ORIGINAL ARTICLE

Randomized Open Comparison of Montelukast and Sublingual Immunotherapy as Add-on Treatment in Moderate Persistent Asthma Due to Birch Pollen

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Abstract

Background: No studies have directly compared the effects of immunotherapy and antileukotrienes due to the long time required to appreciate the clinical effects of immunotherapy. We compared the effect of montelukast (MK) and SLIT added to standard therapy in moderate asthma over 5 years.
Methods: Open randomized controlled trial. Patients with moderate asthma (and rhinitis) solely due to birch pollen were randomized to receive either MK (10 mg/d) or birch sublingual immunotherapy (SLIT) in the pollen seasons, in addition to formoterol/fluticasone. All the patients also received salbutamol and cetirizine as rescue medications. Asthma and rhinitis symptoms were recorded on diary cards from February to May at baseline and after 3 and 5 years of study. In-season nasal eosinophils and bronchial hyperresponsiveness were also evaluated.
Results: Thirty-three adult patients were enrolled and 29 completed the study. The groups were homogeneous at baseline. Bronchial and nasal symptom scores were lower at 3 and 5 years compared to baseline in the SLIT group. Bronchial hyperresponsiveness and bronchodilator use decreased significantly in both groups at 5 years, but only in the SLIT group at 3 years. In the SLIT group there was a significant decrease in nasal eosinophils compared to baseline and to the MK group.
Conclusion: In patients with birch pollen–induced moderate asthma and rhinitis, the addition of SLIT provides a greater clinical benefit than that of MK.

Key words: Sublingual immunotherapy. Montelukast. Moderate asthma. Birch pollen.

Resumen

Antecedentes: Hasta el momento ningún estudio ha comparado directamente los efectos de la inmunoterapia y los antagonistas de los leucotrienos, debido a que se requiere un largo período de tiempo para apreciar los efectos clínicos de la inmunoterapia. En este ensayo se ha comparado el efecto de montelukast (MK) y la inmunoterapia sublingual (ITSL) como complemento del tratamiento estándar del asma moderada durante cinco años.
Métodos: Ensayo controlado, aleatorizado y de diseño abierto. Pacientes con asma moderada (y rinitis) causada únicamente por el polen de

abedul fueron distribuidos aleatoriamente para recibir MK (10 mg/d) o ITSL, junto con formoterol/fluticasona, en las estaciones polínicas. Todos los pacientes recibieron también salbutamol y cetirizina como medicamentos de rescate. Los síntomas de asma y rinitis fueron registrados en un diario de febrero a mayo al inicio del estudio (valor basal) y a los 3 y 5 años. También se evaluaron los eosinófilos nasales y la hiperreactividad bronquial durante la estación polínica.
Resultados: Treinta y tres pacientes adultos fueron incluidos en el estudio y 29 lo completaron. Los grupos eran homogéneos al iniciar el estudio. Las puntuaciones de síntomas bronquiales y nasales fueron inferiores a los 3 y 5 años en comparación con el valor basal en el grupo de ITSL. La hiperreactividad bronquial y el uso de broncodilatadores disminuyeron en ambos grupos significativamente a los 5 años y a los 3 años sólo en el grupo de ITSL. En el grupo de ITSL se produjo una disminución significativa de los eosinófilos nasales, en comparación con el valor basal y el grupo de MK.
Conclusión: En pacientes con asma moderada inducida por polen de abedul y rinitis, la ITSL como tratamiento complementario proporciona un beneficio clínico mayor que el MK.

Palabras clave: Inmunoterapia sublingual. Montelukast. Asma moderada. Polen de abedul.

Introduction

Asthma is clinically characterized by episodes of reversible bronchial obstruction, and bronchial inflammation, together with remodeling, plays a crucial role in the pathophysiology of the disease. The inflammatory process involves a complex network of cells, cytokines, and mediators, among which leukotrienes are one of the most important effectors. This is why anti-inflammatory agents, namely corticosteroids and leukotriene antagonists (LTRAs), are considered the main controller medications [1,2]. In the case of respiratory allergy, however, specific immunotherapy (SIT) is the only treatment capable of modifying the response to allergens at the very early steps of the immune response, and of restoring the imbalance between type 1 helper (T_H1) and T_H2 lymphocyte subsets [3]. In recent years, the sublingual administration of immunotherapy (SLIT) has gained increasing credibility, and is now included in guidelines [4] and used in many European countries. The main advantages of SLIT are self-administration at home and the favorable safety profile in children as well as in adults [5,6]. The clinical efficacy of SLIT has been well-demonstrated for rhinoconjunctivitis, but its effects in asthma are still not clearly defined [7-10].

