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Long-term Changes in Airway-Wall Thickness on Computed Tomography in Asthmatic Patients

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Abstract

Background: Effects of long-term treatment with inhaled corticosteroids (ICSs) on airway-wall thickness in patients with asthma remain unknown.
Objectives: To determine whether airway-wall thickness consistently decreases after long-term ICS treatment, and to analyze factors contributing to long-term airway-wall changes in asthmatics.
Methods: A retrospective analysis of long-term changes in airway-wall thickness using computed tomography was performed in 14 patients with asthma. Wall area corrected by body surface area (WA/BSA) was examined at baseline, 12 weeks after the commencement of ICSs (second measurement), and at least 2 years (mean±SEM. 4.2±0.5) after the second measurement (third measurement). Mean±SEM changes in WA/BSA from the second to the third measurements were analyzed.
Results: The mean change in WA/BSA was not significant between the second and the third measurements (–0.27±0.59 $mm^2/m^2/y$). Overall, the changes were significantly associated with disease duration but not with other clinical indices. When the 14 patients were divided into 2 groups using a cutoff value of 0.32 $mm^2/m^2/y$ for the mean change in WA/BSA, for the 5 patients whose WA/BSA exceeded this cutoff, daily ICS doses were not reduced and both forced expiratory volume in the first second (FEV_1) and forced vital capacity decreased significantly. For the remaining 9 patients, daily ICS doses were reduced and long-term FEV_1 values did not change.
Conclusions: Despite long-term treatment with ICSs, airway-wall thickness did not consistently decrease. One possible mechanism underlying poor response to long-term treatment may be long-standing asthma.

Key words: Asthma. Airway-wall thickening. Computed tomography. Long-term changes.

Resumen

Antecedentes: Hasta la fecha se desconocen los efectos del tratamiento a largo plazo con corticoesteroides inhalados (CI) sobre el grosor de la pared de las vías respiratorias en pacientes con asma.
Objetivos: Determinar si el grosor de la pared de las vías respiratorias se reduce de forma sistemática tras el tratamiento con CI a largo plazo y analizar los factores que contribuyen a los cambios a largo plazo en la pared de las vías respiratorias en pacientes asmáticos.
Métodos: Se realizó un análisis retrospectivo de los cambios a largo plazo en el grosor de la pared de las vías respiratorias mediante tomografía computerizada en 14 pacientes con asma. Se examinó el área de la pared corregida por el área de superficie corporal (AP/ASC) al inicio, 12 semanas después de iniciar el tratamiento con CI (segunda determinación) y al menos 2 años (media±EEM: 4,2±0,5) después de la segunda determinación (tercera determinación). Se analizaron los cambios medios ±EEM en el AP/ASC desde la segunda hasta la tercera determinación.
Resultados: El cambio medio en el AP/ASC entre la segunda y la tercera determinación no fue significativo (–0,27±0,59 $mm^2/m^2/a$). En general, los cambios estuvieron significativamente relacionados con la duración de la enfermedad pero no con otros índices clínicos. Cuando los 14 pacientes se separaron en 2 grupos utilizando un valor de corte de 0,32 $mm^2/m^2/a$ para el cambio medio de AP/ASC, en los 5 pacientes cuya AP/ASC superó este valor de corte no se redujeron las dosis diarias de CI y el volumen espiratorio máximo en el primer segundo (VEM1) disminuyó significativamente. En los 9 pacientes restantes, se redujeron las dosis diarias de CI y los valores de VEM1 no variaron.

Conclusiones: A pesar del tratamiento con CI a largo plazo, el grosor de la pared de las vías respiratorias no disminuyó de forma sistemática. Uno de los posibles mecanismos subyacentes de la respuesta deficiente al tratamiento a largo plazo puede ser el asma crónica.

Palabras clave: Asma. Engrosamiento de la pared de las vías respiratorias. Tomografía computerizada. Cambios a largo plazo.

