Original articles

Aspirin sensitivity and severity of asthma: Evidence for irreversible airway obstruction in patients with severe or difficult-to-treat asthma

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Background: Patients with aspirin sensitivity experience hyperplastic sinusitis and nasal polyposis. We speculated that similar mechanisms could be acting in the lower airway and that these individuals would demonstrate more severe asthma and irreversible loss of lung function.

Objective: We sought to investigate the role of aspirin-exacerbated respiratory disease (AERD) as a risk factor for the development of irreversible airway obstruction.

Methods: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study is a multicenter observational study of subjects with severe or difficult-to-treat asthma. Data were compared between subjects who reported asthma exacerbation after aspirin ingestion and those who did not. The primary measure of bronchodilator-resistant obstruction (possible remodeling) was the maximally achieved postbronchodilator spirometry averaged over the 3-year duration of the study.

Results: Adult subjects (≥18 years) with AERD (n = 459) were compared with subjects with non–aspirin-sensitive asthma (n = 2848). Subjects with AERD had significantly lower mean postbronchodilator percent predicted FEV_1 compared with subjects with non–aspirin-sensitive asthma (75.3% vs 79.9%, $P < .001$). Differences in spirometry between the 2 cohorts persisted after controlling for potential confounding variables. In addition, subjects with AERD were more likely to have severe asthma by means of physician assessment (66% vs 49%, $P < .001$), to have been intubated (20% vs 11%, $P < .001$), to have a steroid burst in the previous 3 months (56% vs 46%, $P < .001$), and to have required high-dose inhaled corticosteroids (34% vs 26%, $P < .001$).

Conclusions: These data suggest that aspirin sensitivity is associated with increased asthma severity and possible remodeling of both the upper and lower airways. (J Allergy Clin Immunol 2005;116:970-5.)

Key words: *Sinusitis, rhinosinusitis, rhinitis, eosinophils, functional endoscopic sinus surgery*

The development of an irreversible decrease in lung function (airway remodeling) is recognized as a complication of asthma. However, there is tremendous variability as to whether remodeling will occur in a given asthmatic subject. For example, Dompeling et al[1] reported aggressive remodeling of more than 80 mL/y in patients 30 years or older, whereas the Childhood Asthma Management Program study[2] found no evidence for remodeling in a large cohort of children with asthma. Although asthma severity and heightened airway reactivity have been proposed as risk factors for the development of fixed obstruction,[3] the importance of these parameters has not been adequately studied in a well-designed prospective investigation. Our research has focused on airway remodeling mechanisms in aspirin-exacerbated respiratory disease (AERD). AERD is characterized by severe persistent asthma, extensive chronic hyperplastic eosinophilic sinusitis (CHES) with nasal polyp formation,[4] and aspirin sensitivity. Asthma in these patients appears to be associated with aggressive remodeling and, in some cases, diminished diffusing capacity.[5] The combination of fibrosis, hyperplasia, and polyp formation in the sinuses with diminished lung function and diffusing capacity in the lungs suggests these are similar pathologic processes occurring in the upper and lower airways, respectively.

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Supported by a grant from Genentech/Novartis and NIH AI50989.

Disclosure of potential conflict of interest: T. Haselkorn has consultant arrangements with Genentech and has received grants from Genentech and Novartis Pharmaceuticals Inc. Y. Deniz has received grants from Genentech and Novartis Pharmaceuticals Inc and is employed by Genentech. D. Miller has consultant arrangements with the Ovation Research Group and has received grants from Genentech and Novartis Pharmaceuticals Inc. E. Bleecker has received grants from Genentech and Novartis Pharmaceuticals Inc, is on the speakers' bureau for Genentech and Novartis Pharmaceuticals Inc, and is on the Genentech TENOR Advisory Board. L. Borish is on the TENOR Advisory Board. K. Mascia has no conflicts of interest to disclose.

Received for publication May 19, 2005; revised July 29, 2005; accepted for publication August 2, 2005.

