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Sublingual immunotherapy in children with allergic rhinoconjunctivitis mono-sensitized to house-dust-mites: A double-blind-placebo-controlled randomised trial☆

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Summary
Background: Although sublingual immunotherapy (SLIT) has been demonstrated to be a safe and efficient treatment in children with seasonal allergic rhinitis (AR), there is little evidence on the efficacy of SLIT with house-dust-mite (HDM) extract in children with isolated perennial AR.
Objectives: We sought to assess the clinical efficacy and safety of HDM-SLIT in children with isolated allergic rhinitis-conjunctivitis mono-sensitized to HDM without asthma symptoms.
Methods: Twenty-two children (aged 5–10 years) with perennial AR and conjunctivitis symptoms mono-sensitized to Dermatophagoides pteronyssinus and Dermatophagoides farinae were enrolled. During a 2 months run-in period, symptom and medication scores, lung functions, bronchial hyperreactivity, nasal provocation and skin prick tests were evaluated.

Subjects were randomized to active or placebo using a double-blind method. A total of eighteen subjects were randomised to receive either active SLIT or placebo for 12 months. Daily

Abbreviations: AIT, Allergen immunotherapy; AR, Allergic rhinitis; Der P, *Dermatophagoides pteronyssinus*; Der f, *Dermatophagoides farinae*; HDM, House-dust-mite; ICS, Inhaled corticosteroids; mBHR, Methacholine-non-specific bronchial hyperreactivity; sNPT, Specific allergen-HDM nasal provocation; SCIT, Subcutaneous immunotherapy; SLIT, Sublingual immunotherapy.

☆ Part of the data of this study were included in a recent a cochrane meta-analysis: Calderon MA, Penagos M, Sheikh A, et al. Sublingual immunotherapy for treating allergic conjunctivitis. Cochrane Database Syst Rev 2011 (7):CD007685.

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symptom and medication scores, baseline lung functions, bronchial hyperreactivity, nasal provocation and skin prick tests were recorded and re-evaluated at the end of treatment.
Results: After one year of treatment, no significant differences were detected in the between groups and within group comparisons based on total rhinitis symptom/medication scores ($p > 0.05$). Skin reactivity to *Dermatophagoides pteronyssinus* was significantly reduced in HDM-SLIT compared to placebo group ($p = 0.018$). A significant reduction in nasal sensitivity was observed in SLIT group after one year treatment when compared to baseline ($p = 0.04$). Total conjunctivitis symptoms were reduced significantly in both active and lacebo group at the end of treatment compared to baseline. The proportion of patients with non-specific bronchial hyperreactivity increased to almost 3-fold in placebo group compared to baseline.
Conclusion: HDM-SLIT was not superior to placebo in reducing isolated rhinoconjunctivitis symptoms within 12 months of treatment. However, HDM-SLIT has a modulating effect on allergen-specific nasal and skin reactivity in isolated perennial AR children.
Clinical Trial Registration: The trial was registered at Anzctr.org.au number, ACTRN1261 3000315718.

Introduction

The prevalence of atopic diseases such as allergic rhinitis has increased in the past three decades in children and adults [1]. House-dust-mites (HDM) are common allergens worldwide and their major allergens *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* mites coexist in most geographical regions. Approximately 85% who have respiratory allergies are typically HDM-allergic [2]. Use of environmental control has been found to be of no effect in reducing asthma/rhinitis symptoms [3,4]. Treating with rescue medications and corticosteroids might control symptoms of allergic rhinitis but does not modify the natural course of the disease.

Allergen immunotherapy (AIT) is the treatment modality that might modify the course of allergic disease by preventing its exacerbation, reducing the risk of new allergic sensitizations and preventing the development of clinical asthma in children treated for seasonal allergic rhinitis (AR) [5].