Introduction

Asthma is an inflammatory airway disease dominated by increases in eosinophils, mast cells, T lymphocytes, and a T_H2-type immune response. Chronic inflammation leads to airway remodeling [1] such as hypertrophy and hyperplasia of airway smooth muscle, submucosal gland hyperplasia, goblet cell hyperplasia, vascular proliferation, and the deposition of extracellular matrix [2,3]. As a net result of these structural changes, the airway walls of patients with asthma thicken, as has been observed in postmortem studies of patients with fatal asthma [4-6] and nonfatal asthma [5] and in recent studies using high-resolution computed tomography (HRCT) [7-11]. Cross-sectional studies using CT to quantitatively assess airway-wall thickness have demonstrated that the degree of thickening correlates with disease severity [7,8] and airflow obstruction [7,9].

Inhaled corticosteroids (ICSs), a first-line therapy for persistent asthma, effectively control airway inflammation by reducing the number and activity of inflammatory cells and suppressing the release of inflammatory cytokines or mediators [12]. However, established airway remodeling such as basement membrane thickening, vascular hyperplasia, and airway smooth muscle hyperplasia might be difficult to fully reverse because delayed intervention only slightly improves pulmonary function [1,12-15]. Using HRCT, we previously showed that a 12-week treatment course with ICSs significantly reduced airway-wall thickness in adults with asthma, but that post-treatment thickness remained greater than that of healthy controls and correlated with disease duration [16]. However, given that progression of established airway remodeling is inhibited by ICSs, as has been shown in an allergen-challenged rat model [17], the disadvantages of delayed intervention might be overcome by long-term treatment. The primary aim of this retrospective study was to determine whether airway-wall thickness consistently decreased after long-term ICS treatment. The secondary aim was to analyze factors contributing to long-term airway-wall changes.

Material and Methods

Patients

Fourteen adult patients with asthma from the outpatient clinic at our hospital were recruited for the long-term evaluation of airway-wall thickness. Of these patients, 9 had previously participated in a short-term 12-week study [16]; the other 5 were newly recruited and underwent CT scanning before (baseline) and after 12 weeks of ICS treatment (second measurement). The third measurement was performed at least 2 years (mean±SEM, 4.2±0.5 years) after the second measurement. All participants fulfilled the American Thoracic Society criteria for asthma [18]. None of the patients had received systemic or inhaled corticosteroids, chromones, or antileukotriene agents prior to baseline. There had also been no asthma exacerbations or respiratory infections in the 8 weeks before each measurement [16]. Eleven patients were lifetime nonsmokers and 3 were ex-smokers with a smoking history of under 10 pack-years.

Either of 2 physicians (H.M. and A.N.) followed up the patients every 4 to 8 weeks. The ICS dose could be decreased if patients remained symptom-free for 6 months or more or increased if symptoms were not well controlled. Adherence to the prescribed ICS regimen was evaluated by reviewing the number of prescriptions, patient diaries (n=10) (which included information on asthma symptoms, peak flow rates, and medications used), and medical charts (n=4). None of the patients moved home during the treatment period. One of the 5 pet owners lost her dog.

Exacerbations were defined as the need for either short courses of systemic corticosteroid therapy to treat increased symptoms such as dyspnea, wheezing and cough, or the increased use of inhaled $ß_2$ agonists as rescue medication.

The ethics committee at our institution approved the study protocol and written informed consent was obtained from each participant.

CT Scans and Analysis of Airway-Wall Thickness

CT scanning and analysis were performed, with slight modifications, as described previously [19,20]. All scans were obtained at suspended end-inspiratory volume. Using a Toshiba X-Vigor CT scanner (Toshiba, Tokyo, Japan), helical CT scanning was performed at 120 kVp, 50 mA, 3 mm collimation, and pitch 1. Images were reconstructed using the FC 10 algorithm at 2-mm spacings. A targeted reconstruction of the right lung was performed using a subject-specific field of view (153-214 mm). These CT data were transferred to a personal computer via a magneto-optical disk and analyzed using custom software written with the C programming language (Symantec C++, Symantec Corp., California, USA). In the present study, to minimize possible errors associated with repeated measurements, several slices were examined from the origin of the apical bronchus of the right upper lobe to below the subsegmental bifurcation, where a round bronchus was obtained; a median of 2 slices (1-3) were examined per time. Airway dimensions in the selected slices were automatically analyzed and then averaged. For automatic measurement, 1 pixel inside the lumen of the bronchus was labeled a seed

