to the imported fire ant in Florida: report of 104 cases. J Fla Med Assoc 1977;64:247-54.
10. Hoffman DR, Jacobson RS, Schmidt M, Smith AM. Allergens in Hymenoptera venome XXIII: venom content of imported fire ant whole body extract. Ann Allergy 1991;66:29-31.
11. Golden DBK, Addison BI, Gadde J, Kagey-Sobotka A, Valentine MD, Lichtenstein LM. Prospective observations on stopping prolonged venom immunotherapy. J ALLERGY CLIN IMMUNOL 1989;84:162-7.
12. Bousquet J, Knani J, Velasquez G, Menardo JL, Guilloux L, Michel FB. Evolution of sensitivity to Hymenoptera venom in 200 allergic patients followed for up to three years. J ALLERGY CLIN IMMUNOL 1989;84:944-50.
13. Reisman RE, Lantner R. Further observations of stopping venom immunotherapy: comparison of patients stopped because of a fall in serum venom specific IgE to insignificant levels with patients stopped prematurely by self-choice. J ALLERGY CLIN IMMUNOL 1989;83:1049-54.
14. Paull BR, Coghlan TH, Vinson SB. Fire ant venom hypersensitivity. 1. comparison of fire ant venom and whole body extract in the diagnosis of fire ant allergy. J ALLERGY CLIN IMMUNOL 1983;71:448-53.
15. Nordvall SL, Johansson SGO, Leford DK, Lockey RF. Allergens of the imported fire ant. J ALLERGY CLIN IMMUNOL 1988;82:567-76.

Inhibitory effect of cetirizine on the bronchial eosinophil recruitment induced by allergen inhalation challenge in allergic patients with asthma

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In patients with asthma there is a recruitment of eosinophils in bronchoalveolar lavage fluid (BALF) after the late asthmatic reaction (LAR). Cetirizine is a selective H_1 antagonist that inhibits the eosinophil recruitment induced by allergen in the skin. The aim of this study was to evaluate whether cetirizine was able to inhibit the LAR-induced inflammatory reaction. Twelve allergic asymptomatic subjects with asthma (aged 18 to 58 years) without any treatment were enrolled in the study; FEV_1 was >83% predicted in each case. An allergen inhalation-challenge test was performed to assess the presence of an LAR. In a double-blind, randomized, placebo-controlled study, the patients were treated for 8 days with either cetirizine, 15 mg twice a day (six patients, group 1), or placebo (six patients, group 2). On day 8, a second allergen inhalation-challenge test with the same allergen was performed, and BAL was realized 24 hours later; as usual 250 ml of saline was instilled by 50 ml aliquots, and the first recovery was analyzed separately. In each case, the LAR observed after treatment was similar to the first one. In placebo-treated patients, an increased number of cells, mainly eosinophils, was observed in the first recovery of BALF compared with the number in subsequent recoveries. These numbers were significantly higher than numbers observed in cetirizine-treated patients. Cetirizine did not modify significantly the allergen inhalation-challenge test, but it inhibited the recruitment of inflammatory cells, mainly eosinophils. (J ALLERGY CLIN IMMUNOL 1992;90:215-24.)

Key words: *Asthma, eosinophils, bronchoalveolar lavage, allergen inhalation challenge, cetirizine*

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Eosinophils are now considered to be one of the main cell types involved in inflammation of the asthmatic lung. Eosinophils can generate a wide range of mediators and play an important role in the pathogenesis of bronchial asthma, including bronchial hyperreactivity,[1-3] bronchial epithelial damage,[4, 5] and probably ageing of the bronchi.[6] Eosinophils are observed even in mild asthma in the BALF,[7-13] as well

as in the bronchial wall.[14] Their number increases significantly both in blood and BALF according to the severity of asthma.[15] Therefore, in addition to the clinical definition of asthma,[16] some authors consider asthma from a pathologic standpoint as "a chronic eosinophilic and desquamative bronchitis."[17]

Eosinophils appear to be recruited to the bronchial tree in asthma since they are always absent in normal healthy subjects,[18, 19] and a small number is found in subjects with very mild asthma.[7] De Monchy et al.[20] was the first author who demonstrated that eosinophils were preferentially observed in BALF 6 hours after an allergen bronchial challenge test in patients who developed an LAR. Their results were developed further by other authors.[21-24] Furthermore, the fall in the peripheral eosinophil count at the time of the LAR,[25] followed by an increase in number 24 hours later,[2] suggests that these cells may have been recruited to the lung. However, the time course and the site of eosinophil recruitment have not yet been fully established.

Cetirizine is a carboxylated analogue of hydroxyzine that has a potent and specific H_1-receptor–blocking activity in the skin, the nose, or the lung. Moreover, it exhibits several other important properties that are potentially relevant in the treatment of asthma. It inhibits eosinophil chemotaxis in vitro[26]; in vivo it inhibits eosinophil, basophil, and neutrophil migration into the skin chamber after antigen-induced allergic reactions[27, 28]; it inhibits eosinophil accumulation in the skin whether the challenge is anti-IgE antibodies, platelet-activating factor, or delayed-pressure urticaria.[29-31] This treatment provides protection against the bronchial histamine challenge,[32] providing a significant dose effect,[33] and appears to be useful in pollen-induced asthma.[34, 35]

Cetirizine disclosed only a weak bronchodilator effect, but it could potentiate the bronchodilatator activity of salbutamol, at least in vitro.[36]

The aim of this study was to evaluate whether treatment with cetirizine is able to inhibit the bronchial eosinophil recruitment after an allergen inhalation challenge.

PATIENTS AND METHODS

Patients

Twelve allergic patients with asthma were enrolled in the study. Asthma was defined according to the criteria of the American Thoracic Society.[16] Patients were required to have very mild asthma with an FEV_1 >80% of predicted values during the study. Severity of asthma was evaluated by the scoring system of Aas.[37]

Allergy was defined by the clinical history of asthma and at least a positive skin prick test to either *Dpt* or GP. All patients had undergone a previous relevant allergen inhalation-challenge test with documented LAR during the previous 12 months and were enrolled at a time when there was a low prevalence of allergen.