Considerable amount of sublingual immunotherapy (SLIT) trials done in pollen induced AR showed successful treatment and long term effect of SLIT in suppressing AR symptoms and reduction of medication in children [6—8], while majority of HDM-SLIT trials in children and adults included more asthmatics patients, showing wide heterogeneity and has been shown to be more effective in asthmatics [9]. Few randomised control trials have evaluated efficacy of SLIT on specific individual components of airway disease such as conjunctivitis or rhinitis, rather global effect on allergic airways [10]. Studies evaluating the efficacy of SLIT in children with isolated perennial rhinitis and or conjunctivitis monosensitised to HDM are needed.

The aim of the present study was to evaluate the clinical efficacy of HDM-SLIT in children with isolated allergic rhinitis and/ conjunctivitis without asthma symptoms monosensitised to HDM by a prospective randomized, double-blind-placebo-controlled trial.

Methods

Study design

Children under 10 years of age suffering from persistent allergic rhinitis according to Aria [11] without asthma, caused by *D. pteronyssinus* and *D. farinae* (monosensitised) confirmed by skin prick and specific IgE were enrolled from allergy clinic. All eligible patients underwent an eight-week run-in period to evaluate their baseline clinical conditions by means of symptom/medication scores, lung functions, methacholine-non-specific bronchial hyperreactivity (mBHR), specific allergen-HDM nasal provocation (sNPT) and skin prick tests reactivity (SPT). Computer-generated randomization at the site of production of the medication was used for allocation of subjects to either active or placebo group in a double-blind manner. Randomization codes were kept securely to be accessed after the end of treatment.

Regular visits for clinical evaluation (symptom and medication score), safety assessment and spirometric pulmonary function tests were scheduled for every 3 months. At the end of one year, mBHR, NPT and SPT were re-evaluated.

The primary outcomes were symptom and medication scores for rhinitis and conjunctivitis. Secondary parameters were the assessment of SPT reactivity, new sensitizations, mBHR and specific-NPT. This study was conducted in accordance with the amended Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Medical Faculty of Marmara University with the approval number MAR-YC-2004-0147 and written consents were taken from all parents of children. The trial was registered at

Anzctr.org.au number, ACTRN12613000315718. The study design is summarized in Fig. 1.

Patients

Children aged between 5 and 10 years of both genders with the history of persistent HDM-induced allergic rhinitis according to ARIA guidelines [11] without asthmatic symptoms were enrolled. Diagnosis of childhood asthma was made according to the Global Initiative for Asthma guidelines [12]. All patients had to have skin test positivity only to HDM (*D. farinae or D. pteronyssinus* or both). Patients with asthma symptoms, polysensitization to other aeroallergens, negative sNPT to Der f1 and Der p1, which are the major allergen extracts of *D. farinae* and *D. pteronyssinus*, respectively, systemic immunologic disorders, previous use of allergen immunotherapy or using oral/inhaled corticosteroids for any reason were excluded from the trial. All patients were instructed to take avoidance measures against HDM including use of impermeable mattress and pillow covers.

Treatment

After an 8-week run-in period, patients were randomly selected to receive either active SLIT or placebo. The standardized extract used throughout the study had the same batch of equal proportions of 50%:50% mixture of *D. pteronyssinus* and *D. farinae* (STALORAL®, Stallergenes SA, Antony, France). The allergen extracts were graded into two concentrations: 10 and 300 IR/ml. The Der p1 and Der f1 contents of 1 ml of 100 IR allergen extract used in this study were 26.3 and 63.4 μg, respectively.

During the first 6 days, the patients took daily increasing doses in the form of 1—10 drops of the 10 IR/mL extract. For reaching maintenance dose, 300 IR/mL concentration vials were initiated on the 7th day starting from 1 and reaching to 8 drops on the 11th day. Following this, all patients took 8 drops sublingually 3 times a week for 12 months. Patients on placebo took their drops in the same manner. Drops were held under the tongue for two minutes and then swallowed, according to the manufacturer's instruction. The cumulative dose was approximately 44500 IR, which was equivalent to 11.7 mg of Der p1 and 28.2 mg of Der f1.