pixel. The luminal area (Ai) was then automatically determined based on the area of pixels contiguous with the seed pixel with CT numbers below thresholds set in several steps. The airway-wall area (WA) and its proportion (WA%) of the total airway area were calculated using values of short and long radii of the lumen, and absolute airway-wall thickness was automatically measured using full-width at half-maximum principles. Airway roundness was assessed by calculating the ratio of the short radius to the long radius. When this ratio was less than 0.5, the program automatically excluded the airways. Because airway size may be affected by body size, WA and Ai were normalized by body surface area (BSA). In this study, WA/BSA was used to represent airway-wall thickness. Long-term changes in airway dimensions were calculated as: (dimension at the third measurement – dimension at the second measurement)/(dimension at the second measurement). When necessary, the changes were normalized by the interval between the 2 measurements.

To assess changes in lung volume, cross-sectional areas of the lung were automatically measured by tracing the outer perimeter of the lung parenchyma on the same slice used for airway measurement using Image J (http://rsb.info.nih.gov/ij).

Pulmonary Function

On each occasion, prebronchodilatory forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) were measured using a Chestac-65V (Chest MI Corp., Tokyo, Japan) in accordance with American Thoracic Society guidelines [21]. The spirometer was calibrated daily with a 3-L syringe.

Blood and Sputum Eosinophils

To assess eosinophil numbers, blood was obtained at baseline and at the third measurement and sputum was obtained at the third measurement only. Sputum induction and processing were performed using the methods reported by Pin et al [22], with slight modifications [20]. In brief, the patients were premedicated with inhaled salbutamol (200 μg) and then instructed to inhale hypertonic saline solution (3%) from an ultrasonic nebulizer (MU-32, Azwell Inc., Osaka, Japan) for 15 minutes. Adequate plugs of sputum were separated from the saliva and treated with 0.1% dithiothreitol (Sputasol, OXOID ltd, Hampshire, UK), followed by Dulbecco's phosphate buffered saline. Cell differentials were determined by counting at least 400 nonsquamous cells stained with May-Grünwald-Giemsa.

Statistical Analysis

Data were analyzed using StatView software 5.0 (SAS Institute Inc, North Carolina, USA). In this long-term study, changes in airway-wall dimensions from the second to the third measurements were analyzed by the Wilcoxon signed-rank test. The Spearman rank-correlation test was used to analyze correlations. The 2 groups were compared using the Mann-Whitney U test or Fisher's exact test. Power was not calculated because of the pilot nature of the study. Data are presented as means±SEM unless otherwise stated. *P* values of .05 or less were considered to indicate statistical significance.

Results

During long-term treatment with ICSs, the WA/BSA of the single apical bronchus examined did not change significantly from the second (20.0±1.2 mm^2/m^2) to the third measurements (20.4±1.5 mm^2/m^2) in 14 patients. The change in WA/BSA normalized by the interval between the 2 measurements was –0.27±0.59 $mm^2/m^2/y$. Overall, WA/BSA changes between the second and third measurements was significantly correlated with disease duration at baseline (r=0.55, *P*=.049; Figure) but not with the duration between the second and third measurements (r=0.30, *P*=.28). There was no significant correlation between changes in WA/BSA and changes in FEV_1 (r=–0.48, *P*=.086). Long-term changes in WA/BSA did not correlate with other clinical indices, including treatment duration. Neither WA% nor Ai changed significantly from the second to the third measurements in 14 patients. Clinical indices, including pulmonary function, did not correlate with long-term changes in either WA% or Ai (data not shown).

The 14 patients were arbitrarily divided into 2 groups using a cutoff value of 0.32 $mm^2/m^2/y$ (mean±SEM change in WA/BSA normalized by the interval between the second and third measurements). Nine patients were included in group 1 (WA/BSA <0.32 $mm^2/m^2/y$) and 5 patients were included in group 2 (WA/BSA >0.32 $mm^2/m^2/y$). Clinical characteristics, such as sputum eosinophil counts and exacerbation frequencies (Table 1), and outcomes did not vary significantly between these 2 groups. However, a within-group comparison showed that for patients in group 1 the daily ICS dose decreased significantly from the second to the third measurements, with no significant changes in pulmonary function. These findings contrasted with those observed in group 2. In that group, there was a significant decrease in FEV_1 and FVC values but not in daily ICS dose between the second and third measurements. There were no significant differences in lung areas between the second and the third measurements in either group (Table 2).

