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Klinik Araştırma

Is House Dust Mite Specific Sublingual Immunotherapy Successful in Termination of Inhaled Corticosteroid Treatment in Children with Asthma

Ev Tozu Akarına Spesifik Dilaltı İmmunoterapi Astımlı Çocuklarda İnhale Kortikosteroid Tedavisini Sonlandırmada Ne Kadar Başarılı?

Elif EROLU*, Elif KARAKOÇ AYDINER, Safa BARIŞ**, Nerin BAHÇECİLER***, Cevdet ÖZDEMİR******

**Sağlık Bilimleri Üniversitesi Ümraniye Eğitim ve Araştırma Hastanesi, Pediatri Anabilim Dalı, Pediatrik Kardiyoloji Bilim Dalı, İstanbul*
***Marmara Üniversitesi Tıp Fakültesi, Pediatrik Allerji ve İmmunoloji Bilim Dalı, İstanbul*
****Yakın Doğu Üniversitesi Tıp Fakültesi, Pediatrik Allerji ve İmmunoloji Bilim Dalı, İstanbul*
*****İstanbul Bilim Üniversitesi Tıp Fakültesi, Pediatrik Allerji ve İmmunoloji Bilim Dalı, İstanbul*

ABSTRACT

Objective: *House dust mite (HDM)- specific sublingual immunotherapy (SLIT) has long-term effects contrary to pharmacotherapy in children with asthma. We aimed to study the long-term effects of SLIT on inhaled corticosteroid usage.*

Material and Method: *Fifty-four asthmatic children who received HDM -specific SLIT for at least 3 years and were followed up for a minimum 5 years after cessation of SLIT in addition to pharmacotherapy and 23 patients who received only pharmacotherapy during the same time period were admitted in the study. SLIT and pharmacotherapy groups were evaluated retrospectively by scanning their medical records in regard to their inhaled corticosteroid (ICS) dose (μg/day), duration (month(s)/year) of ICS, and pulmonary function test (PFT) parameters. Visual analogue scores and symptom scores recorded for 6 months in their daily record cards given to them were evaluated, and dose (μg/day), and duration of ICS therapy (month(s)/year) were calculated PFTs were performed for each patient. Based on the diary card records regarding symptoms, the need for ICS and FEV1%, the patients were grouped as 37 SLIT-responders, 17 SLIT-nonresponders, 15 PT-responders, and 8 PT-nonresponders.*

Results: *Reduction in ICS dose was significantly higher for SLIT (407±252 μg)n group in comparison to pharmacotherapy group (224±174 μg) (p=0.009). Duration of ICS usage reduced by 63% (p=0,001) in SLIT-nonresponder group, but in pharmacotherapy-nonresponder group it decreased by only 11% (p=0,108).*

Conclusion: *SLIT was effective in reducing ICS dose. Duration of ICS treatment did not decrease in the course of time in PT-nonresponder group while decreased in SLIT-nonresponder group.*

Keywords: *allergen specific sublingual immunotherapy, asthma, children, house dust mite, inhaled corticosteroid treatment*

ÖZ

Amaç: *Ev tozu akarı (HDM) spesifik sublingual immünoterapinin (SLİT) astımlı çocuklarda farmakoterapinin (PT) aksine uzun süreli etkileri vardır. SLIT'in inhale kortikosteroid kullanımı üzerine uzun süreli etkilerini incelemeyi amaçladık.*