Abbreviations used

BAL:	Bronchoalveolar lavage
BALF:	Bronchoalveolar lavage fluid
EAR:	Early asthmatic response
LAR:	Late asthmatic response
Dpt:	*Dermatophagoides pteronyssinus*
GP:	Grass pollen
PD_{20}:	Provocative dose causing a 20% fall in FEV_1
PEFR:	Peak expiratory flow rate
b.i.d.:	Twice daily
AUC:	Area under the curve

All patients were nonsmokers and had no history of bronchial or respiratory tract infection or severe exacerbation 3 months before their enrollment. Asthma was controlled by β_2-agonists that were withdrawn at least 12 hours before the challenge. No patient had received oral corticosteroids for at least 1 month, nor inhaled corticosteroids, nedocromil sodium, or cromoglycate sodium during the 15 days before the beginning of the study.

The study was approved by the university ethical committee, and informed consent was signed by each subject.

Allergen bronchial-inhalation challenge

Both the first and the second allergen inhalation-challenge test required by the inclusion criteria were performed in exactly the same manner according to standardized methods.[38]

Lyophilized and standardized extracts of allergen (*Dpt* and GP) were purchased from Stallergenes Laboratories (Paris) and were prepared with two isotonic saline dilutions (1/100 and 1/1000), as previously described.[39]

Allergen preparations were delivered to the patients with a dosimeter device, MEFAR (Brescia, Italy), which consisted of a breath-activated solenoid valve with a source of compressed air. This device was set to deliver 8.4 mg of solution during 1 second.[40] The nebulized particles had a mass median diameter ranging from 1.53 to 1.60 μm. The patients wore a noseclip and inhaled slowly through a mouthpiece going from functional residual capacity to total lung capacity, triggering the delivering device with inspiratory flow; 10 seconds were allowed between breaths. FEV_1 measurements were monitored by a pneumotachograph (Pneumoscreen, Hellige GmbH, Freiburg/Breisgau, Germany) during forced expiration. FEV_1 was recorded before and 10 minutes after inhalation of saline inhalation. If FEV_1 had not fallen by >10% of the baseline value, the inhalation challenge was performed with the allergen.

Inhalation of allergen with doubling doses was performed until a 20% fall in FEV_1 from the postsaline value was reached. The first dose of allergen was 8 μg. Assessment of FEV_1 was made 10 minutes and 30 minutes after each dose of allergen.

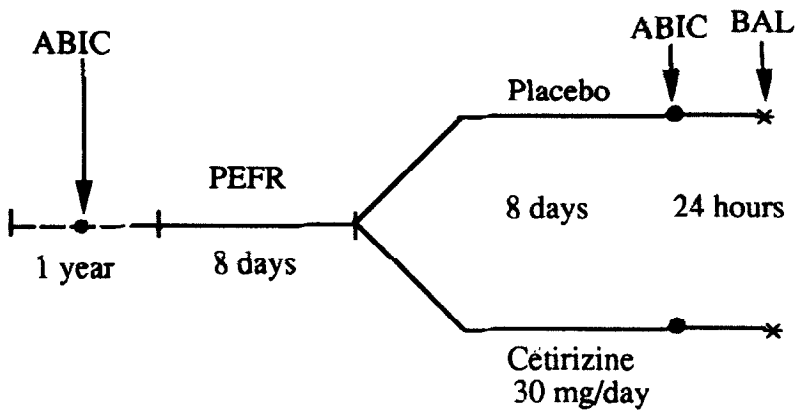

FIG. 1. Study design. Randomized, double-blind, placebo-controlled study in two parallel groups; *ABIC,* allergen bronchial inhalation challenge.

The EAR was monitored by FEV_1 every 10 minutes during the first hour. The LAR was defined by a 15% or greater fall in FEV_1 from the prechallenge value[41] and was assessed by measurement of FEV_1 every hour during the next 7 hours. FEV_1 was also recorded at the twelfth and twenty-fourth hour, and PEFR values were recorded and compared to the run-in period.

BAL

Twenty-four hours after the inhalation-challenge test, a fiberoptic bronchoscopy (BF1TR; Olympus Co., Tokyo, Japan) and BAL were performed as previously described.[42] Briefly, patients were premedicated with diazepam (5 mg) and atropine (0.5 mg); local anesthesia was achieved with lidocaine, 2%; BAL was performed in a subsegmental bronchus of the right middle lobe. Five 50 ml aliquots of saline at room temperature were instilled and gently aspirated with a syringe. The first aliquot was analyzed separately; the other four aliquots were pooled. BALF was filtered through a gauze, kept in plastic tubes on ice, and transported immediately to the laboratory. The same investigator performed all the bronchoscopies double-blind.

Analysis of BALF

The total cell count was obtained on aliquots of 5 ml of each sample with a hemacytometer. Cell differential counts were performed after cytocentrifugation at a speed of 1000 rpm for 10 minutes (Cytospin, Shandon Southern Products, Cheshire, England), and staining was done by May-Grünwald-Giemsa by counting 200 cells on each slide. We did not use the toluidine blue stain because the aim of our study was to analyze total cells and eosinophils and not mast cells. Results were listed both in percentages and absolute numbers of cells per milliliter of fluid recovered. The first and second sample were coded. All the slides were analyzed blindly by the same pathologist who was unaware of the clinical and therapeutic data.

Study design (Fig. 1)

The study was randomized, double-blind, and placebo controlled and was made in two parallel groups.

At the first visit, the inclusion criteria were checked as described. The patients were asked to record PEFR and their symptoms b.i.d. for a week (run-in period) to disclose any instability.

At the second visit, if there was no instability and if the blood eosinophil count was within the normal range, the patient received either placebo or cetirizine (15 mg b.i.d.) for 8 days. Patients were asked to record their symptoms, the presence of any side effects, and their PEFR values b.i.d. on a diary card.

At the last visit, patients arrived at the hospital at 8 AM to undergo the allergen inhalation challenge and a BAL 24 hours later; the last tablet was administered 12 hours before the BAL.

Expression of the results and statistical analysis

The EAR was determined by PD_{20} FEV_1.