Symptoms and medication scores

Patients with/or their parents were instructed to keep a diary during the treatment period, for daily evaluation of symptoms according to a 4-point scoring system: 0 (no symptoms) to 3 (severe symptoms) for each rhinitis and conjunctivitis symptoms (sneezing, nasal discharge, itching and nasal obstruction; itchy, red and watery eyes). Asthma symptoms were recorded as wheezing, breathlessness, dyspnoea and cough. When necessary, patients were allowed to use antihistamines and/or intranasal corticosteroids. Other medications, such as long-lasting antihistamines, inhaled corticosteroid, and oral corticosteroids, were not permitted during the study. The patients had to record on the same diary card whenever they used medications (1 point: one puff of intranasal steroids per nostril, 2 points: one dose of antihistamine). The individual daily symptom and medication scores were recorded on a daily basis for the entire period of the study and the monthly mean scores were recorded at every 3-monthly study visit. Adverse reactions were classified according to the European Academy of Allergy and Clinical Immunology (EAACI) grading system [13].

Skin prick testing

Skin prick tests were performed with 20 common aeroallergens belonging to five groups; mites (*D. farinae*, *D. pteronyssinus*), molds (*Alternaria*, *Aspergillus mix*,

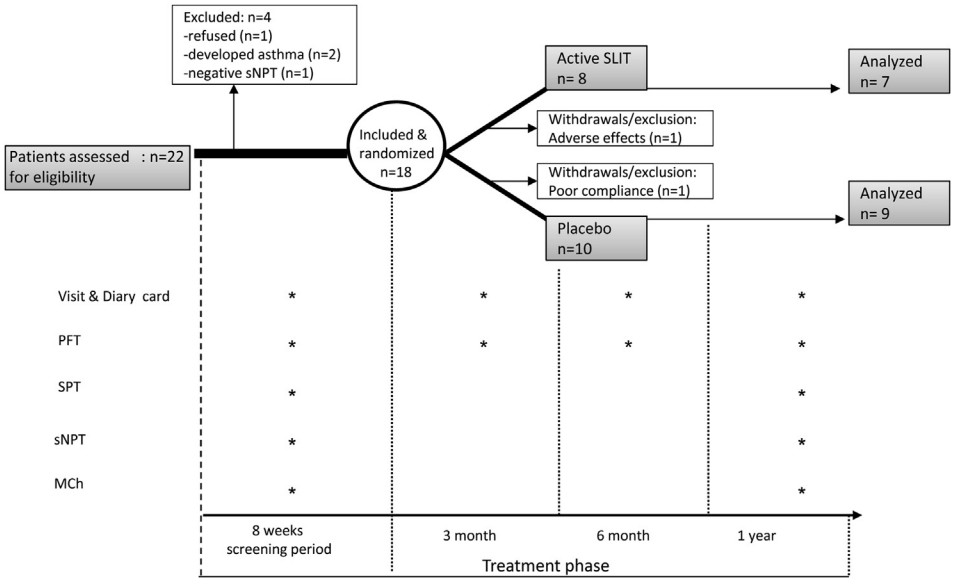

Figure 1 Randomized double-blind-placebo control CONSORT flow diagram of participants through each stage. SLIT, sublingual immunotherapy; PFT, pulmonary function test; SPT, skin prick test; sNPT, specific nasal provocation test; Mch, methacholine provocative test.

Penicillium mix, *Candida albicans*), pollens (*Betulaceeae*, *Aesculus Hippo*, *Olea Europea*, *Plantago*, *Artemisia*, *Parietaria*, *Secale cereale*, *Triticum vulgaris*, *Zea mays*, mixture of 5 grasses), animal dander (feathers mixture, cat hair, dog hair) and insects (cockroach) (Stallergenes, Antony, France). Histamine and saline were used as positive and negative controls, respectively. A drop of each allergen extract was placed on the volar surface of the left forearm and was penetrated with a separate lancet. After 15 min, the wheal reaction was measured as the mean of the longest diameter and the diameter perpendicular to it. A wheal diameter of at least 3 mm greater than those of the negative controls was considered as positive.