Gereç ve Yöntem: *En az 3 yıl boyunca HDM'ye spesifik SLİT almış ve SLIT tedavisinden sonra en az 5 yıl takip edilmiş 54 astımlı çocuk ve aynı dönemde yalnızca farmakoterapi almış 23 çocuk çalışmaya alındı. SLIT ve farmakoterapi grupları, ICS'nin inhale kortikosteroid (ICS) dozu (μg/gün) ve süresi (ay/yıl)/yıl, solunum fonksiyon testi (PFT) parametreleri açısından tıbbi kayıtlardan retrospektif olarak değerlendirildi. Tüm hastaların, 6 ay boyunca kendilerine verilen günlük kartlardaki görsel analog skor ve semptom skorları değerlendirildi ve kullanılan ICS dozu (μg/gün) ve süresi (ay/yıl) hesaplandı, PFT testi yapıldı. Günlük kart kayıtlarındaki semptom, ICS ihtiyacı ve %FEV1'e göre, hastalar 37 SLIT-yanıtlı, 17 SLIT-yanıtsız, 15 PT-yanıtlı, 8 PT-yanıtsız olarak gruplandırıldı.*

Bulgular: *ICS dozunda azalma, SLIT (407±252 μg) için farmakoterapi grubuna (224±174 μg) kıyasla anlamlı olarak daha yüksekti (p=0,009). SLIT-yanıtsız grupta ICS kullanım süresi % 63 (p=0,001) oranında azalırken, PT-yanıtsız grupta bu oran yalnızca % 11 idi (p=0,108).*

Sonuç: *SLIT, ICS dozunu azaltmada etkilidir. Uzun dönemde ICS dozunda anlamlı azalma SLIT alanlarda mevcuttur. Tedaviye yanıtsız olgularda SLIT alanlar yalnızca PT almış olanlara göre daha az süreyle ICS tedavisine gereksinim duymaktadırlar.*

Anahtar kelimeler: *allerjen spesifik immunoterapi, astım, çocuk, ev tozu akarı, inhale kortikosteroid*

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Yazışma adresi: Uz. Dr. Elif Erolu, Sağlık Bilimleri Üniversitesi Ümraniye Eğitim ve Araştırma Hastanesi, Pediatri Anabilim Dalı, Pediatrik Kardiyoloji Bilim Dalı, İstanbul
e-posta: eliferolu@yahoo.com

Yazarların ORCID bilgileri:
E. E. G. 0000-0002-2927-5732, E. K. A. 0000-0003-4150-5200, S. B. 0000-0001-5091-2807, N. B. 0000-0003-1337-2041, C. Ö. 0000-0002-9284-4520

INTRODUCTION

Pharmacotherapy is the standard therapy in the management of allergic disorders. However the major problem is the recurrence of the signs and symptoms after cessation of treatment. Immunomodulation is the key for the permanent treatment of the disease. Allergen-specific sublingual immunotherapy (SLIT) establishes modification in the underlying immunologic mechanisms of the disease in addition to eradication of symptoms [1]. Sublingual immunotherapy was proven to be feasible, safe and effective in allergic respiratory disorders of adults and children [2-6]. Decline in both the occurence of new sensitizations and allergic symptoms in children was proven [7,8].

We indicated a decline in duration and dose of inhaled corticosteroids (ICSs) in children with allergic asthma after completion of 3 years of sublingual immunotherapy in our previous study. Pulmonary functions improved also with this treatment [9].

Although, the effect of SLIT in reduction of medication and symptoms is well-known, long-term effects of SLIT in children are still a matter of research. Some studies revealed long-lasting effects of SLIT [10,11].

In this study, we aimed to assess the long-term efficacy of SLIT in house dust mite (HDM)- sensitized children with asthma compared to control patients receiving pharmacotherapy only, in both prospective and retrospective studies.

MATERIALS and METHODS

Patients

Eighty-three house dust mite (HDM) monosensitized children and adolescents with asthma enrolled into the study. Seventy-seven of them (41 males, 36 females, mean [±SD] age: 15.6±3.8 years, range: 9.3-25.6 years) were available for the final clinical, laboratory and immunological analyses. Fifty-four children received HDM-specific sublingual immunotherapy (SLIT) for at least 3 years in addition to pharmacotherapy and 23 children received only pharmacotherapy during the same time period. All patients and/or their parents gave their informed consents, and the study was approved by the local ethics committee with the approval number of MAR-YC-2008-0300.