It has been repeatedly shown that SIT (and SLIT) can downregulate inflammatory phenomena in the target organs during exposure to allergens [11-13] and also reduce the degree of bronchial hyperresponsiveness [14-16], which is indirectly related to bronchial inflammation. Nonetheless, there are very few studies that have directly compared the effects of medications and SLIT in allergic asthma, and none of these have used LTRAs as a comparator. This is probably because long periods of observation are needed to fully appreciate the effects of SIT. This aspect is still a matter of debate. In order to shed some light on this matter, we planned a randomized controlled study to compare the effects of SLIT and montelukast (MK), as add-on therapy, in patients with birch-induced moderate persistent asthma (and rhinoconjunctivitis) by assessing several parameters over 5 years.

Methods

Study Design

We performed an open randomized controlled trial involving 2 parallel groups of patients with moderate persistent asthma due solely to birch pollen. Patients with an incomplete response to inhaled fluticasone/salmeterol (500/50 mcg twice daily) in the previous seasons were assessed for baseline parameters during the pollen season in 2001 (run-in) and then randomized to receive, in addition to the inhaled therapy mentioned and rescue medications, either MK 10 mg/day or SLIT. The evaluated parameters (seasonal symptoms plus drug intake score, pulmonary function, bronchial hyperresponsiveness, and nasal eosinophils) were assessed at run-in, and after 3 and 5 years of treatment (2004 and 2006). The study design is summarized in Figure 1. Due to the duration of the study, the ethics committee denied permission to blind the treatments and to use a placebo arm. All the patients signed an informed consent form.

Patients and Diagnosis

Outpatients referred to the allergy unit at Cuasso al Monte Hospital in Varese, Italy with moderate persistent asthma and rhinitis due to birch pollen were enrolled for

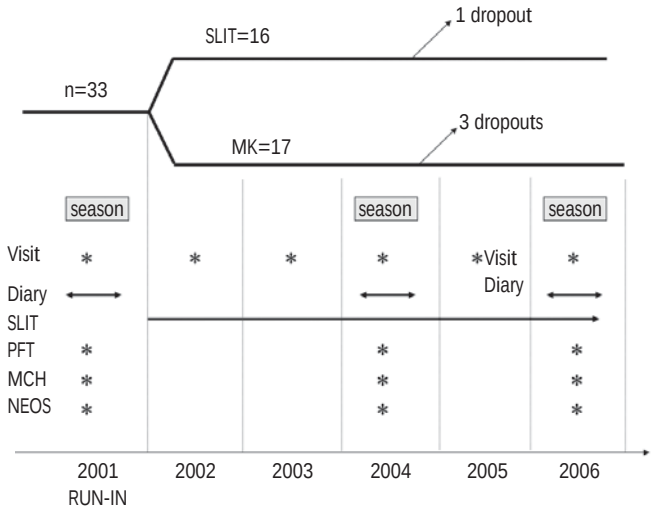

Figure 1. Study design. SLIT indicates sublingual immunotherapy; MK, montelukast; PFT, pulmonary function test; MCH, methacholine challenge; NEOs, nasal eosinophils in scrapings.

the study. Inclusion criteria were *a)* age between 18 and 65 years; *b)* a clinical history of moderate asthma [1] and rhinitis during the local birch season only for at least 2 years; *c)* forced expiratory volume in 1 second (FEV_1) of between 60% and 80% of predicted; and *d)* single sensitization to birch. Exclusion criteria were *a)* intermittent, mild, or severe persistent asthma (<60% of predicted); *b)* skin sensitizations caused by allergens other than birch or symptoms out of the birch pollen season; *c)* previous courses of immunotherapy; *d)* systemic immunological diseases, malignancies, or long-term treatment with systemic steroids; and *e)* major anatomical abnormalities of the nose, including polyps, septal deviation, and turbinate hypertrophy. The diagnosis of moderate asthma was made according to the 1995 Global Initiative for Asthma guidelines [17], which were the guidelines available when the study started. Rhinitis was diagnosed according to the Allergic Rhinitis and its Impact on Asthma guidelines [4]. Response to inhaled medications (salmeterol/fluticasone) was considered incomplete when asthma symptoms persisted despite the treatment. Skin prick tests were performed according to recommendations using a standard panel that included mites, grass, *Parietaria*, birch, olive, mugwort, ragweed, cat, dog, *Alternaria*, and cladosporium (Alk Abello, Lainate, Milan, Italy). Positive (histamine 1%) and negative (diluent) controls were also applied. The result was considered positive for a wheal diameter greater than 5 mm.