Nasal provocation test

The nasal provocation test was performed with Der p1 and Der f1 50/50 allergen extract (Stallergenes, Antony, France) using increasing concentrations of 0.1, 1, 10 and 100 IR/ml at the dosage of one puff (100 μl) into each nostril. A score was established (0: absent, 1: mild 2: moderate, 3: severe) for each of the rhinitis symptoms (sneezing, rhinorrhea, blocked nose and itching). If a total score of at least 8 was not reached with the lowest concentration after 10 min of application, the following doses were sequentially used. Nose clips were immediately applied after application of allergen and children were asked to breathe through their mouth for atleast 1 min to prevent the allergen being inhaled and ensure applied allergen is locally. The test was performed at the beginning and end of the treatment.

PFT and methacholine challenge

Lung functions were assessed with a spirometer (Sensormedics, S3513, California, USA). To induce bronchial provocation, the nebulizer was attached to a dosimeter (Mediprom FDC 88, France) that consisted of a breath-activated solenoid valve and a source of compressed air (pressure, 20 psi). The solenoid valve was set to remain open for 0.4 s when triggered by the subject's inspiratory effort. Methacholine challenge test was performed using American Thoracic Society (ATS) guidelines [14]. Briefly, the baseline FEV_1 was measured, the subjects inhaled five breaths of saline solution diluents and the measurements were repeated after a 2-min interval. Subjects inhaled the aerosolized solutions in five breaths from end-tidal volume to full inspiratory capacity via a mouth-piece. Starting from 0.031 mg/mL concentration, the subsequent methacholine dilutions were increased in a doubling manner until the provocative concentration of an inhaled agonist producing a 20% decrease in FEV_1 (PC_{20}) is achieved compared to the value recorded at baseline. At the end of each experiment, the subjects were given two inhalations of albuterol to reverse any residual bronchoconstriction. A PC_{20} value less than 8 mg/mL was considered as positive for bronchial hyperresponsiveness.

Statistical analysis

Qualitative data were analyzed by the chi-square test or Fisher's exact test. Symptoms, medication intake, skin tests, lung functions, nonspecific bronchial hyperreactivity (BHR), and nasal provocation test were analyzed statistically by nonparametric tests; the Wilcoxon rank sum test was used for intragroup analysis, and the Mann–Whitney *U*-test for intergroup analysis. All tests were two-tailed, and the level of significance was set at $p < 0.05$. Statistical analyses were performed using the Statistical Package for the Social Sciences, SPSS 13.0 (SPSS Inc., Chicago, IL, USA).

Results

Participants

Twenty-two children (mean ± SD age 7.5 ± 2.1 years; range: 5–10 years) suffering from allergic rhinitis without asthma caused by HDM were recruited into the study. Four patients dropped-out during run-in period; of which two developed asthma symptoms, one refused to continue participation and 1 had a negative nasal provocation testing. Overall, 18 patients were included for randomization and all were allocated for interventions (Fig. 1). During the up-dosing period of the treatment, two patients dropped out, one due to side effects and the other lost of follow-up finalizing the study with 16 subjects who had provided at least one primary outcome. The mean duration of rhinitis symptoms was 21.5 ± 16.4 months. All patients had rhinitis symptoms while 3 in active and 6 in placebo group had concomitant conjunctivitis symptoms. The baseline clinical and demographic characteristics of the subjects in both groups were homogeneous (Table 1).

Symptom and medication scores

There were no statistical difference for all four rhinitis individual symptoms scores (sneezing, nasal itching, nasal blockage, and rhinorhea) between active and placebo and within the groups ($p > 0.05$). Total rhinitis symptom and medication scores were not significantly different between active and placebo and within the groups during the whole duration of treatment (Table 2, Fig. 2A).