The LAR was measured by the maximal fall in FEV_1 3 to 8 hours after the allergen inhalation-challenge test. The AUC was also calculated between 3 and 8 hours, as previously described by Townley et al.[43]

All the results were expressed as mean ± SD. When it was appropriate, the median was also indicated. The Mann-Whitney U test was used for all comparisons; p values $<5\%$ were considered to be statistically significant.

RESULTS

The characteristics of the patients were similar in the two groups, and no significant difference was found for age (36.3 versus 24.4 years; $p = 0.24$), sex (four male and two female patients in each group), weight (70.3 versus 69.5 kg; $p = 0.80$), and PD_{20} allergen (37.1 versus 87.1 μg; $p = 0.48$) (Table I). At the beginning of the study, FEV_1 measurements ranged from 83% to 123% of the predicted value (average, 111% ± 14% and 107% ± 17% in the placebo-treated and cetirizine-treated groups, respectively), and it remained similar at visit 2 and just before the allergen inhalation challenge. Four patients

TABLE I. Individual data of patients

No.	Age (yr)	Weight (kg)	Sex	Allergen	FEV_1 % predicted	PD_{20} allergen (μg)
Placebo						
1	38	84	F	*Dpt*	117	42.4
2	23	80	M	*Dpt*	115	41.1
3	21	65	M	GP	123	2
4	56	48	F	GP	113	22
5	19	65	M	*Dpt*	83	17
6	58	80	M	*Dpt*	114	100
Mean	36.3	70.3			111	37.1
SD	17.8	13.6			14	34.2
Cetirizine						
7	19	75	M	*Dpt*	100	16.8
8	33	74	F	*Dpt*	86	72
9	28	67	M	*Dpt*	121	33
10	26	72	M	GP	102	196
11	18	53	F	*Dpt*	122	182
12	20	76	M	GP	116	21
Mean	24.4	69.5			107	87.1
SD	6.3	8.7			17	81.6

were sensitive to *Dpt* and two to GP in each group.

The mean duration of asthma was also comparable in placebo-treated and cetirizine-treated groups and averaged 13 versus 7.5 years, respectively. Four patients had an Aas score of 1 and two had a score of 2 in each group. No patients disclosed any instability.

In spite of the high doses of cetirizine used, there were few side effects. There were two cases of mild drowsiness in the placebo-treated versus one in the cetirizine-treated group.

The allergen PD_{20}, as assessed during the first challenge, was similar in the two groups and averaged 37.1 ± 34.2 μg (median, 31.6) in the placebo-treated group versus 87.1 ± 81.6 μg (median, 52.8) in the cetirizine-treated group. The PD_{20} FEV_1, as assessed at the end of the 8-day treatment period, was unchanged in the placebo-treated group (68 ± 36 μg; median, 69), and was higher in the cetirizine-treated group (655 ± 1110 μg; median, 244), but the difference did not reach statistical significance. Actually, the PD_{20} increased significantly in three patients and remained unchanged in the other three patients (Fig. 2). The EAR, as expressed by maximal fall in FEV_1, was similar in the two groups of patients (data not presented).

The LAR was observed in each patient and was remarkably reproducible in both groups; the FEV_1 maximal fall averaged 31.3% ± 18.6% and 31.2% ± 14.7% before and after treatment, respectively, in the placebo-treated group and 21.9% ± 7.0% and 20.7% ± 8.3%, respectively, in the cetirizine-treated group; the comparison between the two groups of patients disclosed no statistically significant difference. As assessed by the AUC FEV_1 percent (3 to 8 hours), the LAR was also similar before and after treatment in the two groups of patients (Table II).

Bronchoscopy and BAL were well tolerated by each patient. No β_2-agonists were required at the end of the procedure.

The total BALF recovery averaged 141.3 ± 45 ml and 135.8 ± 9 ml in the placebo- and the cetirizine-treated patients, respectively; the difference was not statistically different in the two groups, either for the first recovery or for subsequent recoveries.

The total cell count in the first recovery (Fig. 3) was significantly higher in the placebo-treated group, 358 ± 574 × 10^3 cells per milliliter (median, 140 × 10^3 cells per milliliter), than in the cetirizine-treated patients, 78 ± 38 × 10^3 cells per milliliter (median, 71 × 10^3 cells per milliliter; $p = 0.041$). The total eosinophil count in the first recovery (Table III) was significantly higher ($p = 0.015$) in the placebo-treated group, 105.6 ± 247.7 × 10^3 cells per milliliter (median, 4.2) than in the cetirizine-treated group, 1.3 ± 1.1 × 10^3 cells per milliliter (median, 1.2).

The differential eosinophil count in the first recovery was lower in the cetirizine-treated group compared with that of the placebo-treated group, but the difference was not statistically significant (Fig. 4).

In the subsequent BAL recoveries, the total cell count and the differential cell count were similar in

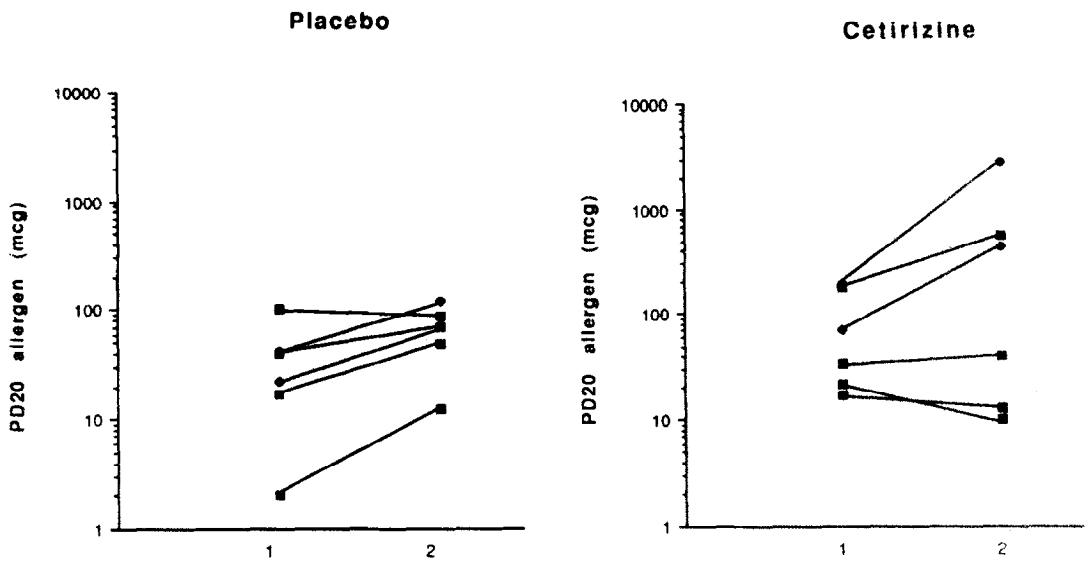

FIG. 2. Changes in allergen PD_{20} (μg): *1*, at baseline; *2*, after treatment either by placebo or cetirizine.