Interventions

SLIT was given as a glycerinated solution, standardized in RAST units (RU/mL, (Anallergo, Florence, Italy) [18], and prepared in vials at 5 different concentrations (100-300-1000-3000-10 000 RU/mL). The build-up lasted for 40 days, with daily increasing doses from each vial, until the concentration of 10 000 RU/mL was reached. The maintenance dose was 5 drops from the 10 000 RU mL vial 3 times a week. The treatment was given continuously from July 2001 until July 2006. The cumulative annual dose was on average 100 mcg Bet v 1, which is about 10 times greater than the amount administered subcutaneously. All patients receiving SLIT were carefully informed about the administration technique and possible side effects. A physician was available for phone contact in case of problems related to SLIT. Patients were instructed to record any troublesome effect related to the technique. The inhaled salmeterol/fluticasone therapy was administered using a commercial device (Seretide Diskus; GSK, Verona, Italy). All the patients were instructed on the correct use of the device, with assessment of inspiratory flow (Optimum Inspiratory Flow, HS Clement Clarke International, Essex, UK). Correct inhalation technique was checked at each control visit.

Adherence to SLIT was assessed by measuring the remaining volume of extract in the returned vials, adherence to MK was measured by counting the returned tablets, and adherence to inhaled therapy was assessed through the dose counter in the diskus device. Adherence was expressed as a percentage corresponding to the ratio between actual and expected consumption according to prescription. All the patients received oral cetirizine 10 mg daily during the pollen seasons in addition to, as rescue medications, inhaled salbutamol (100 mcg per puff, 1-2 puffs on demand) for lower airway symptoms, and nasal budesonide (200 mcg/d) for rhinitis symptoms, according to physician prescription.

Symptom and Drug Intake Scores

The patients were instructed to fill in a diary card from March to May in 2001, 2004, and 2006, recording symptoms and drugs used. Symptoms were subdivided into upper airway symptoms (nasal itching, discharge, sneezing, and obstruction) and lower airway symptoms (cough, wheezing, chest tightness, and nocturnal symptoms). Each symptom was scored from 0 (absent) to 3 (severe). The total possible maximum monthly score was therefore 360 for both. Each dose of rescue medication (inhaled salbutamol or nasal budesonide) was scored 1. A mean monthly score for bronchial symptoms (lower airway score, LAS) and nasal symptoms (upper airway score, UAS) was then calculated for the 3-month period and used for the statistical analysis. The intake of nasal corticosteroids (NCS) and bronchodilators ($ß_2$ agonists) in the same period was also calculated.

Pulmonary Function and Methacholine Challenge

Pulmonary function tests were carried out with a computerized spirometer (Masterlab; Jaeger, Würzburg, Germany) and forced vital capacity and FEV_1 were measured. The methacholine challenge was performed during the pollen season. The test was carried out with an inspiration-activated dosimeter (Jaeger), delivering between 30 and 1200 mcg of methacholine in refracted doses. A computerized dose-response curve identified the provocation dose causing a 20% fall in FEV_1 from baseline (PD_{20}). The test was considered negative if no response was obtained at 1200 mcg of methacholine [19].

Nasal Eosinophils

Nasal smears were collected with a cotton swab from the anterior third of the inferior turbinate. The smears were transferred onto a glass slide, air-dried, stained with May Grünwald-Giemsa, and read using optical microscopy [20]. Eosinophils were expressed as a percentage of the total cells per 10 fields. Smears were collected during the birch pollen season, with patients being advised to discontinue intranasal steroids (if used) at least 10 days beforehand.

Statistical Analysis

Equality of sex ratios in the different treatment groups at baseline were tested using the Fisher exact test, while differences in baseline levels of clinical parameters were tested using the Mann-Whitney test. The different effects of treatments on the clinical parameters each year were also tested with the Mann-Whitney test [21,22], whilst variations in parameters between successive time steps (2000-2001, 2001-2004 and 2004-2006) were compared with the Wilcoxon test for paired comparisons. To increase the statistical power to reach the same level gained by the corresponding parametric statistics computed when all assumptions were met, the probability levels for Pearson χ^2, Mann-Whitney, and Wilcoxon tests were computed using a complete randomization method (permutation or exact test;

PExact) [23] or Monte Carlo simulations based on 100 000 sampled tables (PMC) when computation by the permutation method was not possible. All the statistical analyses were performed using the Statistical Package for Social Sciences (SPSS), version 12.01.