A significant reduction of total conjunctivitis symptoms were observed in both groups at the end treatment when compared to baseline, but no difference with regard to either individual conjunctivitis symptoms or total conjunctivitis symptoms were observed between active and placebo at the end of treatment ($p > 0.05$, Fig. 2B). No significant differences were reported for non-rhinoconjuctivitis symptoms such as cough, wheezing or other asthma symptoms.

Skin reactivity

Evaluation of skin reactivity revealed a significant decrease of *Dermatophagoides pteronyssinus* wheal size after one year of treatment in active group when compared to placebo ($p = 0.018$), whereas there was no significant change observed in *Dermatophagoides farinae* wheal size in between and within the groups ($p > 0.05$, Fig. 3). There were no new sensitizations observed after one year of SLIT.

Table 1 Demographics and clinical characteristics of patients at screening.

	Patient (*n*)	Treatment		
		Active	Placebo	*p* Value
Number of subjects	16	7	9	
Sex (m/f)	12/4	6/1	6/3	>0.5
Mean age (years [±SD])		8.1 ± 2.2	7.3 ± 2.3	>0.5
Mean duration of rhinitis (month [±SD])		22.3 ± 17.9	20.3 ± 17.2	>0.5
Total rhintis symptoms score (mean ± SD)		3.6 ± 3.8	2 ± 1.6	>0.5
Total medication score (mean ± SD)		0.5 ± 0.5	0.3 ± 0.3	>0.5
D.f[a] mean wheal (mm[±SD])		6.4 ± 2.5	3.9 ± 1.8	>0.5
D.p[b] mean wheal (mm[±SD])		5.4 ± 1.1	4.3 ± 0.7	>0.5
FEV (%)		92.8 ± 8.0	103.0 ± 14.8	>0.5
PEF (%)		76.5 ± 5.2	88.1 ± 12.7	>0.5
Methacholine PC_{20}: (mean) mg/mL		2.0 ± 0.8	2.7 ± 0.4	>0.5

[a] *Dermatophagoides farinae*.
[b] *Dermatophagoides pteronyssinus*.

Specific nasal provocation and non-specific bronchial hyperreactivity

There was no significant difference at baseline between the groups for threshold concentration of allergen-specific nasal provocation. There was a significant increase of threshold dose and subsequent nasal insensitivity within the active group when compared to baseline ($p = 0.04$) at the end of treatment. On the other hand, within the placebo group and between groups, there were no statistical significance reached at the end of one year ($p > 0.05$ for both) (Table 2).

Bronchial hyperreactivity to methacholine was detected in 31% of the patients enrolled. Bronchial hypereactivity was present in 66% of the patients in the SLIT group at baseline and 50% at the end of one year. On the other hand, although 20% of patients had BHR at baseline, this increased to 75% of patients in the placebo group. Although, methacholine test positivity of the two groups was not significantly different at baseline ($p > 0.05$), it was

Table 2 Clinical and laboratory parameters within and between the groups.