Available online October 3, 2005.

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0091-6749/$30.00

doi:10.1016/j.jaci.2005.08.035

Abbreviations used
AERD: Aspirin-exacerbated respiratory disease
BMI: Body mass index
CHES: Chronic hyperplastic eosinophilic sinusitis
COPD: Chronic obstructive pulmonary disease
FVC: Forced vital capacity
NSAID: Nonsteroidal anti-inflammatory drug
TENOR: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens

These patients demonstrate intense eosinophilic inflammation[6] that might be responsible for this fibrosis in large part through the production of TGF-β.[7-12] We therefore hypothesized that aspirin sensitivity might be a risk factor for individuals at particularly high risk for the development of fixed obstructive lung disease.

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study is an observational study of 4756 subjects with severe or difficult-to-treat asthma.[13] Because irreversible decrease in lung function in patients with aspirin sensitivity is a mechanism likely to produce severe asthma, we expected these subjects to be well represented in the TENOR cohort. We hypothesized that subjects with aspirin sensitivity would be distinguished from other subjects in the TENOR cohort by their degree of obstruction, refractoriness to β-agonist therapy, and severity of disease.

METHODS

Subjects

TENOR is 3-year, multicenter, observational study in the United States that, in 2001, began to enroll patients with asthma aged 6 years or older who were under the care of a pulmonary or allergy specialist. Subjects were required to have severe or difficult-to-treat asthma, as determined by their physician; subjects with mild or moderate asthma were eligible for enrollment if their physician considered their asthma difficult to treat and they met the additional inclusion and exclusion criteria[13]: 2 or more unscheduled care visits for asthma, 2 or more oral corticosteroid bursts during the 12 months before enrollment, current use of 3 or more medications or chronic daily high doses of inhaled corticosteroids, or use of 5 mg or more of oral prednisone per day. Subjects were excluded if they were heavy smokers (≥30 pack-years) or had a diagnosis of cystic fibrosis. Current smokers were included in TENOR but excluded from the current analysis. Patients were evaluated at study entry and every 6 months thereafter during a 3-year follow-up period. Data for the present analysis included information from spirometric testing, physician assessments, medical record reviews, patient interviews, and self-report questionnaires at baseline. Additional details of the study design have been reported previously.[13] All subjects were required to provide informed consent.

Aspirin sensitivity

Subjects were considered to have aspirin sensitivity if at the baseline visit they selected "taking aspirin" from a list of asthma triggers after the following question: "Have you ever had a cough, wheeze, or other symptom of asthma as a result of exposure to any of the following circumstances?"

Spirometry

The primary outcome measure was spirometric data obtained after administration of a bronchodilator. Spirometric data were collected annually, and an average over the 3-year study period was computed for each patient for each measure. All centers were required to have a certified device for performing flow spirometry that was calibrated daily. Data that were evaluated included FEV_1, forced vital capacity (FVC), and FEV_1/FVC ratio before and after administration of a β-agonist.

Asthma severity–health care use

The TENOR study population was comprised of subjects older than 6 years with severe or difficult-to-treat asthma; subjects with mild or moderate asthma were eligible for enrollment if their physician considered their asthma difficult to treat and they met the additional inclusion and exclusion criteria.[13] Health care use was assessed as previously described[13] and included data on emergency department visits, unscheduled office visits, corticosteroid bursts during the previous 3 months, and ever having been intubated.

Medication data

Subjects in the 2 cohorts were evaluated for use of high-dose inhaled corticosteroids according to the National Asthma Evaluation and Prevention Program criteria, as previously described,[14] and for use of leukotriene modifiers.