Results

Thirty-three patients fulfilling the inclusion criteria were randomized to SLIT (16 patients) or MK (17 patients), and 29 of them completed the study. There were 4 dropouts during the first year: 3 in the MK group (2 lost to follow-up and 1 who did not comply with the diary card requirements) and 1 in the SLIT group (lost to follow-up). The pollen counts were comparable in the 3 years studied (Figure 2).

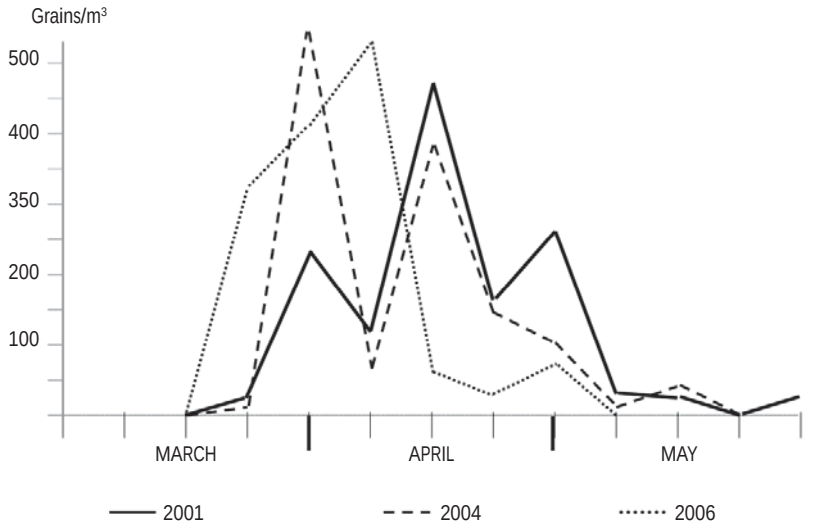

Figure 2. Pollen counts in years 2001, 2004, and 2006.

There were no significant differences for sex ratio (χ^2=0.022, *P*=0.881), age (U=106.5, W=259.5, P_{Exact}=.292), or clinical parameters at baseline (Table 1). Direct comparisons

Table. Summary of Parameters Evaluated at Baseline (2001) and in Subsequent Pollen Seasons

Clinical Parameters		Treatment						
			Montelukast		Sublingual Immunotherapy			
		Mean	SEM	Mean	SEM	W	Z	P_{Exact}
2001	UAS	93.6	7.4	82.0	7.0	242	-1.081	.288
	LAS	166.4	7.9	186.1	10.3	253	-1.298	.204
	NCS	16.6	1.0	15.8	1.1	258.5	-0.488	.636
	ß$_2$	19.4	.9	20.1	.7	264.5	-0.887	.385
	NEOs	15.6	1.1	16.0	.9	285	-0.145	.894
	FEV$_1$	76.4	1.3	78.5	1.0	250.5	-1.391	.169
	MEF	64.3	2.1	58.1	2.0	218	-1.947	.052
	MCh	288.6	44.9	326.4	50.1	271	-0.648	.533
2004	UAS	90.9	7.8	47.5	4.8	171.5	-3.487	.000
	LAS	164.1	9.6	80.4	6.7	140	-4.675	.000
	NCS	15.7	.7	8.9	1.0	157	-4.043	.000
	ß$_2$	17.1	1.0	9.4	.6	151.5	-4.251	.000
	NEOs	13.6	1.3	9.4	1.3	212.5	-1.945	.052
	FEV$_1$	78.1	1.3	91.9	1.6	146.5	-4.437	.000
	MEF	63.9	1.9	75.5	2.9	188.5	-2.848	.004
	MCh	315.0	38.3	804.5	69.5	149	-4.334	.000
2006	UAS	86.4	10.6	26.8	2.8	139	-3.756	.000
	LAS	158.9	7.6	39.4	5.6	120	-4.583	.000
	NCS	15.0	1.0	4.3	.7	120	-4.591	.000
	ß$_2$	15.8	1.0	4.0	.9	121.5	-4.528	.000
	NEOs	14.0	1.1	3.9	.9	124	-4.426	.000
	FEV$_1$	81.2	1.4	96.2	1.2	110.5	-4.348	.000
	MEF	67.6	1.8	85.5	2.2	116	-4.107	.000
	MCh	478.7	76.2	919.3	85.7	137	-3.186	.001

Abbreviations: ß$_2$, bronchodilator; FEV$_1$, forced expiratory volume in 1 second; LAS, lower airway score; Mch, methacholine challenge; MEF, midexpiratory flow; NCS, nasal corticosteroids; NEOS, nasal eosinophils; UAS, upper airway score.

