

Effect of high-dose sublingual immunotherapy on respiratory infections in children allergic to house dust mite

Salvatore Barberi¹, Giorgio Ciprandi^{2,*}, Elvira Verduci¹, Enza D'Auria¹, Piercarlo Poli¹, Benedetta Pietra¹, Cristoforo Incorvaia³, Serena Buttafava⁴, Franco Frati⁴, and Enrica Riva¹

¹Department of Pediatrics, San Paolo Hospital, 20142 Milan, Italy

²Department of Medicine, IRCCS-Azienda Ospedaliera Universitaria San Martino, 16132 Genoa, Italy

³Allergy/Pulmonary Rehabilitation, ICP Hospital, 20100 Milan, Italy

⁴Medical and Scientific Department, Stallergenes Italy, 20155 Milan, Italy

Background: Allergic rhinitis is characterized by eosinophil inflammation. Allergic inflammation may induce susceptibility to respiratory infections (RI). House dust mite (HDM) sensitization is very frequent in childhood. Allergen immunotherapy may cure allergy as it restores a physiologic immune and clinical tolerance to allergen and exerts anti-inflammatory activity.

Objective: This study investigated whether six-month high-dose, such as 300 IR (index of reactivity), HDM-sublingual immunotherapy (SLIT) could affect RI in allergic children.

Methods: Globally, 40 HDM allergic children (18 males; mean age, 9.3 years) were subdivided in 2 groups: 20 treated by symptomatic drugs (group 1) and 20 by high-dose HDM-SLIT (group 2), since September 2012 to April 2013. The daily maintenance dose of HDM-SLIT was 4 pressures corresponding to 24, 4.8, and 60 μ g, respectively of the major allergens *Dermatophagoides pteronyssinus* (*Der p* 1), *Der p* 2, and *Dermatophagoides farinae* (*Der f* 1). RI was diagnosed when at least 2 symptoms or signs, and fever were present for at least 48 hours. A family pediatrician provided diagnosis on a clinical ground.

Results: SLIT-treated children had significantly ($p = 0.01$) less RI episodes (3.5) than control group (5.45). About secondary outcomes, SLIT-treated children had less episodes of pharyngo-tonsillitis ($p < 0.05$) and bronchitis ($p < 0.005$), and snoring ($p < 0.05$) than control group. In addition, SLIT-treated children had less fever ($p < 0.01$) and took fewer medications, such as antibiotics ($p < 0.05$) and fever-reducers ($p < 0.01$), than control group.

Conclusion: This preliminary study might suggest that also a short course (6 months) of high-dose SLIT, titrated in μ g of major allergens, could reduce RI in allergic children.

Key words: Respiratory Tract Infections; Mites; Child; Sublingual Immunotherapy; Allergens

Correspondence: Giorgio Ciprandi
Department of Medicine, IRCCS-Azienda Ospedaliera
Universitaria San Martino, Viale Benedetto XV 6, 16132
Genoa, Italy
Tel: +39-10-35331820
Fax: +39-10-3538664
E-mail: gio.cip@libero.it

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INTRODUCTION

Social and economic costs of allergic rhinitis (AR) are relevant as AR may significantly impact school attendance and performance, quality of life, sleep, and is associated with many comorbidities, including asthma and respiratory infections (RI) [1, 2].

The AR immunopathology is characterized by T helper 2 (Th2)-dependent inflammation and Th1-response impairment. This imbalance is sustained by dysfunction of immune system: allergic patients have a functional defect of allergen-specific T regulatory cells, so Th2 cells may polarize the immune response to allergen and produce large quantity of some interleukins, including interleukin (IL) 4, IL-5, and IL-13, that in turn promote IgE synthesis and eosinophil production, recruitment, and activation at nasal level. Th2-cytokines up-regulate the endothelial and epithelial expression of adhesion molecules (such as intercellular adhesion molecule [ICAM-1]), which interact with other adhesion molecules (e.g., leukocyte functional adhesion-1 expressed by leukocytes) to induce the mucosal infiltration by eosinophil. In addition, involvement of other T helper subsets, namely Th17 and Th9, has been reported. Severity of AR may be associated with increased levels of IL-17 and IL-9. This complex pathogenesis highlights the relevant impairment of immune response in AR. In addition, Th2-, Th1-, and Th9-dependent cytokines are involved in inflammatory events. Therefore, allergic inflammation represents the main characteristic of AR.