TABLE II. LAR as assessed by maximal fall in FEV_1 percent or AUC FEV_1 percent (3 to 8 hours) in cetirizine-treated and placebo-treated groups (mean ± SD)

		Placebo	Cetirizine	*p*
1	Maximal fall in FEV_1	31.3 ± 18.6	21.9 ± 7.0	NS
2	Maximal fall in FEV_1	31.2 ± 14.7	20.7 ± 8.3	NS
1	AUC FEV_1% (3 to 8 hr)	111.4 ± 71.4	86.5 ± 42.0	NS
2	AUC FEV_1% (3 to 8 hr)	97.7 ± 67.0	77.8 ± 26.6	NS

1, Before treatment; *2*, after treatment; *NS*, not significant.

TABLE III. BAL: Total and differential cell counts in the bronchial sample ($\times 10^3$ cells per milliliter)

		Placebo	Cetirizine	*p* Value
Total cells	10^3 cells/ml	358 ± 574	78 ± 38	0.041*
Macrophages	Mean	161.0 ± 177.9	64.8 ± 31.0	0.093
	Median	90.6	59.4	
Lymphocytes	Mean	14.3 ± 19.9	4.4 ± 4.2	1
	Median	4.1	2.6	
Eosinophils	Mean	105.6 ± 247.7	1.3 ± 1.1	0.015*
	Median	4.2	1.2	
Neutrophils	Mean	39.5 ± 78.7	2.8 ± 4.6	0.18
	Median	3.9	0.9	
Epithelial cells	Mean	35.0 ± 59.1	5.1 ± 5.3	0.485
	Median	12.5	3.1	

*p Value, <0.05.

the two groups of patients (Fig. 5). The percentage of eosinophils was 1.3% ± 1.6% and 2.0% ± 1.4% in the placebo-treated group and the cetirizine-treated group, respectively.

DISCUSSION

Twenty-four hours after an allergen bronchial-challenge test, a BAL was performed in 12 patients with asthma. The total number of cells and eosinophils was

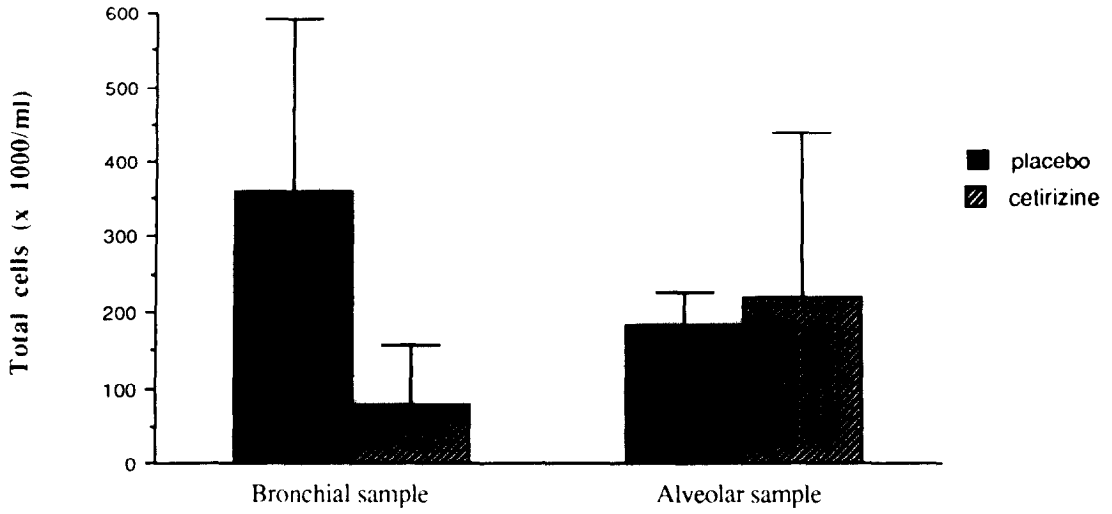

FIG. 3. Total cell count in bronchial and alveolar sample of BAL.