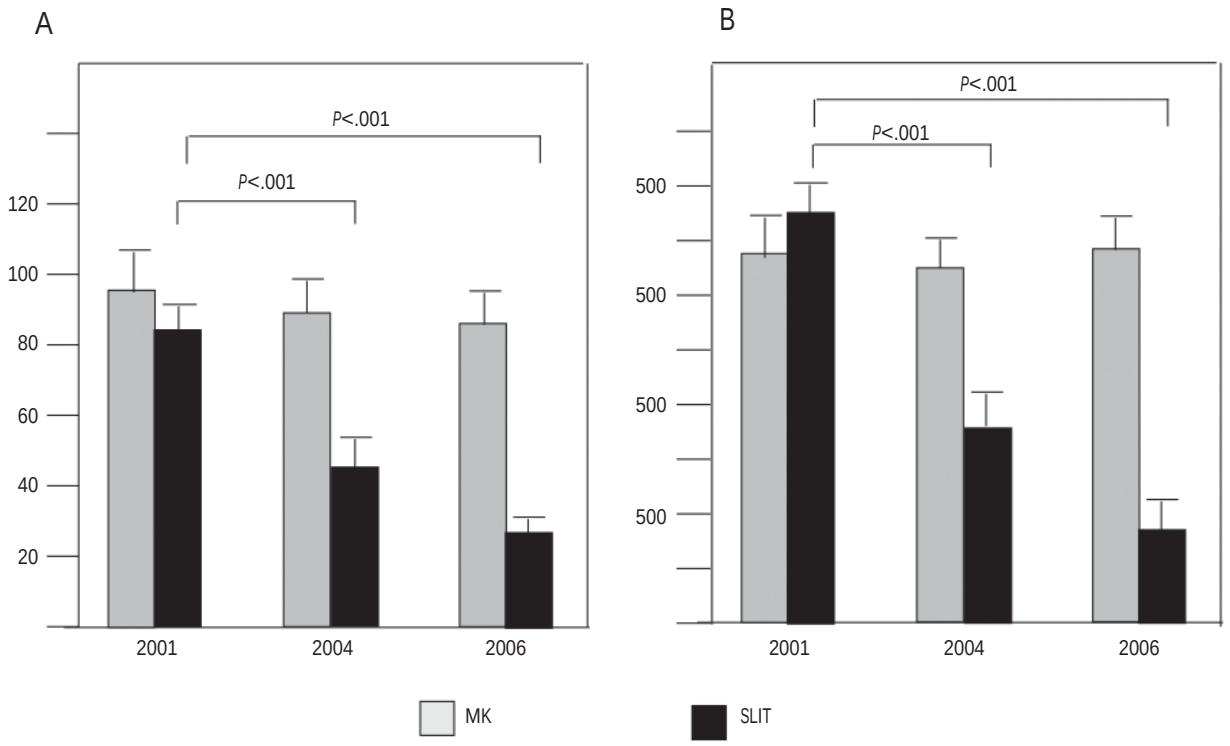

Figure 3. A, Upper airway scores (mean ±SEM). B, Lower airway scores (mean ±SEM). Significant differences with respect to baseline are shown above the bars. MK indicates montelukast; SLIT, sublingual immunotherapy.

of clinical parameters between the 2 groups evidenced a significant difference at 3 and 5 years of treatment (Table 1) for all parameters except nasal eosinophils (P_{Exact}=.052), whose difference become significant only at 5 years.