It is strengthened belief that allergic patients could present higher susceptibility to contract RI than nonallergic subjects. In this regard, it has been evidenced that allergic children have more numerous and severe RI than nonallergic children [3]. The involved pathways may be: (1) impaired immune defence because of interferon (IFN)- γ defective production, consequent to Th2-polarization [4, 5], (2) overexpression of ICAM-1 (the main rhinovirus receptor) depending on allergen exposure, (3) augmented mucus production together with impaired mucus consistency, and (4) persistent mucosal inflammation as *pabulum* for microbes overgrowth [5, 6]. In addition, it is well known that AR is a main risk for asthma [7], both concerning the onset and the worsening [8]. In other words, allergic reaction may be considered the promoter of different sequential steps: (1) allergen exposure induces expression of adhesion molecules, (2) so allergic inflammation flares, (3) symptoms occur, (4) overexpression of ICAM-1 favours viral adherence, (5) RI cause asthma attack. Therefore, adequate control of allergic inflammation in AR patients is important as it induces

symptom relief and could prevent infections recurrence [9]. In this regard, allergen immunotherapy (AIT) may restore a physiological immune and clinical tolerance to the causal allergen and exert anti-inflammatory effects, mainly concerning a fast increase of IFN- γ production after AIT [10, 11]. In addition, it has been reported that sublingual immunotherapy (SLIT) may reduce the number of RI in children with AR [12]. Children treated with SLIT actually had less allergic symptoms than control children as well as they had significantly less sore throat, headache, productive cough, and antibiotic use than children treated with medications alone [12]. In this regard, it may be hypothesized that these beneficial effects might be based on a restored physiological Th1-polarization and a damping of allergic inflammation [13].

House dust mite (HDM) sensitization is very frequent in childhood and is characterized by a persistence of Th2-dependent allergic inflammation [14]. Therefore, the present preliminary study investigated whether six-month SLIT at high dose may reduce the number of RI in HDM allergic children.

MATERIALS AND METHODS

Patients

Forty children, aging between 7–14 years, with AR to HDM were included. For inclusion, patients had to have typical symptoms of AR (such as sneezing, itching, watery rhinorrhea, and nasal obstruction) throughout the year with fall-winter peak for at least 2 consecutive years, moderate-severe AR (according to Allergic Rhinitis and its Impact on Asthma [ARIA] criteria), and a documented positive skin prick test to HDM extracts consistent with symptom occurrence after exposure to dust. The main exclusion criteria were AR caused by cosensitization and likely to influence symptoms evaluation during the study, previous AIT, and the usual contraindications to AIT.

Study design

This observational study was conducted at Pediatrics Department of the San Paolo Hospital (Milan, Italy) from September 2012 to April 2013. Allergic children were subdivided in 2 groups: 20 patients were treated by symptomatic drugs (antihistamines, nasal corticosteroids) (group 1) and 20 children by high dose, such as 300 IR (index of reactivity) SLIT (group 2).

AR severity was assessed according to the ARIA criteria, such as AR could be intermittent or persistent on the basis of the

symptom duration [1].

The primary objective of the study was to investigate whether high-dose SLIT was able to reduce the total number of RI in patients with HDM-AR.

The secondary objectives were to assess whether high-dose SLIT could affect: the number of episodes of acute rhinosinusitis, otitis, pharyngotonsillitis, laryngitis, bronchitis, and pneumonia, the presence of fever, the snoring, the use of antibiotics, anti-inflammatory drugs, oral corticosteroids, and fever-reducers.

For data collection, parents had a diary card. Parents daily collected on the card the presence of signs and symptoms, including fever, rhinorrhea, stuffy and dripping nose, snoring, sore-throat, earache, dysphonia, cough, and dyspnea.