Symptoms & medications	Active		*p*[d]	Placebo	
	0 Month	12 Month		0 Month	12 Month
Sneezing	1.0 ± 0.9	1.1 ± 0.7	>0.05	0.7 ± 0.5	0.9 ± 0.7
Nasal blockage	0.8 ± 1.1	0.6 ± 0.8	>0.05	0.5 ± 0.3	0.8 ± 0.8
Nasal itching	0.8 ± 1.0	0.9 ± 0.7	>0.05	0.5 ± 0.8	0.8 ± 0.8
Rhinorrhea	1.0 ± 1.0	0.8 ± 0.7	>0.05	0.2 ± 0.2	0.8 ± 0.8
Total nasal symptom score	3.6 ± 3.8	3.4 ± 2.7	>0.05	2 ± 1.6	3.3 ± 3
Watery eyes	0.15 ± 0.2	0.1 ± 0.3	>0.05	0.07 ± 0.07	0.02 ± 0.04
Red eyes	0.3 ± 0.4	0.3 ± 0.5	>0.05	0.1 ± 0.2	0.02 ± 0.04
Itchy/Gritty eyes	0.2 ± 0.4	0.3 ± 0.5	>0.05	0.1 ± 0.1	0.01 ± 0.01
Total ocular symptom scores	3.6 ± 3.8	0.7 ± 1.3[c]	>0.05	2.0 ± 1.5	0.04 ± 0.1[c]
Total medication score	0.5 ± 0.5	0.2 ± 0.4	>0.05	0.3 ± 0.3	0.8 ± 1.4
Skin prick test					
D.f[a] mean wheal (mm[±SD])	6.4 ± 2.5	3.8 ± 3.0	>0.05	3.9 ± 1.8	7.2 ± 2.7
D.p[b] mean wheal (mm[±SD])	5.4 ± 1.1	3.6 ± 2.3	**0.018**	4.3 ± 0.7	8.0 ± 3.0
Nasal and lung function test					
Specific nasal challenge (%)	100%	14%[c]	>0.05[e]	100%	22%
FEV_1 (%)	92.8 ± 8.0	100.5 ± 5.7	>0.05	103 ± 14.8	110 ± 9.1
PEF (%)	76.5 ± 5.2	98.8 ± 14.2	>0.05	88.1 ± 12.7	107.6 ± 6.1
Methacholine PC20 positivity (%)	66%	50%	>0.05[e]	20%	75%

[a] *Dermatophagoides farinae*.
[b] *Dermatophagoides pteronyssinus*.
[c] Statistical significance for intragroup differences between 0 and 12 months : $p < 0.05$ Wilcoxon.
[d] Comparison between groups at 12th month (Mann–Whitney *U*).
[e] Comparison between groups at 12 th month (chi-square).

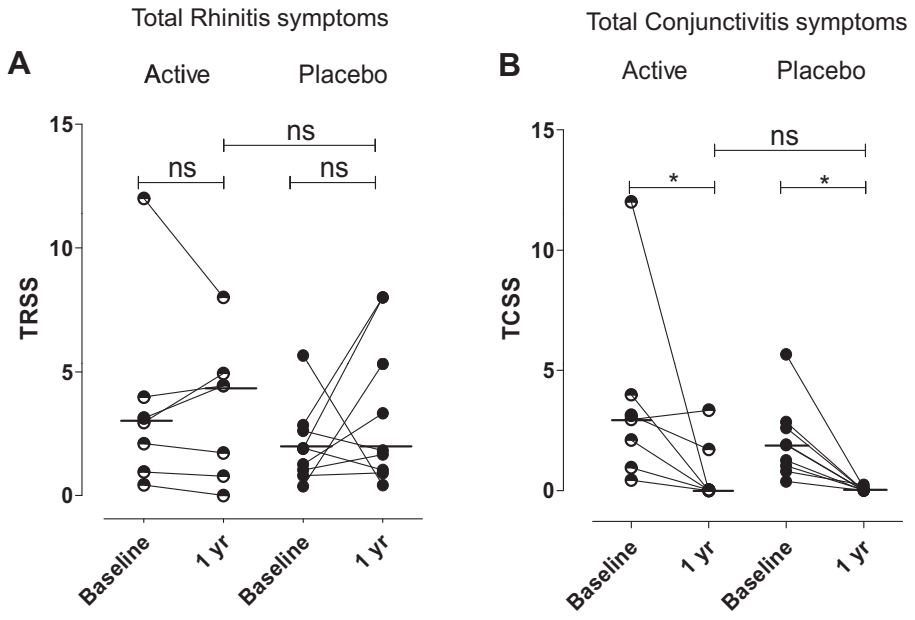

Figure 2 Comparison of rhinoconjunctivitis symptoms between baseline and 1 year after treatment: (A) total rhinitis symptom scores (TRSS); (B) total conjunctivitis symptom scores (TCSS); SLIT, half open circles and Placebo, complete circle. *$p < 0.05$; ns, non-significance.

higher in the placebo group at the end of 12 months compared to baseline (Table 2).