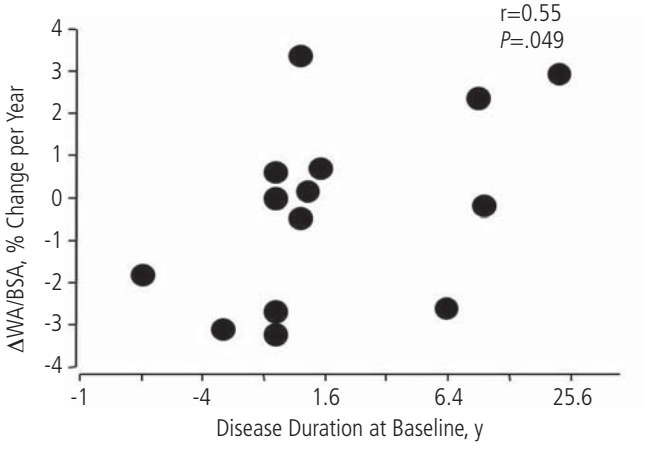

Figure. Correlation between disease duration and ΔWA/BSA. $\Delta WA/BSA = 100 \times [(WA/BSA^{third\ measurement} - WA/BSA^{second\ measurement})/WA/BSA^{second}]$ measurement /the interval between the 2 measurements.

Table 1. Demographic Data of the Patients

	Group 1[a] (n=9)	Group 2[a] (n=5)	*P* Value
Age at baseline, y[b]	61 (38-73)	62 (34-67)	.89
Sex, M/F	4/5	3/2	>.99
Disease duration at baseline, y[b]	0.9 (0.2-9.5)	1.5 (0.9-22.4)	.16
Atopic status at baseline, yes/no	4/5	3/2	>.99
IgE at baseline, IU/mL[b]	207 (10-1030)	411 (148-1601)	.16
Ex-smoker[c] at baseline, no.	2	1	>.99
Owned pet at baseline, no.	4 (dog)	1 (cat)	.58
Sinusitis, rhinitis, yes/no	6/3	4/1	>.99
Disease severity (GINA step 2/3/4)	6/3/0	2/2/1	.40
Blood eosinophils			
Baseline, %[b]	6.6 (1.7-24.0)	9.6 (6.1-17.0)	.26
Third measurement, %	1.8 (0.6-11.6)	6.4 (3.1-10.8)	.23
Sputum eosinophils, 10^5/g at third measurement[b]	2.7 (0.03-16.4)	3.0 (0.09-35.2)	.36
Interval between second and third measurements, y[b]	3.5 (2.2-7.5)	4.7 (2.4-7.8)	.32
Frequency of exacerbations requiring short courses of systemic steroids, y[b]	0 (0-1.7)	0.3 (0-3.0)	.51
Adherence to ICSs (used >80% of prescribed / used 50% to 80% of prescribed)	7/2	5/0	.51
Use of other controllers, yes/no	5/4	2/3	>.99
LABA/SR theophylline /LTRA/OCS, no.	1/4/2/0	0/1/1/2	

Abbreviations: GINA, Global Initiative For Asthma 2002; ICSs = inhaled corticosteroids; IgE, immunoglobulin E; LABA, long-acting ß$_2$-agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; SR, sustained-release.
[a]Long-term changes in WA/BSA, normalized by the interval, for patients in group 1 were <0.32 mm^2/m^2/y, whereas WA/BSA in patients in group 2 increased by >0.32 mm^2/m^2/yr from the second to the third measurements.
[b]Values are shown as medians (range).
[c]<10 pack-years.