Written informed consent was obtained by both parents before entering the study. The study was conducted in accordance with good clinical practice guidelines. The study was approved by the Ethics Committee of the San Paolo Hospital (Milan, Italy).

RI diagnosis was based on a clinical ground [15]. The RI diagnosis was made when symptoms, reported by parents in the diary, and fever (axillary temperature $\geq 38^{\circ}\text{C}$) were present for at least 48 hours. The symptoms (in addition to fever) taken into consideration for this diagnostic purpose were: (1) mucopurulent rhinorrhea, stuffy or dripping nose, headache for <10 days for common cold, for >10 days for rhinosinusitis, (2) sore-throat, and cough for pharyngotonsillitis, (3) otalgia (earache) for otitis, (4) dysphonia and dry cough for laryngitis, (5) cough (dry and/or productive) and dyspnea for lower RI. RI diagnosis was usually confirmed by a family pediatrician.

The most widely used antibiotic was amoxicillin (or amoxicillin with clavulanic acid), and it was usually prescribed for 7 days at a dose of 50 mg/kg per day, divided into 3 doses. Clarithromycin was the second most prescribed antibiotic by pediatricians at a dose of 15 mg/kg per day, divided in 2 doses, and prescribed for 14 days. Cefpodoxime proxetile was prescribed only 3 times for 10 days at a dose of 8 mg/kg per day, divided in 2 doses.

Allergen Immunotherapy

SLIT was performed using an allergen extract of HDM at 300 IR/mL (Stallergenes S.A., Antony, France). Staloral 300 contains equal proportions of *Dermatophagoides pteronyssinus* (*Der p*) and *Dermatophagoides farinae* (*Der f*) and is available as a minipump-predosed actuator. It was administered according to a 6-month schedule. The daily maintenance dose of HDM SLIT was 4 pressures corresponding to 24, 4.8, and 60 μg , respectively of the

major allergens: *Der p* 1, *Der p* 2, and *Der f* 1. Any local or systemic adverse effect of SLIT was recorded by the patients.

Visits

Children were checked at the clinic every two months. During each visit, diary cards were assessed, physical examination was performed, and SLIT compliance and tolerance were considered.

Statistical analysis

The sample size was calculated by log-rank test with power at 90% and a error at 5%: 20 subjects per arm were considered

Table 1. Demographic and clinical characteristics in children treated with SLIT and in control group

Variable	SLIT-treated children	Control group
Age (yr)	8.3 \pm 1.5	7.9 \pm 1.1
Male sex	11	9
Intermittent AR	4	5
Persistent AR	16	15
RI number in the previous year	6.3 \pm 0.8	6.5 \pm 0.7

Values are presented as mean \pm standard deviation or number. SLIT, sublingual immunotherapy; AR, allergic rhinitis; RI, respiratory infections.

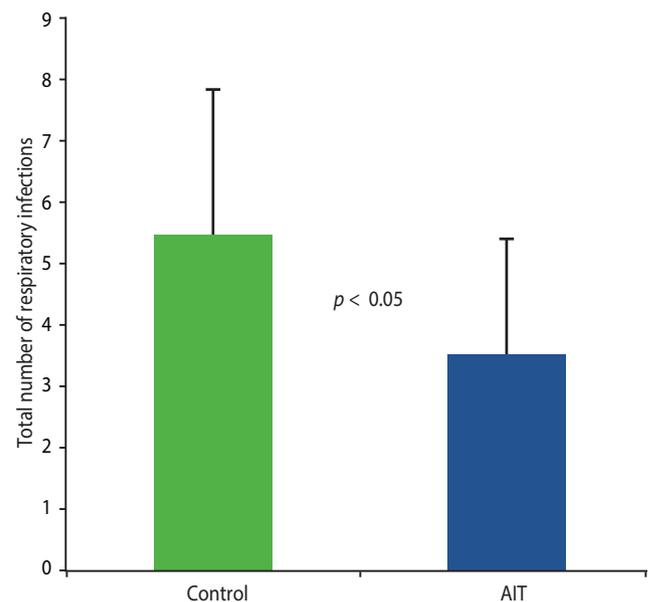


Fig. 1. Total number of respiratory infections in the control group and in children treated with allergen immunotherapy (AIT).