Children followed up in Marmara University Pediatric Allergy and Immunology Division who met the inclusion criteria were included in the study: (i) diagnosis of asthma in children for at least 5 yrs, (ii) monosensitization to HDM (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), (iii) passed at least 2 years after SLIT (v) lack of any previous history of immunotherapy for pharmacotherapy group, or (vi) chronic illness.

Study Design

SLIT group were evaluated retrospectively from the medical records in regard to dose (μg/day) and duration (month(s)/year) of their inhaled corticosteroid (ICS) therapy, pulmonary function test (PFT) parameters. All these parameters were recorded also for the pharmacotherapy group. At the time of enrollment, all patients were advised to record their symptoms and medications into the dairy cards which were given to them for the duration of 6 months and all patients were evaluated for pulmonary functions. According to the diary card records and FEV1% values, patients were assigned 3 points if daily ICS need persists, 2 points for FEV1% less than 60 and 1 points for the presence of any of the following parametres: night symptoms, daily symptoms at least twice a week, hospital admissions, β2 agonist need at least twice a week, and FEV1% 60-80. Patients having a total score of >2 points were grouped as non-responders and ≤2 points as responders to treatment. During the same time period, all patients were evaluated for dose (μg/day) and duration (month(s)/year) of ICS, PFT parameters. Study design was shown in Figure.

Symptom and medication scores and Visual analogue scale

All patients were asked to fill their symptoms in the daily diary cards including cough, wheezing, chest tightness for asthma. Each symptom had to be scored according to severity scale: 0=absent, 1=slight, 2=moderate, 3=severe. Sum of total asthma score per day resulted in total asthmatic symptome score (TASS). Visual analogue score (VAS) was determined from a scale 0 (no symptom) to 10 (symptoms at maximum level) demonstrating the severity of

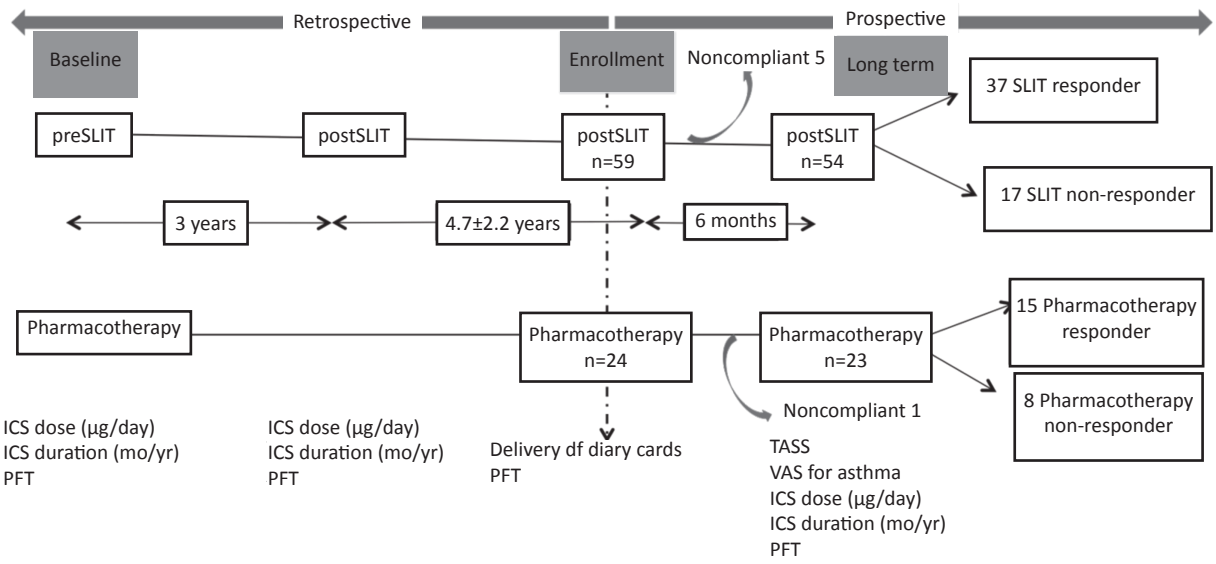

Figure. Study design. ICS; inhaled corticosteroids, mo; month, PFT; pulmonary function test, yr; year, SLIT; sublingual immunotherapy, TASS; total asthma symptom score, VAS; visual analogue scale