Statistical analyses

Data from subjects with non–aspirin-sensitive asthma were compared with data from subjects with AERD. Continuous outcomes, such as age at baseline (years), height, weight, BMI, and spirometry (FEV_1, FVC, and the FEV_1/FVC ratio before and after administration of a β-agonist), were analyzed by using the Student *t* test. Categoric outcomes related to health care use were assessed for the 2 cohorts by using the χ^2 test or the Mantel-Haenszel test. Because the 2 cohorts differed in some of the demographic characteristics (Table I), models were developed to control for potential confounding. Analysis of covariance was used for the spirometric measures, and logistic regression was used for the binary health care use outcomes. Covariates included were age at baseline (years), sex, ethnic origin, BMI (in kilograms per square meter), allergic rhinitis, duration of asthma, smoking history, (former or never), and pack-years. The TENOR questionnaire asks patients whether a doctor has told them they have chronic obstructive pulmonary disease (COPD) or emphysema. Multivariable analysis was repeated, adding the COPD-emphysema variable as a covariate; those results did not differ appreciably from the results presented, which do not adjust for COPD-emphysema.

RESULTS

Subjects

From January 2, 2001, to October 10, 2001, 4923 subjects were screened for inclusion in TENOR. Of these, 4756 subjects were enrolled and completed a baseline study visit. Aspirin sensitivity was reported in only 6 (1%) of 770 pediatric subjects aged less than 13 years and 11 (2%) of 497 adolescents aged 13 to 17 years. This result is consistent with studies that show AERD is generally an adult-acquired disease.[15] Because of the

TABLE I. Demographic and clinical characteristics of adults with non–aspirin-sensitive asthma and AERD in TENOR

	Non–aspirin-sensitive asthma (n = 2848)	AERD (n = 459)	*P* value*
Age at baseline, y (mean ± SD)	49.8 ± 14.9	49.9 ± 14.3	NS
Sex, % female (n)	70 (1995)	78 (356)	.001
Ethnic origin, % (n)			.002
White	81 (2309)	75 (342)	
Black	11 (307)	15 (69)	
Asian or Pacific Islander	2 (48)	1 (6)	
Hispanic	5 (154)	7 (33)	
American Indian or Alaskan native	<1 (4)	1 (4)	
Other	1 (24)	1 (4)	
Unknown	<1 (2)	<1 (1)	
Height, cm (mean ± SD)	166.2 ± 10.0	164.8 ± 9.8	.003
Weight, kg (mean ± SD)	84.0 ± 21.8	83.1 ± 23.3	NS
BMI, kg/m^2 (mean ± SD)	30.4 ± 7.6	30.6 ± 8.0	NS
Duration of asthma, y (mean ± SD)	23.6 ± 17.0	25.7 ± 15.3	.011
Smoking status			.013
Never, % (n)	66 (1874)	72 (329)	
Past, % (n)	34 (974)	28 (130)	
Pack-years (mean ± SD)	12.1 ± 13.8	10.9 ± 10.4	NS
Presence of allergic rhinitis, % (n)	70 (2000)	79 (360)	<.001
Chronic bronchitis, % (n)	36 (1007)	39 (179)	NS
COPD-emphysema, % (n)	9 (244)	8 (37)	NS
Positive skin test results (% of total reporting being skin tested)	94	92	NS
IgE, IU/mL (median)	89	80	NS

NS, Not significant.
*Reported *P* values are based on *t* tests for continuous outcomes and χ^2 tests for categoric outcomes.

overrepresentation of adults in the AERD cohort, all further analyses were limited to 3307 adult TENOR subjects. In adults (≥18 years) aspirin sensitivity was reported in 459 (14%) of 3307 subjects who were not current smokers at the time of enrollment.

Demographic and clinical characteristics for subjects with non–aspirin-sensitive asthma and those with AERD are summarized in Table I. Subjects reporting aspirin sensitivity were more likely to be women and minorities. Subjects in both cohorts had similar body habitus and reported durations of asthma that were not meaningfully different. Subjects with AERD were more likely to have never smoked compared with subjects with non–aspirin-sensitive asthma. No discernible differences in atopic predisposition were recognized in the 2 cohorts. Among subjects reporting having undergone allergy skin testing, a similar percentage of subjects in both cohorts reported positive test results. The 2 cohorts displayed clinically similar self-reported prevalence of chronic bronchitis, COPD-emphysema, and total IgE concentrations.