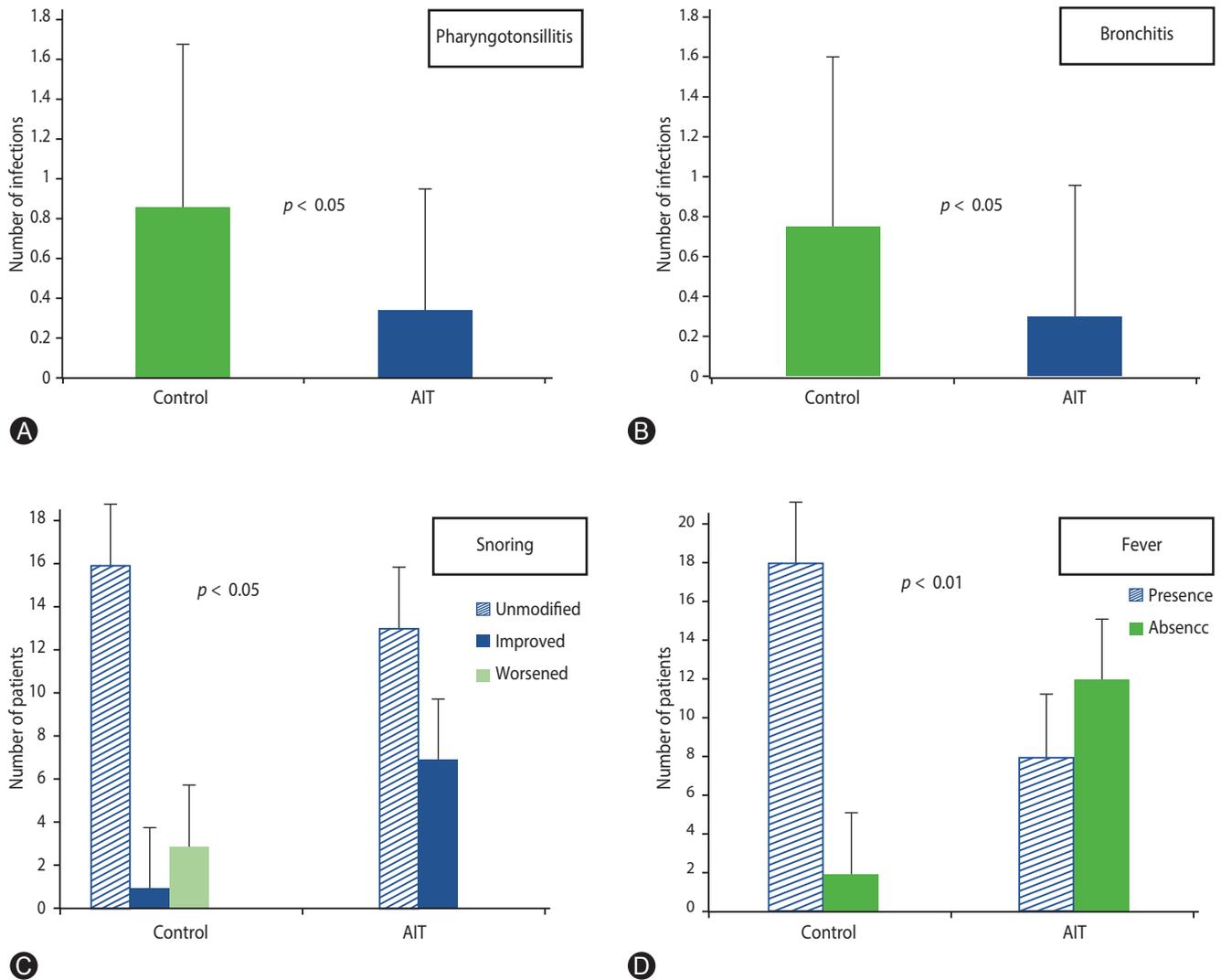


Fig. 2. (A) Number of pharyngotonsillitis episodes in control group and allergen immunotherapy (AIT) group; (B) Number of bronchitis episodes in control group and AIT group; (C) Number of patients with unmodified, improved, or worsened snoring in control group and AIT group; (D) Number of patients with fever in control group and AIT group.

sufficient based a supposed difference in efficacy of at least 20%.