symptoms within a week. Average of the four weeks was taken to estimate the final VAS score. Each route of administration of the medications (when needed) were asked to be noted in the daily cards (e.g salbutamol 1 puff, budesonid 1 puff). In addition, daily dose (μg/day), and duration (month(s)/year) of ICS treatment for each patient were calculated from daily cards.

Pulmonary function test

Maximal forced expiratory volume curves were used in pulmonary function tests (Sensormedics, S3513, Yorba Linda, CA, USA). The patients asked to take deep breath and blow as quickly as possible into the mouthpiece while standing up with a nose clip. The average of three successful maneuvers was expressed as the percentage of forced vital capacity (FVC), forced expiratory volüme in 1 second (FEV1), peak expiratory flow rate (PEF), and forced mid-expiratory flow rate (FEF25–75%).

Treatment

SLIT therapy was defined as at least 3 years administration of 300 IR Dermatophagoides farina 50% and Dermatophagoides pteronyssinus 50% mixture as droplets according to manifacturer's instructions (Staloral, Stallergenes Greer, Alexis de Tocqueville, France). All patients could use medications when needed; inhaled or oral corticosteroids and antihistaminics depending on the severity of symptoms as recommended in Global Initiative for Asthma (GINA) [12]. In addition, patients in both groups were asked to avoid getting in contact with allergens at home.

Statistical analysis

Values were presented as mean±standard deviation (SD) and median (range), unless otherwise specified. Statistical significance was set at $p< 0.05$. Statistical Package for the Social Sciences (SPSS) (Release 16.0; SPSS Inc. Chicago, Illinois, USA) was used for analyses. For qualitative data, the two groups were compared using the Mantel–Haenszel chi-square tests. The Willcoxon signed rank test was used for paired comparisons among the individuals and the Spearman rank order correlation test for paired comparison of groups. The Mann–Whitney U-test was used for unpaired comparison of groups, and paired t test for paired comparison of groups. Repeated Measures Anova test was used for comparison among three or more paired groups. Freidman test was used for comparison of nonparametric repeated paired groups.

RESULTS

Patients

Fifty-four (29 M, 25 F; mean age,15.9±4.13 years) patients in SLIT and 23 (12 M, 11 F, 14.7±3.07) in

the pharmacotherapy group were included in final analyses. Demographic data of SLIT at baseline, post-SLIT and enrollment and data of pharmacotherapy group at baseline and enrollment are presented in Table 1. In addition to these, demographic data of 37 SLIT-responders, 17 SLIT-nonresponders, 15 pharmacotherapy-responders, and 8 pharmacotherapy-nonresponders are presented in Table 2.

Table 1. Demographic, clinical and laboratory data of sublingual immunotherapy group at the beginning, at the end of therapy (preSLIT and postSLIT, respectively) and at long term in addition to pharmacotherapy group at baseline and long term.

	Baseline SLIT	PostSLIT	Long term SLIT (54)	P	Baseline PT	Long term PT (23)	P
Clinical Data							
Age (years)	8.2±5.7	12.1±3.39	15.9±4.32		9.2±3.2	14.7±3.07	
Gender n (%)					11,(47.8%)		
♂	25 (46.3%)				12 (52.2%)		
♀	29 (53.7%)				4.67±2.87		
Onset of symptoms (years)	3.90±47				7.37±3.93		
Age at admission (years)	5.1±3.1						
TASS			0.02 (0-0.27)			0 (0-0.20)	
VAS for asthma			0.25 (0-1.14)			0 (0-0.50)	
ICS dose (budesonide μg/day)	451±259	206±245	61±122	**0.015**	330±146	99 ± 150	**0.001**
ICS duration (months/year)	9±4	4.8±5.05	1.4±3.2	**0.001**	9 (9-12)	3 (1-11)	**0.001**
Laboratory Data							
FVC%	93±16	92±9	96±14	0.050	90±14	97±12	0.58
FEV1%	96±15	98±8	93±12	0.26	94±14	100±10	0.95
FEF25-75%	97±33	93±18	92±24	0.32	97±19	106±28	0.43
PEF%	90±22	89±14	91±14	0.62	82±16	95±14	0.059

FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity, ICS: Inhaled corticosteroid score, PEF: Peak expiratory flow, PT: Pharmacotherapy, TASS: Total asthma symptom score, VAS: Visual analog scale.

Table 2. Demographic, clinical and laboratory data of SLIT-responder, SLIT-nonresponder groups and Pharmacotherapy-responder, Pharmacotherapy-nonresponder groups.

	SLIT- Responder (37)	SLIT-Nonresponder (17)	P	PT-Responder (15)	PT-Nonresponder (8)	P
Clinical Data						
Age (years)	16.1±3.8	18.2±4.6	0.24	14.2±2.2	15.6±4.0	0.32
Gender n (%)						0.036
♂	17	8	0.93	4	7	
♀	20	9		10	2	0.91
Onset of symptoms (years)	4.0±2.4	3.1±2.4	0.34	4.72±2.2	4.57±4.03	0.49
Age at admission (years)	4.9±3.0	5.6±3.5	0.31	6.91±2.98	8.21±5.46	
Age at SLIT	8.2±2.5	10.2±4.5	0.07			0.028
TASS	0 (0-0.4)	0.14 (0.01-0.54)	0.030	0 (0-0.02)	0.18 (0-1.01)	0.001
VAS for asthma	0 (0-0)	0.62 (0.20-2.25)	0.026	0 (0-0.50)	1 (0-2)	0.0001
ICS dose	0 (0-16)	154 (40-533)	0.0001	0 (0-0)	282 (17-400)	0.0001
(budesonide μg/day)	0.42±2.5	206±143	0.0001	0	262±121	
ICS duration (months/year)	0 (0-0.5)	4 (3-7)	0.0001	0	3 (1-11)	0.0001
ICS cessation	37	0	0.0001	15	0	0.0001
Laboratory Data						
FVC%	96±15	94±13	0.55	98±9	94±11	0.37
FEV1%	95±12	90±13	0.23	96±6	90±9	0.15
FEF25-75%	97±22	81±26	0.021	113±24	78±21	0.004
PEF%	93±13	89±15	0.31	98±13	83±13	0.30

FEF25-75%: Forced expiratory flow 25-75%; FEV1: Forced expiratory volume in one second, FVC: Forced vital capacity, ICS: Inhaled corticosteroid score, PEF: Peak expiratory flow, PT: Pharmacotherapy, TASS: Total asthma symptom score, VAS: visual analog scale.

Clinical Outcomes

Symptom and Medication Scores and Visual Analogue Scale

Visual analogue scale, symptom and medication scores for asthma were not different statistically between SLIT and PT groups.

Dose and Duration of Inhaled Corticosteroid Therapy

ICS dose and duration of SLIT and pharmacotherapy groups significantly decreased at long term when compared to baseline (p=0,015, p=0,001 for SLIT group and p=0,001, p=0,001 for pharmacotherapy group, respectively). Moreover, reduction in ICS dose was significantly higher for SLIT (407±252 μg) in comparison to pharmacotherapy group (224±174 μg) (p=0,009).

ICS dose and duration at the end of SLIT decreased according to the begining of immunotherapy (p=0.001, p=0.001). Likewise, the final evaluation of ICS dose and duration was found to be lower with respect to the end of the SLIT (p=0,002, p=0,001).

No significant differences were observed in the dose and duration of ICS at baseline and final evaluation between SLIT and PT groups.