Safety

There were no local or systemic adverse events reported in placebo group. One patient in the active group reported having persistence nausea and vomiting immediately after commencement of maintenance (300 IR) dose during updosing, which necessitated the discontinuation of treatment within the first month of treatment (Fig. 1).

Discussion

This study evaluated the efficacy of SLIT in children with AR sensitized to HDM. This randomized, double-blind study compared HDM-SLIT treatment with an active allergen extract and placebo. The results of our study demonstrated

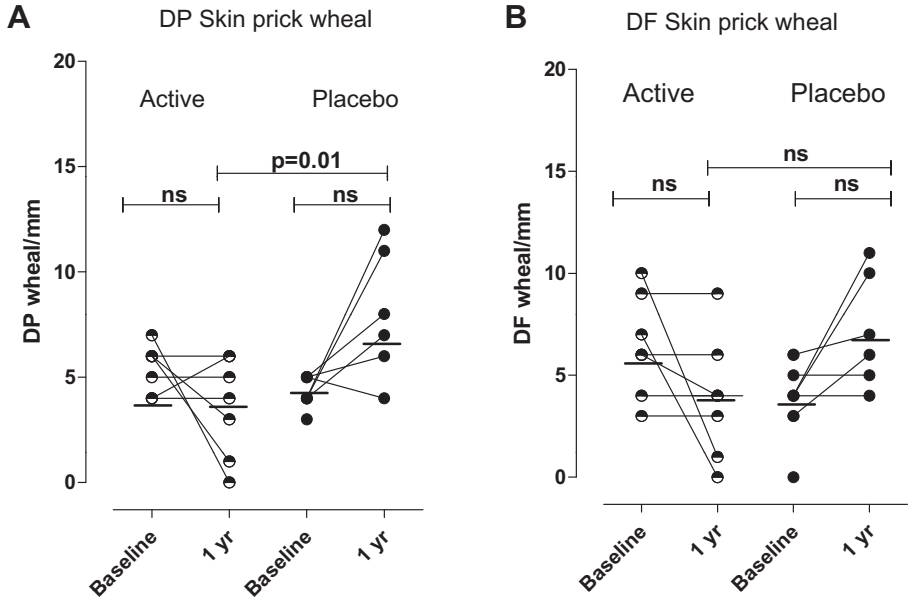

Figure 3 Comparison of skin reactivity wheal against HDM (mm) between baseline and 1 year after treatment. (A) *Dermatopharmagoides pteronissinuss* (DP); (B) *Dermatopharmagoides farinae* (DF); SLIT, half open circles and Placebo, complete circle.

that 0ne year treatment with HDM-SLIT was not better than placebo in reducing rhinitis symptoms in HDM-allergic children. However, SLIT was capable of decreasing the skin reactivity to the sensitized allergen and reduced the specific allergen nasal reactivity and ameliorated development of BHR in children with AR sensitized to HDM.

Present study was designed solely to evaluate the effect of SLIT on rhinitis patients. The sample size anticipated to be studied was not satisfactory in that, only 22 patients with eligible criteria as being exclusively perennial AR who were mono-sensitized to HDM and aged less than 10 years were available for the study. During a two months run-in period, 2 patients withdrew due to development of asthmatic symptoms. The inclusion criteria used in this study was more specific for a group with high risk for development of asthma which made it difficult in selecting and recruiting patients with isolated HDM-rhinitis. It has been also noted that the highest incidence of asthma occurred at earlier ages compared to AR [15]. Hence, most of those who are sensitized to perennial allergens such as HDM have increased risk of developing asthma at early age of life [16].