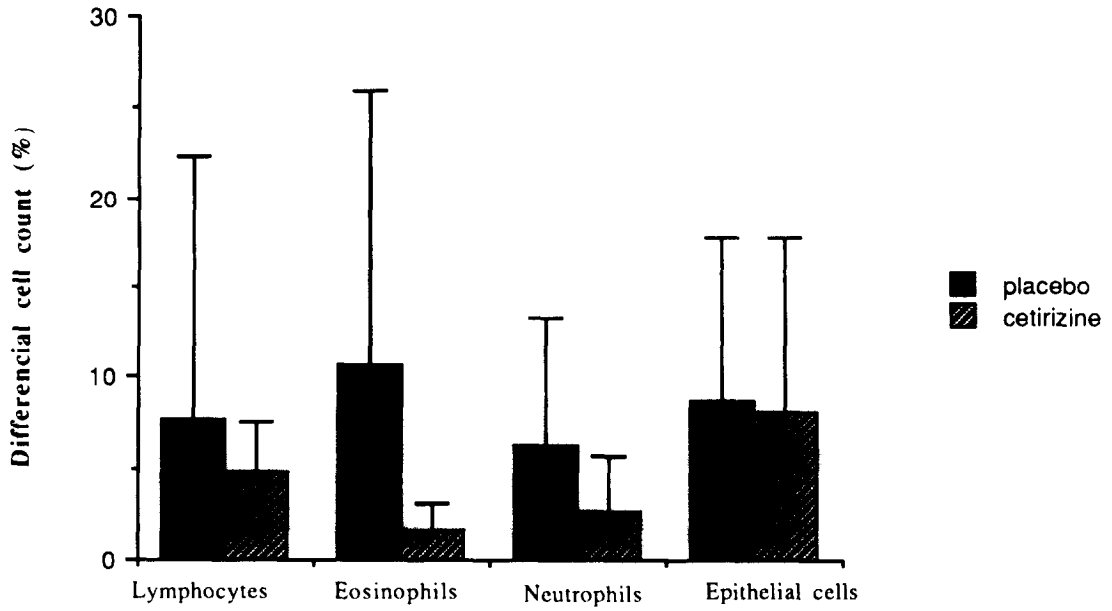

FIG. 4. Differential cell count of the bronchial sample of BAL. (Alveolar macrophages averaged 66% ± 20% and 82% ± 9% in the placebo-treated and cetirizine-treated groups, respectively.)

significantly lower in bronchial samples of BAL in cetirizine-treated patients (15 mg b.i.d. for 8 days) than in placebo-treated patients.

In our study, in spite of the high doses of cetirizine used, there were few side effects observed. Patients were treated for several days because, in general, at least 4 days were required to arrive at a steady state.

A hallmark of bronchial asthma is the presence of eosinophils in the bronchial submucosa and BALF.[7-13] Eosinophils are involved in the inflammatory processes of asthma because of (1) potential release of their highly cytotoxic cationic protein (eosinophil cationic protein, major basic protein, and eosinophil-derived neurotoxin) and (2) the generation of lipid-derived mediators that are bronchoconstrictors (leukotriene C_4 and platelet-activating factor) and can increase the bronchial vascular leakage.[44] The eosinophilic inflammation has been correlated to the severity of asthma as assessed by the scoring system of Aas.[15]

There is no doubt that there is an increased number of eosinophils in chronic asthma as well as in exper-

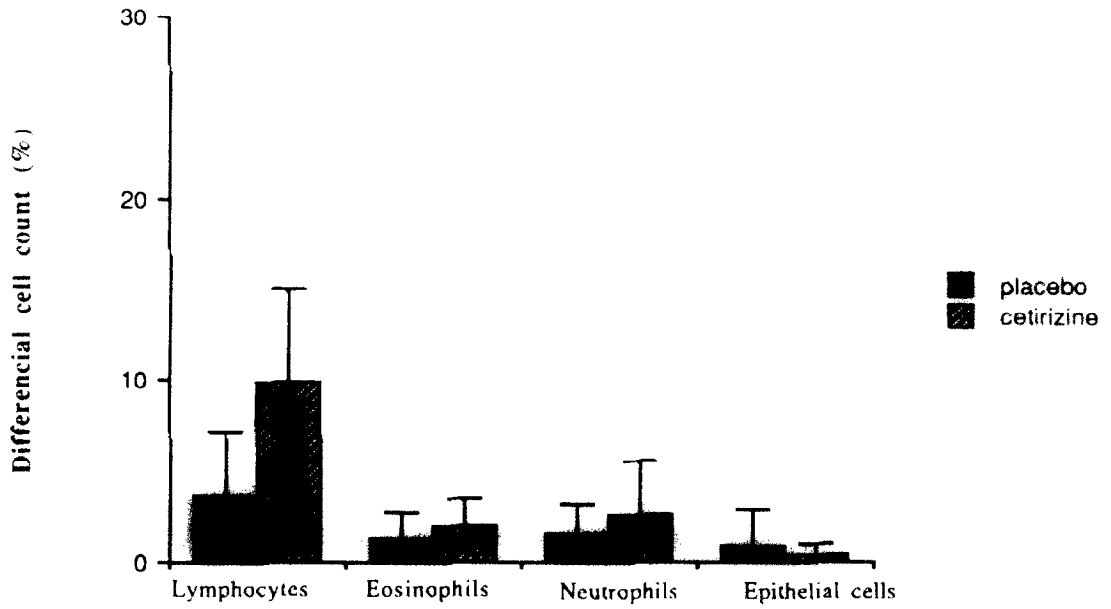

FIG. 5. Differential cell count of the alveolar sample of BAL. (Alveolar macrophages averaged 92% ± 4% and 85% ± 4% in the placebo-treated and cetirizine-treated groups, respectively.)

imental models of human asthma, especially in cases in which subjects develop an LAR.[20-24]

The LAR is a useful clinical model of asthma; it is characterized by bronchial inflammation followed by nonspecific bronchial hyperreactivity that may last for several days[45] and, occasionally, for weeks. It has been demonstrated to be comparable to that occurring in pollen-sensitive subjects with asthma during the seasonal exposure.[46]

Numerous cell types and chemical mediators have been implicated in the pathophysiology of the LAR, and eosinophils may also play an important role. For all these reasons, the LAR would appear to be a relevant clinical tool for studying the pathophysiology of asthma and for evaluating new therapeutic compounds. Previous studies performed in our clinic have demonstrated the reproducibility of results of bronchial-challenge tests.[39] In our study, no patient had a documented LAR at the first visit; therefore, the first test was performed between 2 and 6 months before the study to permit the patient to be included. A detailed case history of these patients was maintained between the first test and the beginning of the study, and subjects who were not in a stable stage of asthma were excluded. We respected a delay of at least 2 months between the two tests because it is known that a bronchial challenge can induce a bronchial hyperreactivity that can least several weeks.

This study was designed specifically to evaluate the effect of cetirizine on eosinophil recruitment after an LAR. It is the reason we chose to increase doses of allergen to obtain an EAR and to be in the best conditions to have an LAR. However, the difference between the doses used in the first and the second test was not statistically significant. After 8 days of treatment by cetirizine, three of the six patients had an increased PD_{20} allergen (the difference in PD_{20} between the two tests was >1 $\log_2$ dose),[47] whereas all patients in the placebo-treated group had similar values throughout the study (the difference was ≤ 1 $\log_2$ dose). Our results are in accordance with results of another study[48] that demonstrated that cetirizine provides a slight, but not statistically significant protection against the EAR.