At the time of the begining of sublingual immunotherapy, mean daily doses of ICS in SLIT-nonresponder, and responder groups were 618±230 μcg, and 380±235 μcg which were significantly lower than those of the SLIT-nonresponder group (p=0,017). Mean daily dose of ICS in the SLIT-nonresponder group declined from mean 618±230 μcg to 206±143.3 μcg (p=0.003). Duration of ICS usage was similar between SLIT-nonresponder and responder groups (p=0,159). In pharmacotherapy-nonresponder group mean daily dose of ICS was 392±54 μcg which was not statistically significantly different from pharmacotherapy-responder group (311±200 μcg) (p=0,159) while duration of ICS usage was comparable between groups (p=0,420).

Mean daily dose of ICS of SLIT-nonresponder group was greater than mean daily dose of ICS of pharmacotherapy-nonresponder group (p=0,025).

Duration of ICS usage reduced by 63% (p=0,001) in SLIT-nonresponder group, but in pharmacotherapy-nonresponder group this decrease was at rate of only 11% (p=0,108).

Pulmonary Function Parameters

Pulmonary function test results were not different between SLIT and PT groups. SLIT group showed significant increase in FVC (%) after the end of sublingual immunotherapy (p=0.050). While FEF%25-75 values in PT-nonresponder and PT-responder groups were similar at baseline (p=0,100), and at final evaluation, FEF%25-75 values were significantly lower in PT-nonresponder group compared to PT-responder patients (p=0.004).

DISCUSSION

Sublingual allergen-specific immunotherapy has many superiorities among pharmacotherapy in allergic asthma. SLIT causes long-term permanent changes in disease course. Immunotherapy was shown to be effective in the supression of all phases of allergic responses [13]. Also immunotherapy was shown to be effective in preventing development of new sensitizations and allergies [14,15].

Many researches confirmed short-term and long-term efficacy and safety of SLIT in allergic rhinitis and asthma [4,5,16]. We aimed with this study to determine whether a long-lasting effect of SLIT exists in reducing or stopping inhaled corticosteroid treatment as the determinant of treatment response. The long-term effect of SLIT in children with asthma due to HDM was proven by demonstration of decrease in symptoms and medications after cessation of immunotherapy for 4-5 years [17].

In another study in which 117 adults with allergic rhinitis and intermittent asthma received SLIT and were followed up for 13 years. In these patients improvement in symptom scores, and bronchial hyperreactivity were maintained even after six years [18].

In our study SLIT resulted in a significant decrease in the need for medication (inhaled corticosteroid requ-

irements) and this decrease was still prominent in the long-term evaluation. On an average 4.7±2.2 years after discontinuation of SLIT , decrease in mean daily ICS dose of SLIT was 1,8 fold higher relative to PT group. We previously declared in another study that success rates in cessation of ICS treatment just after a 3 years of SLIT course were52.4 % and 9.1% in patients who received SLIT, and only pharmacotherapy, respectively [9].

SLIT-nonresponders achieved a significant decrease in both mean daily dose and duration of ICS in the course of time. Higher mean daily dose of ICS and lower FEF25-75 (%) values at baseline according to long-term ICS dose and FEF25-75 (%) values were considered to relate the SLIT response.

As presented in this study, pulmonary functions of the small airways showed improvement after sublingual immunotherapy which was explained by immunologic remodelling [19].

Marogna et al showed that SLIT has a protective effect on the pulmonary functions contrary to pharmacoterapy [20].

FEF25-75% of SLIT-nonresponder and PT-nonresponder groups was lower than SLIT-responder and PT-responder patients, respectively, but in the course of time PT-nonresponder group showed significant decline in FEF%25-75 values compared to SLIT-nonresponder group. SLIT has a protective, and long-lasting effect on small airways. Moreover, SLIT caused a significant increase in FVC (%) after discontinuation of therapy.

CONCLUSION

Our study has demostrated that SLIT causes a satisfactory decrease in ICS dose even in SLIT-nonresponder patients and has protective effects on airways.

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