A central organization (IBIS Informatica, Milan, Italy) undertook the data entry and statistical analysis. Nominal and discrete parameters were reported as contingency tables (frequency and percentage). The statistical analysis was conducted with parametric (analysis of variance) and nonparametric methods (Mann-Whitney test). The contingency tables were assessed through chi-square test with Yate correction in the case of 2x2 tables. Statistical analysis was carried out using BMDP Dynamic 2009 ver. 8.2 (BMDP Statistical Software, Inc., Los Angeles, CA, USA).

RESULTS

We assessed 40 paediatric patients (18 males; mean age, 9.3 ± 1.8 years), 20 undergoing symptomatic drugs alone (group 1) and 20 treated by SLIT (group 2).

The two groups were well matched concerning age, gender, AR severity, RI episodes in the previous year, as reported in Table 1.

The total number of infections was significantly different in the two groups: Group 1 had more ($p < 0.05$) RI episodes (5.45) than SLIT group (3.5) (Fig. 1). In particular, the number of pharyngotonsillitis episodes was minor ($p < 0.05$) in SLIT-treated patients

(Fig. 2A) as well as the bronchitis episodes was significantly minor ($p < 0.05$) in group 2 (Fig. 2B). Snoring was significantly ($p < 0.05$) reduced in SLIT group in comparison with control group as shown in Fig. 2C. About fever, 18 children treated with medications alone had fever, whereas only 8 SLIT-treated children had fever ($p < 0.01$), as shown in Fig. 2D. On the other hand, there was no difference about the number of common colds episodes in the two groups: 3.1 in control group and 2.2 in SLIT group.

SLIT-treated children took significantly less antibiotics ($p < 0.05$) and fever-reducers ($p < 0.01$) than control group (Fig. 3).

DISCUSSION

Th2-dependent inflammation is the hallmark of AR. Allergic inflammation promotes frequent RI episodes. Previously, it has been evidenced that allergic patients have a two-fold increase of RI risk, and duration almost 3 weeks longer of the symptoms than in nonallergic subjects [16]. In addition, it has been demonstrated that rhinovirus-induced infection in atopic subjects heightened susceptibility to the detrimental effects of colds both concerning immunological and clinical aspects [17]. Another study reported that atopic asthmatics suffer from more frequent lower-respiratory-tract infections and have more severe and persistent lower-respiratory-tract symptoms than normal subjects [18]. Thus,

a relevant link between RI and AR exists as underlined by several studies [19-26]

Allergen-specific immunotherapy exerts profound effects on immune response, mainly concerning the balance between Th1 and Th2 cells. Particularly, immunotherapy induces an increased IFN- γ production [27]. Therefore, this study aimed at evaluating whether high-dose SLIT may affect RI in children with AR due to HDM sensitization.

Effectively, SLIT-treated patients showed a significant reduction of the total number of RI, associated with diminished use of both antibiotics and fever-reducers in comparison with drug-treated patients. A possible explanation of this relevant effect might be due to the modulation of Th2-polarized immune response in SLIT-treated patients. Indeed, it has been evidenced that SLIT was able of both increasing IFN- γ production and reducing allergic inflammation, assessed by the biomarker soluble HLA-G [28].

The present study confirms a previous multicentre real-life study that evidenced the SLIT ability in exerting “extra antiallergic” effects, mainly concerning RI [12]. Therefore, there is evidence that SLIT is an effective a safe route of AIT [29, 30] and may have additional activity as provided by preliminary studies, including this preliminary experience.