Table 2. Changes in Inhaled Corticosteroid (ICS) Maintenance Doses, Pulmonary Function, and Airway-Wall Thickness in 2 Patient Groups[a]

Group 1[b] (n=9)	Baseline	Second Measurement	Third Measurement	P Value
Daily ICS dose[d], µg	–	889±59	556±80	.024
FEV_1,[c] % of predicted	78.9±12.7	108.9±5.1	104.5±5.7	.11
FVC,[c] % of predicted	86.6±9.1	115.7±2.4	111.1±4.0	.09
FEV_1/FVC,[c] %	69.8±5.1	79.5±2.8	76.8±2.9	.17
WA, mm^2/m^2	33.8±2.8	30.5±3.0	29.3±2.9	.038
WA/BSA, mm^2/m^2	21.3±1.5	19.2±1.7	18.3±1.7	.015
WA%, %	64.3±2.3	61.8±2.4	62.1±3.2	.95
Ai/BSA, mm^2/m^2	12.7±2.0	12.9±2.1	12.7±2.3	.59
Lung area/BSA, cm^2/m^2	71.0±2.0	72.2±1.5	71.2±2.2	.26
Group 2[b] (n=5)				
Daily ICS dose[d], µg	–	800±0	880±196	.65
FEV_1,[e] % of predicted	71.7±11.2	102.6 ±2.3	93.6±3.0	.043
FVC,[e] % of predicted	74.7±11.7	103.7±6.6	94.8±6.8	.043
FEV_1/FVC,[e] %	78.9±2.9	82.9±3.0	82.4±3.5	.50
WA, mm^2/m^2	36.1±2.8	35.0±3.2	38.0±3.4	.043
WA/BSA, mm^2/m^2	22.3±1.5	21.5±1.5	24.0±2.3	.043
WA%, %	69.9±1.3	66.6±2.0	65.0±2.3	.50
Ai/BSA, mm^2/m^2	9.5±0.4	10.9±1.1	12.4±1.2	.50
Lung area/BSA, cm^2/m^2	68.4±2.6	68.5±4.0	67.1±3.3	.35

Abbreviations: ECP, eosinophil cationic protein; EIB, exercise-induced bronchoconstriction; FE_{NO} fractional exhaled nitric oxide concentration; FEV_1 forced expiratory volume in 1 second; Ig, immunoglobulin; PC20 histamine FEV_1 provocative concentration of histamine that caused a 20% fall in FEV_1.
[a] Data are presented as mean (SD).
[b] Values significantly different from patients with EIB, *P*< .05.
[c] Values significantly different from patients without EIB, *P*< .05.

Discussion

To our knowledge, this is the first study to evaluate long-term changes (4.2±0.5 years) in airway-wall thickness on CT scans in asthma. Despite long-term ICS treatment, airway-wall thickness did not decrease consistently, and disease duration was associated with long-term changes in airway-wall thickness. A between-group comparison of 2 patient groups divided according to long-term changes in airway-wall thickness failed to identify mechanisms potentially underlying these changes. However, a within-group comparison delineated distinct features in the 2 groups.

Delayed introduction of ICS is generally considered to cause airway remodeling as determined by pulmonary function [23-25]. We provided morphological evidence of this in an earlier short-term study, in which disease duration at baseline was associated with post-treatment wall thickness [16]. In the present long-term study, disease duration at baseline was still associated with changes in wall thickness between the second and third measurements. This is consistent with findings of Kurashima et al [26], who found that a 1-year course of ICSs significantly decreased airway-wall thickness when assessed semi-quantitatively by CT in asthmatics with disease durations of fewer than 5 years, but not in those with long-standing asthma [26]. It is difficult to determine whether the airway-wall thickness detected at the third measurement in our study was mainly attributable to remodeling that took place before institution of ICS therapy or to structural changes that occurred during long-term follow-up, or to both. Elegant studies of allergen-challenged animals models have shown that neither established hyperplasia/hypertrophy of airway smooth muscle [27] nor fibronectin deposition [28] is reversed by ICSs. It has been seen, however, that further progression of established airway remodeling is inhibited by ICSs [17]. We therefore hypothesized that long-term treatment with ICSs may decrease wall thickness in all patients who adhere to therapy. However, we did not find a significant decrease in airway-wall thickness in the 14 patients we analyzed, despite long-term treatment with ICSs. Our findings are inconsistent with those of Lee et al [29], who demonstrated that airway-wall thickening was significantly attenuated in 12 asthmatics after a median follow-up period of 16.8 months after initiating ICSs. The reason for the discrepancy between those findings and ours is unknown but it may be due to differences in the length of follow-up. Our findings imply that long-standing asthma without ICS treatment may still affect susceptibility to subsequent treatment with ICS. Reversibility of hypervascularity, submucosal gland hyperplasia, and sub-basement membrane thickening by ICSs depend on dose (>1500 μg daily) [14,15] and treatment period (>12 months) [1,13,27]. Corticosteroids have been seen to inhibit the proliferation of airway smooth muscle in a rat model of chronic allergic asthma [30] but not that of cultured smooth muscle cells from asthmatic patients [31]. ICSs may not fully reverse or consistently prevent the development of airway-wall thickening in some clinical conditions such as long-standing asthma.

