ‖, ¶, **, ††, ‡, ‡‡, §§, ‖‖, ¶¶ $p < 0.001$, ‡‡, ‡‡‡, §§ $p = 0.017$, ‡ $p = 0.002$

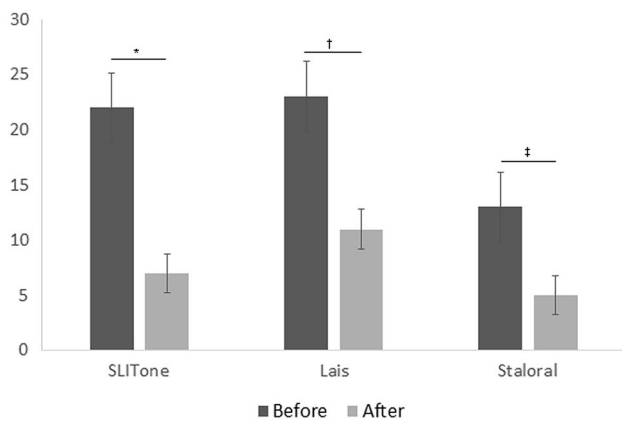


Fig. 2 Effect of sublingual immunotherapy on total nasal symptom scores. SLITone®, Lais®, and Staloral® significantly decreased total nasal symptom scores. *,†,‡ $p < 0.001$

the Staloral® group than other two groups ($p = 0.024$). The reasons for quitting SLIT were determined by a telephone survey. The lack of efficacy was the most common reason, followed by difficulty to use, and economic burden (Table 3).

Adverse events

No patients had systemic adverse effects or anaphylaxis related to the SLIT. However, 1 in the Staloral® group of 82 enrolled patients (1.2%) complained of local side effects of itching and swelling in the mouth floor but resolved without treatment.

Discussion

Allergen-specific immunotherapy has been recognized as the only curable treatment for AR and may prevent AR from evolving to asthma [15]. Both SCIT and SLIT, in contrast to anti-allergic drugs, have been shown to have disease-modifying properties with clinical benefits that can persist for 2–3 years after discontinuation of immunotherapy [16]. Although SCIT has been the gold standard

Table 3 Dropout rate among sublingual immunotherapy medicines

	SLITone	Lais	Staloral	<i>p</i> value
Complete	22	26	15	0.024
Dropout	4 (15.4)	4 (13.3)	11 (42.3)	
Total	26	30	26	

Data are expressed as the number (percentage)

for the management of AR, SLIT has emerged as a novel, effective, and safe alternative [17–19]. The Cochrane databases for seasonal disease implied that SCIT might be more effective than SLIT although both SCIT and SLIT were effective in reducing symptoms and requirement for rescue medication in patients with AR [20, 21]. However, on the grounds of tolerability and safety, indirect comparisons favored SLIT over SCIT. SCIT can be associated with anaphylaxis, necessitating close supervision. For SLIT, several studies showed that systemic side effects are rare, anaphylaxis is extremely rare, and SLIT can be safely self-administrated [22–24].

Allergen-specific immune responses in SLIT were shown to be mediated by resident dendritic cells (DCs) within oral mucosal tissue [25]. When antigens are administered sublingually, phagocytosis by antigen-presenting cells (APCs) occurs in the oral mucosa within 15–30 min [26]. Most of these APCs are DCs, called oral Langerhans cells, which phagocytose antigens via IgE-FcεRI [27]. Furthermore, upregulation of regulatory T cells and increases in several soluble factors such as transforming growth factor-β and interleukin-10 play critical roles in alleviating allergic inflammation through SLIT [28]. However, the use of different SLIT modalities such as drop or tablet forms and various administration methods including conventional escalation regimen with a buildup phase followed by a maintenance regimen and once-daily SLIT without escalation has been approved. Although these differences in the modalities and administration methods lead to significant changes in their adherence and clinical outcomes, there were no studies comparing the adherence and efficacy among the various SLIT regimens.