A substantial progress has been made in obtaining clinical evidence of allergen immunotherapy in children with respiratory allergy, with some unmet needs identified recently [17]. There are few published DBPC trials that evaluated efficacy of HDM-SLIT on AR in children with contradictory results [18—22]. Recently, Yuksel et al compared head to head the efficacy of SCIT and SLIT in HDM-allergic children and reported that SCIT significantly reduced rhinitis symptoms compared to SLIT and placebo, with no difference between SLIT and placebo [23]. It might be argued that most of the studies reported previosly included patients with multiallergen and other comorbidities such as asthma, hence effectivity of SLIT to treat perennial AR could be obscured. The present study is robust in that, we included HDM monosensitised perennial AR and/conjunctivitis children without asthma symptoms and followed for one year with daily evaluation of their symptoms.

Although SLIT was found to be globally effective from recent systemic reviews and meta-analysis, inconclusive results were reported when sub-analyses were conducted by selecting HDM-trials [9,24—26]. Recently, Compalati et al analysed HDM-SLIT trials in both children and adults, demonstrating weak efficacy in rhinitis compared to asthma symptoms [9]. Furthermore, treatment of AR with SLIT in pediatric patients, involving 10 trials were analysed showing that SLIT with pollen extracts was effective compared to those treated with HDM-SLIT [24]. The possibility of underreporting of negative results of HDM-specific immunotherapy studies should also be considered [27]. Our study which used high dose SLIT, has demonstrated that HDM-SLIT can reduce skin reactivity and non-specific BHR and increase allergen-specific nasal provocation threshold with no effect on rhinitis or conjunctivitis symptoms which is in line with previously reported evidence [28]. Furthermore, no significant changes between active and placebo on total or individual conjunctivitis symptoms was found in the current study, which is in accordance with a recent meta-analysis of the effect of SLIT on perennial conjunctivitis [29].

On the contrary, efficacy of HDM-SLIT has been demonstrated in a number of studies to be effective in reducing asthmatic symptoms [9,17]. Further to this, a long term treatment of low dose HDM-SLIT as an adjunct to pharmacotherapy resulted in reduction of both the duration and dose of inhaled corticosteroids (ICSs) and successful discontinuation along with improvement in lung functions in HDM-allergic children with asthma [30]. Our study has also demonstrated that 31% of allergic rhinitis children had BHR which was comparable with the magnitude found in other studies [31]. There is evidence showing that HDM-SLIT may be an effective treatment in reducing BHR for patients with rhinitis. Marogna et al. demonstrated that SLIT therapy given for 2—3 years might be sufficient to maintain the benefits of reduction in BHR even after 5—6 years post treatment [32]. This effect on BHR was also observed by Pichler et al in which SCIT with mite exerted continuous improvement in BHR throughout the 3 years of treatment [33]. Therefore, the results of one year treatment in our study are in accordance with the previous findings. We could not evaluate the effect of SLIT on asthma prevention due to the low number of subjects and treatment duration.

A decrease in early skin reactivity to HDM extract after SLIT has already been documented before [17,34]. The immunologic mechanism underlying this effect was proposed to be both downregulation of pro-inflammatory cells and upregulation of blocking IgG antibodies as well as IL-10 production which occurs within days following immunotherapy [35]. This was further demonstrated that AIT results in early induction of peripheral IL-10 responses, serum concentration of IgG4 and IgA antibodies as early as 3 months which in turn results in suppression of cutaneous allergen responses [36]. In the present study, we found significant reduction of HDM-specific skin reactivity in active treatment group compared to placebo with no correlation to clinical efficacy.

In conclusion, results of this study implicates that, HDM-SLIT has a modulating effect on allergen-specific nasal, skin reactivity and bronchial responsiveness, with no superiority clinical effect on rhinitis symptoms compared to placebo in HDM-sensitized rhinitics children after one year of treatment.

Conflict of interest

None.

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