The UAS improved significantly in the SLIT group at years 3 and 5 compared to baseline (Figure 3A), as did the LAS (Figure 3B); no such changes were seen in the MK group. The intake of ß$_2$ agonists was significantly reduced at 5 years compared to baseline in both groups. At 3 years the reduction was significant only in the SLIT group. (Figure 4). A similar behavior was seen for methacholine reactivity, which was lower than baseline at year 3 in the SLIT group only (Figure 5). FEV_1 displayed a constant increase for the SLIT group, with a significant difference between 2001 and 2006, but this trend was not detected in the MK group (Figure 6). Nasal eosinophils were significantly reduced at years 3 and 5 compared to baseline but only in the SLIT group (data not shown).

Adherence to SLIT over the study period was >80% in 10 patients and >60% in 5 patients; adherence to MK was >80% in the 14 patients who completed the study. Adherence to inhaled therapy was on average 73% in the SLIT group and 79% in the MK group, with no significant differences. The treatments were equally well tolerated, with no reported adverse events for either SLIT or MK. None of the dropouts was related to possible treatment side effects.

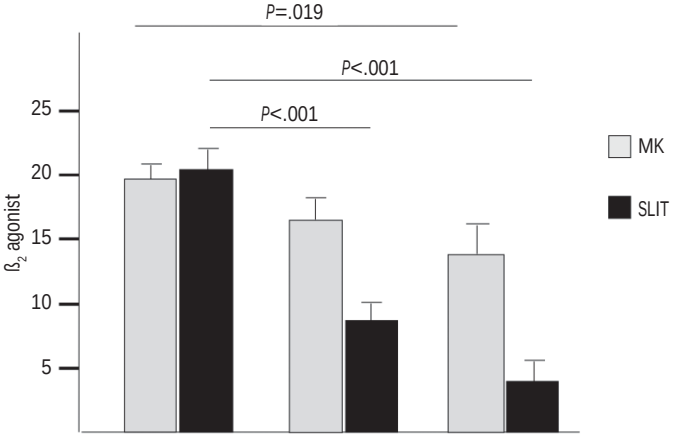

Figure 4. ß$_2$ agonist intake. Significant differences with respect to baseline are shown above the bars. MK indicates montelukast; SLIT, sublingual immunotherapy.

Discussion

SIT has a complex mechanism of action, essentially affecting the early steps of the immune response to allergens [3]. This mechanism involves the selective downregulation of T_H2 cytokine and cell responses, presumably mediated by T regulatory cells. The final result is a broad spectrum of anti-inflammatory actions at the target organ level. Clinical effects are not, therefore, immediate as with traditional drugs such as

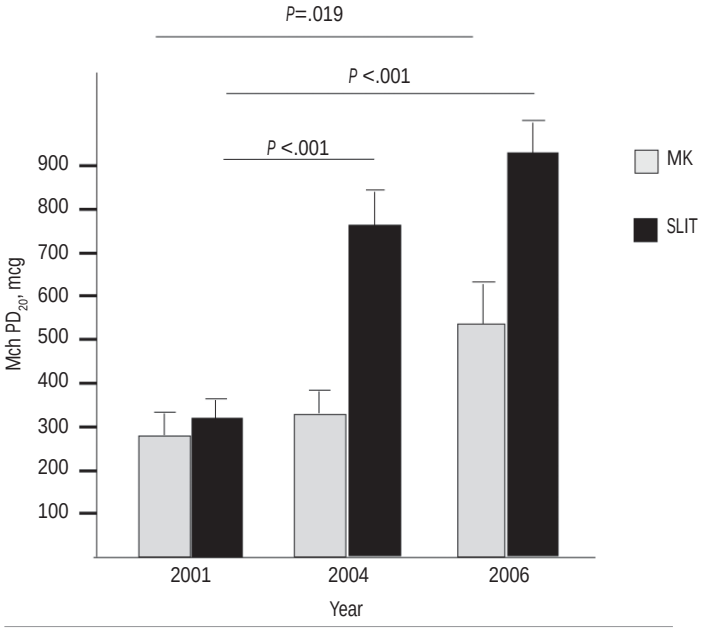

Figure 5. Methacholine PD_{20} (provocative dose causing a 20% decrease in forced expiratory volume in 1 second with respect to baseline) (mean ±SEM). Significant differences with respect to baseline are shown above the bars. MK indicates Montelukast; SLIT, sublingual immunotherapy.