TABLE II. Spirometric results

	Non–aspirin-sensitive asthma (n = 2848)	AERD (n = 459)	*P* value
Unadjusted results*			
Prebronchodilator	Mean (SD)	Mean (SD)	
FEV_1 (%)	75.2 (22.5)	70.7 (21.2)	<.001
FVC (%)	86.1 (20.0)	82.6 (19.5)	.001
FEV_1/FVC	0.71 (0.11)	0.70 (0.12)	.107
Postbronchodilator	Mean (SD)	Mean (SD)	
FEV_1 (%)	79.9 (22.0)	75.3 (21.0)	<.001
FVC (%)	90.2 (19.1)	86.7 (19.2)	<.001
FEV_1/FVC	0.72 (0.12)	0.71 (0.12)	.085
Adjusted results†			
Postbronchodilator	Mean (SE)	Mean (SE)	
FEV_1 (%)	80.0 (0.4)	75.3 (1.0)	<.001
FVC (%)	90.2 (0.3)	87.2 (0.9)	.002
FEV_1/FVC	0.72 (0.002)	0.71 (0.005)	.005

**P* values are based on the 2-sided Student *t* test for means.
†Multivariate modeling with analysis of covariance to account for differences in age at baseline (years), sex, ethnic origin, BMI (kilograms per square meter), allergic rhinitis, duration of asthma, smoking history, and pack-years.

Spirometry

We hypothesized that subjects with AERD would demonstrate more severe obstruction and that the obstruction would be more refractory to bronchodilators. Our primary outcome parameter was therefore the average percent predicted postbronchodilator FEV_1 measured on multiple occasions throughout the 3-year duration of the TENOR study to reflect the presence of consistently bronchodilator-resistant airway obstruction (possible remodeling). Spirometric data are summarized in Table II. The means were significantly different between the 2 cohorts (average of 79.9% of predicted postbronchodilator FEV_1 in the non–aspirin-sensitive asthma cohort compared with 75.3% predicted in the AERD cohort, $P < .001$). Statistically significant differences were also observed in mean postbronchodilator *FVC* values, as well as in mean prebronchodilator data. Multivariate modeling with analysis of covariance was performed to verify whether the differences between the 2 cohorts for mean postbronchodilator FEV_1 remained significant after accounting for covariates, such as age, sex, ethnic origin, BMI, duration of asthma, allergic rhinitis, smoking status, and pack-years. The differences in mean postbronchodilator FEV_1 between subjects with non–aspirin-sensitive asthma and subjects with AERD persisted after adjusting for these potential confounding variables (Table II).

Asthma severity, health care use, and medication use

According to physician assessment of asthma severity, a greater percentage of subjects with AERD were considered to have severe asthma (Table III). Subjects with AERD also demonstrated increased health care use, including increased likelihoods of an emergency department

visit, unscheduled office visits, or corticosteroid bursts in the previous 3 months. A higher proportion of patients with AERD (20%) reported ever being intubated compared with subjects with non–aspirin-sensitive asthma (11%). Increased asthma severity in the non–aspirin-sensitive asthma cohort is strongly reflected in the greater effect of all of these parameters despite the increased use of both systemic corticosteroids and what would be considered high doses of inhaled corticosteroids, according to the National Asthma Evaluation and Prevention Program criteria.[14] Finally, subjects with AERD were more likely to be using a leukotriene modifier (Table III).