We did not find any significant difference in the occurrence and the intensity of the LAR between the two groups of patients. We cannot draw a conclusion on the effects of cetirizine on the LAR since its intensity has been correlated to the dose provoking the EAR.[49, 50] Wasserfallen et al.[51] found an inhibition of LAR, but their methodology was different from our methodology because they always used the same dose of allergen for the two challenge tests.

Although fiberoptic bronchoscopy with BAL has been largely used for more than a decade in patients with a variety of lung disorders, it is only recently that it has been extended to patients with asthma.[42] Several studies indicate that this procedure can be performed as a research tool. No BAL was performed in our patients before the trial, but it is clear from the literature[11] and from our personal experience[15] that patients with asthma with a low degree of severity

and no recent exacerbation have few eosinophils in BALF, even if the percentage of eosinophils is significantly higher than in normal subjects. In this study, all patients had very mild and stable asthma.

The question of the site of airway obstruction has been highlighted by Platts-Mills et al.,[52] and they demonstrated that bronchoconstriction induced by allergen inhalation challenge is more centrally located compared with that in chronic asthma. Terral et al.[53] made the same observations. To evaluate better the site of eosinophil recruitment, we chose to separate the first recovery of BAL (that samples, preferentially, the central airways) from the other BAL recoveries (that sample the peripheral airways) according to the method of Van Vyve et al.[54] We observed a greater number of total cells and eosinophils in the BALF of the placebo-treated group than in each cetirizine-treated patient. It is interesting to note that in the cetirizine-treated group, the three patients with a greatly increased PD_{20} had similar BAL results with that of the other three patients, with low total cell number and low eosinophil number. Therefore, we cannot not differentiate a subgroup of responders.

With regard to the alveoli sample, there was no difference in samples between the two groups of patients either for the total cell number or for the eosinophil number (expressed as a percentage or as total number). In the study of de Monchy et al.,[20] there is no result concerning the cellular content of the bronchial wash that accounts for the discrepancy with our findings.

We found a slight, but not significant, inhibition of neutrophils by cetirizine. Previous studies reported a significant increase in neutrophils 4 hours[22] or 6 hours[21] after a challenge, whereas de Monchy et al.[20] did not report this increase. In our study, this absence of difference of neutrophil count between the two groups might be due to type II statistical error.

Mast cells were not detectable by May-Grünwald-Giemsa staining, and we did not use specific staining for the metachromatic stain because (1) none of the stains is satisfactory to take into account all the mast cells and basophils, and (2) the aim of this study was to focus on the potentially recruited cells, such as granulocytes. Furthermore, we know that mast cells might be degranulated after a challenge test; therefore, they will be missed in the process of cellular appreciation.

Eosinophil recruitment has been linked to the LAR. However, these are not the only cells potentially involved in the development of the LAR that may result from a complex interaction between various types of inflammatory cells and mediators. The pathogenesis of LAR is not fully understood. Naclerio et al.[55] emphasize a role for basophils, and other studies support the view that macrophages[56] or mast cells might be implicated in the LAR.[57]

Some discrepancies between the cellular infiltration and the appearance of a modification in the local reactivity has already been observed by Klementsson et al.[58] in the nose. They demonstrated a decrease of the nasal nonspecific hyperreactivity unrelated to local eosinophilia. In contrast, long-term treatment with inhaled corticosteroids has been demonstrated to reduce the inflammatory cell infiltration and epithelium damage, whereas bronchial hyperresponsiveness was still present.[59]

In conclusion, in this study, the total cells and eosinophils were significantly lower in the bronchial sample of the BALF in cetirizine-treated patients compared with that of placebo-treated patients who underwent an LAR after antigen challenge. Cetirizine inhibited the recruitment of inflammatory cells, mainly eosinophils in the bronchi in this experimental model of asthma. This study is of importance concerning the development of LAR that appears to be possible without occurrence of BALF eosinophilia. Further studies are needed to assess the activation of eosinophils and other cells after an LAR. Cetirizine might affect the in vivo eosinophil behavior, which might be helpful in the clinical management of bronchial asthma.

The statistical analysis was made by DICE (Data Investigation Co., Europe, Brussels, Belgium) under the responsibility of Professor L. Kaufman (PhD) and Dr. M. P. Derde (PharmD), whom the authors thank for their skillful assistance.

REFERENCES

1. Wardlaw AJ, Dunnette S, Gleich GJ, Collins JV, Kay AB. Eosinophils and mast cells in bronchoalveolar lavage in subjects with mild asthma: relationship to bronchial hyperreactivity. Am Rev Respir Dis 1988;137:62-9.
2. Durham SR, Kay AB. Eosinophils, bronchial hyperreactivity, and late-phase asthmatic reactions. Clin Allergy 1985;15: 411-8.
3. Taylor KL, Lukza AR. Peripheral blood eosinophil counts and bronchial responsiveness. Thorax 1987;42:452-6.
4. Venge P, Dalh R, Fredens K, Peter CG. Epithelial injury by human eosinophils. Am Rev Respir Dis 1988;138:S54-7.
5. Filley WV, Holley KE, Kephart GM, Gleich GJ. Identification by immunofluorescence of eosinophil granule major basic protein in lung tissues of patients with bronchial asthma. Lancet 1982;2:11-6.
6. Van Schayck CP, Dompeling E, Van Herwaarden CLA, Wever AMJ, Van Weel C. Interacting effects of bronchial hyperresponsiveness and atopy on the decline in lung function and the exacerbation rate in asthma [Abstract]. Am Rev Respir Dis 1991;143:145-415.
7. Adelroth E, Rosenhall L, Johansson S, Linden M, Venge P. Inflammatory cells and eosinophilic activity in asthmatics investigated by bronchoalveolar lavage: the effects of antiasthmatic treatment with budesonide or terbutaline. Am Rev Respir Dis 1990;142:91-9.