Disease was not difficult to control and adherence was good in the 5 nonresponders who had WA/BSA changes of >0.32 $mm^2/m^2/y$ despite long-term ICS treatment. However, the pulmonary function levels in these patients were decreased, albeit not severely impaired, and their ICS maintenance dose could not be reduced. These findings contrast with those observed in the 9 responders with WA/BSA changes of <0.32 $mm^2/m^2/y$. Although the small sample size, the inclusion of heterogeneous patients, and the lack of a between-group difference may preclude the generalization of the present findings, the features of the 5 patients detected by our within-group comparison may provide directions for future research in this area.

In the present study we focused on WA/BSA as the main measure of airway-wall thickness, because in our previous cross-sectional study, WA and WA/BSA were better correlated with asthma severity and airflow limitation than WA% [7]. Furthemore, neither Ai nor Ai/BSA have been found to differ between 4 groups of asthmatics with different disease severities and controls [7]. Finally, we do not think that the changes we detected in airway-wall thickness are attributable to changes in lung volumes since there were no differences in lung areas between the second and third measurements in either group.

Controllers other than corticosteroids, i.e., long-acting $ß_2$ agonists, sustained-release theophylline, and leukotriene receptor antagonists have been used with no significant differences between responder and nonresponder groups. While limited, studies examining the effects of these controllers on airway remodeling in animal models have shown favorable outcomes when used in isolation [27-32] or in addition to ICSs [33]. Studies with larger sample sizes are needed to examine whether combination therapy using ICSs and these controllers alleviates the progression of airway remodeling in humans. Our strategy to treat patients may be another limitation of this study as the maintenance ICS dose in nonresponders could not be reduced. If the patients had been treated according to degree of airway responsiveness [13] or sputum eosinophil counts [34] or indeed treated with fixed high doses of ICSs in combination with other controllers, the airway wall might have decreased consistently, even in nonresponders. Indeed, when patients with refractory eosinophilic asthma despite high doses of ICS and a history of recurrent severe exacerbations were treated with the anti-interleukin-5 monoclonal antibody mepolizumab for 1 year, they showed significantly greater decreases in wall area and total airway area on CT than their untreated counterparts [35]. This finding highlights the possibility that aggressive antieosinophilic treatment may consistently reverse and prevent airway remodeling in patients with refractory eosinophilic asthma.

A single bronchus may not be representative of the entire airway, and measuring a single bronchus may be a limitation of the present study. However, we previously showed that the WA of the bronchus examined in this study correlated with that of other bronchi [7,19]. In addition, in order to minimize the risk of errors due to repeated measurements, we carefully determined the slices of the corresponding airway levels based on anatomic landmarks, including the accompanying blood vessels and bronchi. We therefore believe that the results of this follow-up study were not seriously biased by the single-bronchus measurement. Since age did not correlate with WA in a previous study [7], a control group was not included to avoid unnecessary radiation exposure.

In conclusion, airway-wall thickness may not consistently decrease despite long-term treatment with ICS. One of the mechanisms underlying poor response to long-term treatment may be long-standing asthma. A long-term prospective study is needed to predict poor response in such patients and to identify an optimal strategy to prevent the progression of airway remodeling.

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