TABLE III. Asthma severity, health care use, and medication use

	Non–aspirin-sensitive asthma (n = 2848)	AERD (n = 459)	*P* value*
Physician assessment of "severe" asthma, % (n)	49 (1378)	66 (304)	<.001
History of intubation, % (n)	11 (322)	20 (92)	<.001
Unscheduled office visit in previous 3 mo, % (n)	44 (1264)	54 (249)	.001
Emergency department visit in previous 3 mo, % (n)	13 (372)	18 (81)	.017
Hospitalized in previous 3 mo, % (n)	5 (131)	6 (29)	.068
Corticosteroid burst in previous 3 mo, % (n)	46 (1319)	56 (258)	<.001
Use of high-dose inhaled corticosteroids, % (n)	26 (727)	34 (157)	<.001
Use of leukotriene modifier, % (n)	57 (1615)	67 (308)	<.001

*Adjusted for age at baseline (years), sex, ethnic origin, BMI (kilograms per square meter), allergic rhinitis, duration of asthma, smoking history, and pack-years.

DISCUSSION

AERD is characterized by a spectrum of components, including severe asthma, extensive CHES with nasal polyp formation, and intolerance to aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs). CHES is an inflammatory disease characterized by the accumulation of eosinophils, fibroblasts, goblet cells, and T_H2-like lymphocytes.[16,17] The prominent accumulation of eosinophils is considered the diagnostic feature of this condition.[17-20] CHES is frequently associated with asthma and can occur in as many as 74% to 90% of all asthmatic patients.[21-23] AERD is distinguished by the extensiveness of the sinus disease,[4] more frequent association with nasal polyps, and, if untreated, the frequent need for repeat polypectomies.[5,24,25] These patients also demonstrate an eosinophilic infiltration in the respiratory tissue that is significantly more intense than that observed in aspirin-tolerant patients.[6] Through their ability to activate TGF-β and other remodeling factors, eosinophilic inflammation is an important cause of fibrosis.[7-12] In a recent study, patients with extensive sinusitis were shown to be more likely to demonstrate evidence of airway remodeling, including increased functional residual capacity on spirometry and diminished diffusing capacity.[5] Although this study did not fully evaluate the presence of aspirin sensitivity in these subjects, it is likely that subjects with AERD were overrepresented in the cohort of asthmatic subjects with more extensive sinus disease. We therefore hypothesized that AERD is a syndrome characterized by aggressive remodeling, extensive eosinophilic inflammation, and fibrosis of both the upper and lower ends of the respiratory tract. We propose that in AERD the hyperplasia, fibrosis, and polyp formation occurring in the sinuses predicts the presence of remodeling and fibrosis in the lower airways.

We investigated this hypothesis by using the TENOR cohort. We reasoned that a syndrome characterized by aggressive remodeling and irreversibility would contribute to the development of severe or difficult-to-treat asthma and that as such, aspirin-sensitive subjects would be well represented in this study. In TENOR 14% of the subjects reported aspirin sensitivity, which is consistent with previously reported observations regarding the frequency of aspirin sensitivity in asthma.[15,26] Numerous mechanisms might contribute to severity and difficulty in controlling asthma, including the presence and extensiveness of an allergic disorder compounded with the degree of allergen exposure, other environmental exposures, genetic predisposition, availability and access to appropriate therapeutics, patient compliance, and many other factors. We predicted, however, that among the subjects with AERD, we would be more likely to identify evidence for irreversible obstruction (remodeling) as a factor driving the severity of the disease. Our data strongly support this hypothesis. Most importantly, subjects with AERD displayed significantly diminished lung function compared with that seen in subjects with non–aspirin-sensitive asthma (Table II). This is particularly impressive insofar as the diminished lung function occurred despite increased recent use of systemic corticosteroids, higher dosing of inhaled corticosteroids, and more frequent use of leukotriene modifiers in these subjects with AERD. The more frequent use of leukotriene modifiers in subjects with AERD might reflect the increased role of cysteinyl leukotrienes in this disorder[6,27] and the perceived increased efficacy of these agents.[28,29] It is noteworthy that almost twice as many subjects in the AERD cohort reported having been intubated. Although this might reflect the increased severity of their disease, no information was available regarding these events, and it is plausible that many of the episodes were consequences of their exposure to aspirin or other NSAIDs.