8. Godard P, Aubas P, Calvayrac P,Taib J, Michel FB. Endoscopie et lavage bronchiolo-alvéolaire chez l'asthmatique allergique. Nouv Presse Med 1981;10:3141-8.
9. Flint KC, Leung K, Hudspith B, Brostoff J, Pearce F, Johnson N. Bronchoalveolar mast cells in extrinsic asthma: a mechanism for the initiation of antigen specific bronchoconstriction. Br Med J 1985;291:923-6.
10. Kelly C, Ward C, Stenton CS, Bird G, Hendrick DJ, Walters EH. Number and activity of inflammatory cells in bronchoalveolar lavage fluid in asthma and their relation to airway responsiveness. Thorax 1988;43:684-92.
11. Fick RB, Richerson HB, Zavala DC, Hunninghake GW. Bronchoalveolar lavage in allergic asthmatics. Am Rev Respir Dis 1987;135:1204-9.
12. Diaz P, Galleguillos FR, Gonzalez MC, Pantin CF, Kay AB. Bronchoalveolar lavage in asthma: the effect of disodium cromoglycate (cromolyn) on leukocyte counts, immunoglobulins, and complement. J ALLERGY CLIN IMMUNOL 1984;74:42-8.
13. Crystal RG, Reynolds HY, Kalica AR. Bronchoalveolar lavage: the report of an international conference. Chest 1986;90:122-31.
14. Cutz E, Levison H, Cooper DM. Ultrastructure of airways in children with asthma. Histopathology 1978;2:407-21.
15. Bousquet J, Chanez P, Lacoste JY, et al. Eosinophilic inflammation in asthma. N Engl J Med 1990;323:1033-9.
16. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive disease (COPD) and asthma. Am Rev Respir Dis 1987;136:225-45.
17. Reed CE. New therapeutic approaches in asthma. J ALLERGY CLIN IMMUNOL 1986;70:537-43.
18. ATS statement. Clinical role of bronchoalveolar lavage in adults with pulmonary disease. Am Rev Respir Dis 1990;142:481-6.
19. Kirby JG, Hargreave E, Gleich GJ, O'Byrne PM. Bronchoalveolar cell profiles of asthmatic and nonasthmatic subjects. Am Rev Respir Dis 1987;136:379-83.
20. de Monchy JGR, Kauffman HF, Venge P, et al. Bronchoalveolar eosinophilia during allergen-induced late asthmatic reactions. Am Rev Respir Dis 1985;131:373-6.
21. Diaz P, Gonzalez MC, Galleguillos FR, et al. Leukocytes and mediators in bronchoalveolar lavage during allergen-induced late-phase asthmatic reaction. Am Rev Respir Dis 1989;139:1383-9.
22. Metzger WJ, Richerson HB, Worden K, Monick M, Hunninghake GW. Bronchoalveolar lavage of allergic asthmatic patients following allergen bronchoprovocation. Chest 1986;89:477-83.
23. Beslay R, Roche WR, Roberts JA, Holgate ST. Cellular events in the bronchi in mild asthma and after bronchial provocation. Am Rev Respir Dis 1989;139:806-17.
24. Lam S, Leriche J, Phillips D, Chan-Yeung M. Cellular and protein changes in bronchial lavage fluid after late asthmatic reaction in patients with red cedar asthma. J ALLERGY CLIN IMMUNOL 1987;80:44-50.
25. Cookson WO, Craddock CF, Benson MK, Durham SR. Falls in peripheral eosinophil counts parallel the late asthmatic response. Am Rev Respir Dis 1989;139:458-62.
26. Leprevost C, Capron M, De Vos C, Tomassini M, Capron A. Inhibition of eosinophil chemotaxis by a new anti allergic compound (cetirizine). Int Arch Allergy Appl Immunol 1988;87:9-13.
27. Charlesworth EN, Kagey-Sobotka A, Norman PS,Lichtenstein LM. Effects of cetirizine on mast cell-mediator release and cellular traffic during the cutaneous late-phase reaction. J ALLERGY CLIN IMMUNOL 1989;83:905-12.
28. Fadel LR, Herpin-Richard N, Rihoux JP, Henocq E. Inhibitory effect of cetirizine 2HCL on eosinophil migration in vivo. Clin Allergy 1987;17:373-9.
29. Henocq E, Rihoux JP. Does reverse-type anaphylaxis in healthy subjects mimic a real allergic reaction? Clin Exp Allergy 1990;20:269-72.
30. Fadel R, David B, Herpin-Richard N, Borgnon A, Rassemont R, Rihoux JP. In vivo effects of cetirizine on cutaneous reactivity and eosinophil migration induced by platelet-activating factor (PAF-acether) in man. J ALLERGY CLIN IMMUNOL 1989;86:314-20.
31. Kontou-Fili K, Maniatakou G, Demaka P, Gonianakis M, Paleologos G. Therapeutic effects of cetirizine in delayed pressure urticaria. Part I. Effects on weight tests and skin-window cytology. Ann Allergy 1990;65:517-9.
32. Ghosh SK, De Vos C, Mc Ilroy I, Patel KR. Effects of cetirizine on histamine and leucotriene (LTD_4)-induced bronchoconstriction in patients with atopic asthma. J ALLERGY CLIN IMMUNOL 1991;87:1010-3.
33. Brik A, Tashkin DP, Gong H Jr, Dauphinee B, Lee E. Effect of cetirizine, a new histamine H_1 antagonist, on airway dynamics and responsiveness to inhaled histamine in mild asthma. J ALLERGY CLIN IMMUNOL 1987;80:51-6.
34. Dijkman JH, Hekking PRM, Molkenboer JF, et al. Prophylactic treatment of grass pollen induced asthma with cetirizine. Clin Exp Allergy 1990;20:483-90.
35. Kurzeja A, Riedelslheimer B, Hulhoven R, Bernheim J. Cetirizine in pollen associated asthma. Lancet 1989;8637:556.
36. Advenier C, Candenas ML, Naline E, De Vos C. The effect of cetirizine on the human isolated bronchus interaction with salbutamol. J ALLERGY CLIN IMMUNOL 1991;88:104-13.
37. Aas K. Heterogeneity of bronchial asthma: subpopulations or different stages of the disease. Allergy 1981;36:3-10.
38. American Thoracic Society. Guidelines for bronchial inhalation challenge with pharmacologic and antigen agents. ATS News 1980:11-9.
39. El Khawn Rifai, Clauzel AM, Visier S, Dhivert H, Benali R. Allergen provocative challenge: reproducibility of the dose-response curves in asthmatic patients [Abstract]. Am Rev Respir Dis 1989;142:592.
40. Balzano G, Schiano M, Cocco G, D'Amato G, Mellilo G. A new dosimeter MEFAR in bronchial provocation testing with pharmacological agents. The Fourth Congress of the International Society for aerosols in medicine. Brno, Czechoslovakia, June 1982.
41. O'Byrne PM, Dolovich J, Hargreave FE. State of the art. Late asthmatic responses. Am Rev Respir Dis 1987;136:740-51.
42. Godard Ph, Bousquet J, Lebel B, Michel FB. Le lavage bronchoalvéolaire chez l'asthmatique. Bull Eur Physiopathol Respir 1987;23:73-83.
43. Townley RG, Bewtra AK, Nair NM, Brodkey FD, Watt GD, Burke KM. Methacholine inhalation challenge studies. J ALLERGY CLIN IMMUNOL 1979;64:569.
44. Djukanovic R, Roche WR, Wilson J, et al. State of the art: mucosal inflammation in asthma. Am Rev Respir Dis 1990;142:434-57.
45. Cartier A, Thompson NC, Frith PA, Roberts R, Hargreave FE. Allergen-induced increase in bronchial responsiveness to histamine: relationship to the late asthmatic response and change in airway caliber. J ALLERGY CLIN IMMUNOL 1982;70:170-7.
46. Boulet LP, Cartier A, Thomson NC, Roberts RS, Dolovich J, Hargreave FE. Asthma and increases in nonallergic bronchial responsiveness from seasonal pollen exposure. J ALLERGY CLIN IMMUNOL 1983;71:399-406.
47. Kopferschmitt-Kubler MC, Bigot H, Pauli G. Allergen bronchial challenge tests: variability and reproducibility of the early response. J ALLERGY CLIN IMMUNOL 1987;80:730-40.