Table 2 Comparative analysis of treatment outcomes among sublingual immunotherapy medicines

Symptoms	SLITone vs. Lais vs. Staloral	SLITone vs. Lais	SLITone vs. Staloral	Lais vs. Staloral
Sneezing	0.087	0.362	0.051	0.106
Rhinorrhea	0.025	0.548	0.011	0.056
Nasal obstruction	0.056	0.240	0.068	0.177
Itching	0.562	0.274	0.567	0.697
TNSS	0.006	0.115	0.001	0.099

Data are expressed as the *p* value

TNSS total nasal symptom score

This study showed all of the nasal symptoms scores and TNSS were significantly decreased in the SLITone[®], Lais[®], and Staloral[®] group. Furthermore, the level of symptom improvement in the rhinorrhea and TNSS was higher in the SLITone[®] than Staloral[®] group. Although SLITone[®] is a once-daily same dosage without escalation, Lais[®] and Staloral[®] have an escalation period. Lais[®] and Staloral[®] are administrated by a rush escalation regimen with an initial 4-day buildup phase and 11-day buildup phase followed by a maintenance regimen, respectively. Therefore, we may speculate that high concentration of allergen extracts applied every day for SLITone[®] treatment improves its clinical effects. However, there was no difference among three groups in the adverse events. No patients had systemic adverse effects and only one patient had local side effects of itching and swelling in the mouth floor but resolved without treatment.

Patient adherence is a challenge that impacts the treatment of all chronic illnesses and adherence to immunotherapy has also been raised as a potential issue [29]. Although adherence to immunotherapy is essential for effective AR management, adherence to SCIT as well as SLIT is generally poor, which leads to a reduction of clinical efficacy in the long term [30, 31]. Therefore, evaluation of the dropout rate and reasons for dropout is important in the improving adherence to immunotherapy in daily clinical practice. Generally, SLIT had higher preference from the patient's perspective than SCIT due to the convenience of home IT administration [32].

A meta-analysis of the dropout rate for SLIT was performed and a composite dropout rate of 14% was observed [29]. Although patients' age, type of allergic diseases, number of sensitization, type of allergen used for IT, allergen formulation (drop or tablets), treatment duration, and treatment schedule (perennial, preseasonal, and co-seasonal) may affect the dropout rate, there were no differences in the dropout rate in the age, sensitizations, formulation, schedule [29]. However, better adherence was observed in patients with AR in comparison with patients with both asthma and AR [29]. Furthermore, common barriers to adherence include inconvenience, efficacy concerns, and the cost of treatment [33–35]. Previous study showed inconvenience of clinic visits and cost of therapy were found to be most common barriers to SLIT [36]. In this study, the dropout rates were 15.4% and 13.3% in the SLITone[®] and Lais[®] group, respectively, which were similar to previous studies. However, the dropout rate of Staloral[®] group was 42.3%, which was highest in all three groups. The poor adherence to Staloral[®] concerning the highest dropout rate might be related to the complexity of administration method by exerting pressure on the pump during the buildup and maintenance phase, leading to a significant reduction of in clinical efficacy. Furthermore, the lack of efficacy and difficulty to use was the most common

reasons for discontinuing SLIT. Therefore, better clinical efficacy and the ease of administration without schedule changes during the buildup period may underlie the greater patients' satisfaction in the SLITone[®] group.

The limitations of the current study are the relatively limited number of patients and its retrospective designs. The objective outcomes including immunological parameters were not evaluated. Therefore, additional prospective studies with a larger sample size and investigation of objective outcomes are needed to confirm our findings.

Conclusion

Although all three SLIT medicines are effective in improving AR symptoms, the adherence was the lowest in the Staloral[®]. Therefore, we should consider the medication adherence when prescribing SLIT medicines, especially Staloral[®] for successful treatment outcomes.

Compliance with ethical standards

Conflict of interest The authors have no funding, financial relationships, or conflicts of interest to disclose.

Ethical approval This study protocol was approved by the Institutional Review Board of Pusan National University Hospital (PNUHIRB 1804-013-066).

Informed consent Written informed consent was not obtained from each parent prior to the patient's participation in the study because of retrospective chart reviews.

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