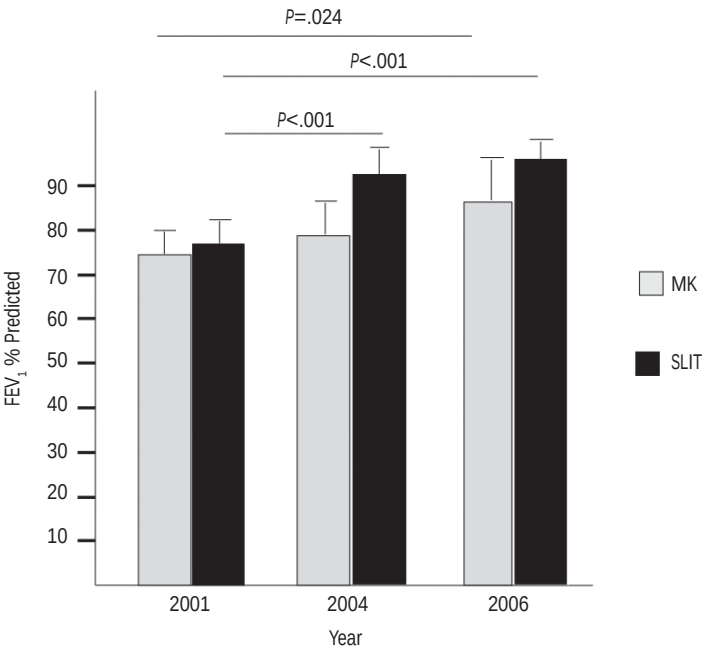

Figure 6. Forced expiratory volume in 1 second as % of predicted (mean ±SEM). Significant differences with respect to baseline are shown above the bars. MK indicates Montelukast; SLIT, sublingual immunotherapy.

bronchodilators and antihistamines, but the immunomodulation is profound and long-lasting. It is therefore currently recommended that SIT should not replace drugs, but be used in addition to them, in order to achieve the maximum benefit [4]. Nevertheless, the direct comparison of the effects of drugs and SIT is still a matter of debate. The main problem in such comparison studies is that the clinical benefits of SIT can be appreciated only in the long term, whereas pharmacotherapy has a prompt action that can be measured within days. Another problem is that a rigorous head-to-head comparison would require a double-blind, double-dummy design, which is difficult to do for long periods.

Very few studies have compared SIT and drug therapy. Rak et al [24], in a double-blind study, showed that nasal steroids were more effective than SIT in controlling rhinitis in the short term, although SIT decreased seasonal bronchial hyperresponsiveness in asthmatic patients. Similarly, Pajno et al [25], in a placebo controlled trial, demonstrated that the clinical efficacy of SLIT plus fluticasone is equal to that of fluticasone alone, but that the addition of SLIT also improved nonbronchial symptoms. Shaikh [26] compared SIT and inhaled budesonide in an open study and found that the steroid produced a more rapid and relevant benefit than SIT, but that SIT maintained its effects after discontinuation. Overall, these short-term studies failed to demonstrate a clear advantage of immunotherapy over drugs. On the other hand, another randomized controlled trial comparing SLIT and inhaled budesonide in mild asthma showed that SLIT achieved a greater benefit than the inhaled steroid over a 5-year period, with the additional value of a reduction in nasal symptoms [27]. In the present study we compared SLIT and oral MK as add-on therapy in patients with moderate persistent asthma, taking into account different parameters. Evaluations were made at 3 and 5 years in order to fully appreciate the effects of SLIT. Bronchial and nasal scores and nasal eosinophils improved significantly compared to baseline in SLIT patients only, thus corroborating the systemic effect of SLIT. The intake of $ß_2$ agonists and bronchial hyperresponsiveness changed in both groups at 5 years, but only in the SLIT group at 3 years.

The main limitation of this study is the absence of a placebo control, which was not allowed by the ethics committee due to the long duration of the study. A double-dummy design was also not feasible for practical reasons. In order to ensure maximum patient adherence to the study protocol and to fully appreciate the slow-onset benefits, the investigational parameters were assessed after 3 and 5 years of treatment. Obviously, some data are missing with this design but this was counterbalanced by the very "clean" model, i.e. we studied just monosensitized patients with symptoms only during the pollen season. It is worthy of note that the definition of moderate asthma has changed since the study was initiated [17]. The patients enrolled in our study would now be classified as having severe asthma. In this regard, our results would suggest that SLIT may also be used with a favorable safety profile in severe asthma according to the current classification.

In conclusion, adding SLIT to standard antiasthma treatment produces a greater benefit overall than adding

oral MK in patients with moderate asthma and rhinitis due to birch: It also downregulates local nasal inflammation and nonspecific bronchial responsiveness.

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