48. Kopferschmitt MC, Couchot G, Pauli G. Evaluation of the effect of oral cetirizine on antigen-induced early response. Eur Respir J 1990;3:229s.
49. Crimi E, Brusasco V, Losurdo E, Crimi P. Predictive accuracy of late asthmatic reaction to *Dermatophagoides pteronyssinus*. J ALLERGY CLIN IMMUNOL 1986;78:908-13.
50. Lai C, Beasley R, Holgate S. The effect of an increase in inhaled allergen dose after terfenadine on the occurrence and magnitude of the late asthmatic response. Clin Exp Allergy 1989;19:209-16.
51. Wasserfallen JB, Leuenberger Ph, Pécoud A. Effect of cetirizine on the early and late allergic reactions in a bronchial provocation test (BPT) [Abstract]. All Clin Immunol News 1991;(suppl 1):185.
52. Platts-Mills TAE, Heymann PW, Chapman MD, Mitchell EB, Hayden ML, Wilkins SR. Immunologic triggers in asthma. J ALLERGY CLIN IMMUNOL 1987;80:214-9.
53. Terral C, Bourgoin-Karaouni D, Jonquet O, Godard Ph, Préfaut C. Effet de l'hélium-oxygène au cours des tests de provocation bronchique chez l'asthmatique. Bull Eur Physiopathol Respir 1983;19:51-8.
54. Van Vyve T, Chanez P, Bousquet J, et al. Comparison between bronchial and alveolar samples of bronchoalveolar lavage fluid in asthma [Abstract]. Am Rev Respir Dis 1991;143:26.
55. Naclerio RM, Proud D, Togias AA, et al. Inflammatory mediators in late antigen-induced rhinitis. N Engl J Med 1985;313:65.
56. Tonnel AB, Gosset P, Joseph M, Fourier G, Capron A. Stimulation of alveolar macrophages in asthmatic patients after local provocation test. Lancet 1983;1:406-8.
57. Crimi E, Chiaramondia M, Milanese M, Rossi G, Brusasco V. Increased numbers of mast cells in bronchial mucosa after the late phase asthmatic response to allergen. Am Rev Respir Dis 1991;144:1282-6.
58. Klementsson H, Andersson M, Pipkorn U. Allergen-induced increase in nonspecific nasal reactivity is blocked by antihistamines without a clear-cut relationship to eosinophil influx. J ALLERGY CLIN IMMUNOL 1990;86:466-72.
59. Lundgren R, Söderberg M, Hörstedt P, Stenling GR. Morphological studies of bronchial mucosal biopsies from asthmatics before and after ten years of treatment with inhaled steroids. Eur Respir J 1988;1:883-9.

Serum IgE in nonatopic smokers, nonsmokers, and recent exsmokers: Relation to lung function, airway symptoms, and atopic predisposition

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The influence of smoking on serum IgE (s-IgE) was studied in a selected nonatopic population. The variation in s-IgE was followed during 1 year of smoking abstinence. The study included 287 smokers and 137 never smokers. IgE was higher in smokers compared with IgE in never smokers ($p < 0.005$). Male smokers had higher s-IgE than female smokers ($p < 0.01$). S-IgE was independent of age and claims of atopy among first-degree relatives. Weighted pack-years consumption was defined for cigarette smokers by modifying pack-years consumption by nicotine content of the brand smoked. Weighted pack-years consumption was associated with level of s-IgE ($p < 0.05$). S-IgE was higher in smokers with airway symptoms compared with that in smokers without symptoms ($p < 0.01$). In smokers older than 50 years of age, there tended to be decreased FEV_1 residuals ($0.05 < p < 0.06$), and presence of airway symptoms was ($p < 0.03$) associated with high levels of s-IgE independent of each other. In 92 quitters, s-IgE increased during the first 26 weeks of abstinence ($p < 0.05$), and after 1 year, s-IgE had returned to baseline. The increase was only observed in smokers younger than 40 years and had no relation to variations in FEV_1 during the 1-year follow-up. The increase in s-IgE after smoking cessation was transient, of minor clinical importance, and probably caused by a relief from an immunosuppressive influence. (J ALLERGY CLIN IMMUNOL 1992;90:224-9.)

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