Remodeling in AERD presumably reflects a synergism between profibrotic mechanisms unique to these patients and the general influences of asthma severity and duration on the development of irreversible obstruction. AERD has replaced previous terms, such as "aspirin-intolerant asthma," in recognition that many of these patients do not

have asthma and their reactions are limited to the upper airway. Nonasthmatic patients with AERD are unlikely to experience irreversible obstruction. Similarly, although associated with more severe asthma,[5] patients with AERD whose asthma remains mild are less likely to experience fixed obstruction. Insofar as the subjects in TENOR all had severe or difficult-to-treat asthma, this represents a unique cohort in which the profibrotic influences that underlie aspirin sensitivity were more likely to be expressed.

There are limitations regarding the use of epidemiologic questionnaire-based studies to categorically establish these conclusions. Our diagnosis of aspirin sensitivity is based on the patients' subjective feeling that exposure to aspirin was associated with cough, wheeze, or other symptoms of asthma. Aspirin sensitivity is properly diagnosed only by performing graded aspirin challenge or, experimentally, topical challenges with lysine-aspirin.[30-32] Because of the inherent variability of lung function in asthma, temporal worsening of asthma in association with aspirin ingestion can easily be confused with evidence for hypersensitivity. Data show that fewer than 85% of patients reporting aspirin sensitivity have AERD.[30-32] Similarly, many subjects not reporting aspirin sensitivity might have reacted to other NSAIDs that were not addressed in our survey, or they had no recent exposures to these therapies. Had it been feasible to verify aspirin sensitivity in this study, we might have been able to demonstrate more pronounced differences in bronchodilator-resistant airflow obstruction associated with this condition. Finally, although we attempted to control for potential confounding, we cannot rule out the presence of residual confounding in these data.

Our goal for this study was to correlate aspirin sensitivity with evidence of airway remodeling. Ideally, we would have performed extensive pulmonary function testing, including body plethysmography and assessments of diffusion capacity, and, more importantly, properly discerned the degree of reversibility by administering high-dose systemic corticosteroids for several weeks. However, for large-scale epidemiologic studies, FEV_1 determined after administration of a bronchodilator is the best and most practical technique.[2] Spirometric data were collected and averaged over the 3-year duration of the TENOR study and therefore are more likely to reflect consistent bronchodilator-resistant obstruction (remodeling) and not the temporal variability characteristic of lung function in asthmatic subjects. Although abnormal postbronchodilator lung function might still not necessarily reflect irreversible mechanisms, normal lung function is fairly good evidence that significant remodeling has not occurred. As such, the presence of normal lung function in the plurality of TENOR subjects has important implications. Previous studies have suggested that remodeling is a frequent occurrence in asthma and is regarded as a function of severity and duration of disease.[1,3,33-35] All of the patients in TENOR have severe or difficult-to-treat asthma.[13] Despite a mean duration of asthma in this study of approximately 25 years, most of the patients with non–aspirin-sensitive asthma had little evidence of remodeling, as shown by their normal lung function. These data are similar to the results derived from the Childhood Asthma Management Program, which found no evidence for remodeling in their subjects.[2] These data have the important implication that remodeling is not a universal feature of asthma, even severe asthma of several decades' duration. Other features must determine which subjects are destined to have irreversible lung function. Our data support the concept that aspirin sensitivity might be one characteristic predicting the development of lung fibrosis and remodeling.

In summary, in TENOR AERD was associated with increased asthma severity. This might reflect a greater effect of airway remodeling in these subjects, as shown by their significantly diminished postbronchodilator lung function. We conclude that AERD is a disease characterized by extensive remodeling, hyperplasia, eosinophilic inflammation, and fibrosis involving both the upper airways (sinuses) and lower airways (lungs). Aspirin sensitivity might be a predictive factor for asthmatic patients at risk for the development of fixed obstructive lung disease. Finally, aspirin desensitization[25,36,37] and leukotriene modifiers,[29] including 5-lipoxygenase inhibitors[28] in particular, are uniquely effective treatments for patients with AERD. It is important to demonstrate whether these interventions alter the natural history of progressive airflow obstruction.

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