However, the present study should be considered preliminary because it has some main limitations: it was an open study, recruiting a relatively restricted number of patients; cytokines,

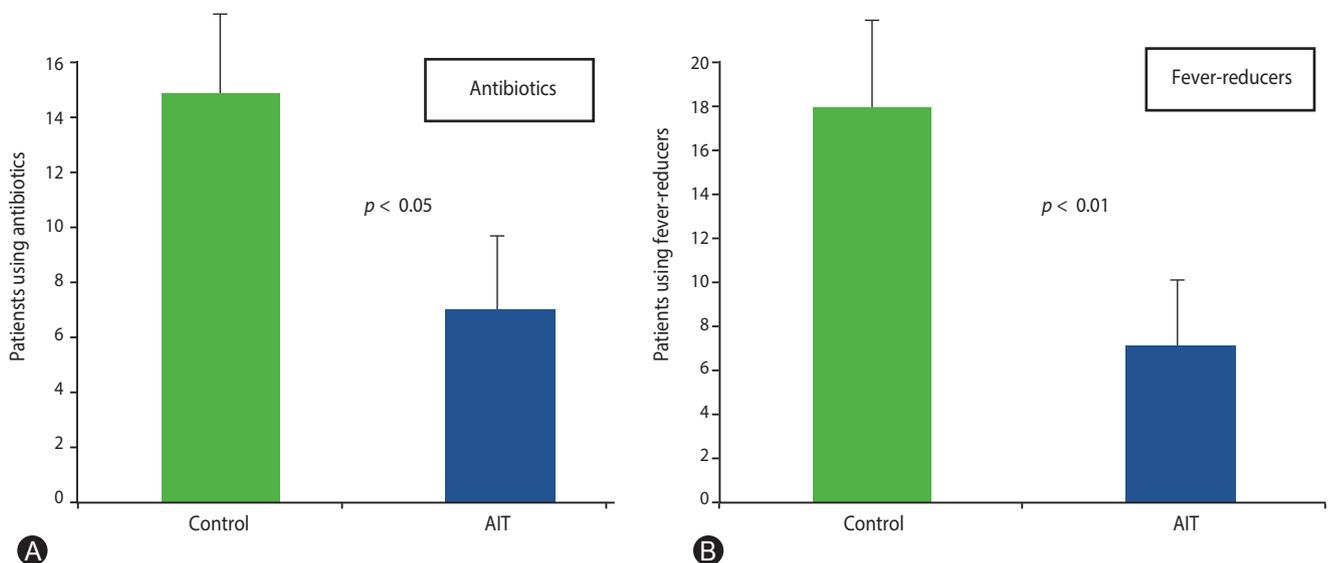


Fig. 3. (A) Number of patients using antibiotics in control group and allergen immunotherapy (AIT) group; (B) Number of patients using fever-reducers in control group and AIT group.

chemokines, and mediators, including adhesion molecules, were not evaluated; the SLIT treatment duration was short (6 months) as well as the clinical observation period was short. We decided to design this short course because it is well known that AIT is a long-term treatment, but this involves a relevant drawback: an inadequate adherence to AIT. Thus, the perception of achieving clinically relevant outcome, such an impact on RI, could reinforce the awareness of AIT efficacy. We have to consider another important limitation: the absence of cultural, viral or bacterial, determination. In addition, as RI are more common in younger children, such as from 3 to 6 years old, the present study in children aged 7 onward gives preliminary and partial information. Therefore, this preliminary experience should be confirmed by controlled and lab-based trials recruiting larger cohorts, mainly enrolling younger children (<6 years) and considering longer SLIT treatment and observation time.

Additionally, it is to consider that also omalizumab administration was able to eliminate spring and fall asthma exacerbations [31], which are primarily caused by viral RI [32].

In conclusion, AR should be adequately treated, mainly concerning the comorbidities, including RI, as its impact on social and economic aspects is relevant. This preliminary study might suggest that also a short course (6 months) of high-dose SLIT, titrated in μg of major allergens, could reduce RI in allergic children.

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