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ORIGINAL ARTICLE

Gender Differences in IgE-Mediated Allergic Asthma in the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) Study

JUNE H. LEE, M.D.,[1,*] TMIRAH HASELKORN, PH.D.,[1] BRADLEY E. CHIPPS, M.D.,[2] DAVE P. MILLER, M.S.,[3] SALLY E. WENZEL, M.D.,[4] FOR THE TENOR STUDY GROUP[†]

[1]*Genentech, Inc., South San Francisco, California, USA*
[2]*Capital Allergy and Respiratory Disease Center, Sacramento, California, USA*
[3]*Ovation Research Group, San Francisco, California, USA*
[4]*National Jewish Medical and Research Center, Denver, Colorado, USA*

Background. The TENOR study consists of a large cohort of subjects with severe or difficult-to-treat asthma. The objective of this analysis was to evaluate demographic and clinical characteristics of subjects 12 years of age or older with immunoglobulin E (IgE)-mediated allergic asthma (skin test positive with an IgE level ≥30 to ≤700 IU/mL), and specifically, to assess gender differences in this cohort. *Methods*. A total of 4,756 subjects were enrolled by 283 US study sites between January and October 2001. Of those subjects 12 years or older at baseline with an IgE measure and who were skin tested ($n = 2,843$), 1,783 (63%) were skin test positive and had an IgE level between ≥30 to ≤ 700 IU/mL. *Results.* Compared to males, females reported significantly greater healthcare utilization (steroid bursts in previous 3 months: 50% *vs* 42%, $p < 0.001$; unscheduled office visits in previous 3 months: 50% *vs* 36%, $p < 0.0001$; missed 1+ days of work/school in previous 2 weeks: 14% *vs* 10%, $p < 0.01$). Females also reported significantly more asthma control problems and lower asthma-related quality of life (4.6 ± 1.3 *vs* 5.2 ± 1.2; $p < 0.0001$); the difference was clinically meaningful. Asthma triggers and allergic comorbidities, such as allergic rhinitis and atopic dermatitis, were more common in female subjects. Despite their overall worse health outcomes, female subjects demonstrated better lung function, had similar treatment patterns, and showed no differences in physician-assessed asthma severity when compared with males. *Conclusions.* The reasons for these gender differences in subjects with IgE-mediated allergic asthma are complex, but results from this analysis suggest that detailed evaluations of asthma patients, including symptom-related questions and asthma-related healthcare utilization, are needed to accurately assess asthma severity and control.

Keywords asthma, gender, IgE-mediated, allergic, healthcare utilization

INTRODUCTION

Although asthma incidence is higher in boys than girls before the age of 12, with increasing age, asthma becomes more common in women (1, 2). More importantly, perhaps, asthma-related morbidity in the United States affects a disproportionate number of females (3) and is associated with excess mortality risk (compared with the general population). Visits to the emergency room (ER) for asthma are also higher in females than in males (4). Whether such differences reflect a gender disparity in susceptibility to asthma or differences in the prevalence of risk factors such as smoking and obesity (5), disease severity, hormonal influences (6, 7), or treatment patterns between males and females are topics of much interest (2, 4, 8). Moreover, while gender differences in disease-associated morbidity and mortality in asthmatics as a whole have been well-characterized, there is little data specifically in patients with IgE–mediated allergic asthma, particularly those with severe or difficult-to-treat asthma.

In the majority of patients, asthma is associated with some type of IgE-mediated allergic reaction (9). Higher levels of total serum IgE are associated with bronchial hyperresponsiveness (10, 11), increased visits to the ER (12), and disease severity (11). Therefore, determining whether gender differences are seen in this phenotype of asthma is important.

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study consists of a large cohort of subjects with severe or difficult-to-treat asthma (13).The objective of this analysis was to evaluate clinical and demographic characteristics of subjects 12 years of age or older with IgE–mediated allergic asthma (skin test positive with an IgE level ≥30 to ≤700 IU/mL), and, specifically, to assess gender differences in this cohort.

METHODS

Study Design and Participants

The TENOR study was a prospective, observational 3-year study conducted in the United States in subjects with severe or difficult-to-treat asthma who received care from either a pulmonologist or an allergist. A detailed description of

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[†]For a complete list of TENOR Study Group members, please contact Genentech, Inc.

[*]Corresponding author: June H. Lee, M.D., Genentech, Inc., 1 DNA Way, MS 59B, South San Francisco, CA 94080, USA; E-mail: junelee@gene.com

the study design and inclusion/exclusion criteria is provided elsewhere (13). No experimental intervention was involved; subjects continued to receive medications and treatments for their asthma as indicated by their asthma specialist. The design and protocol for the TENOR study were approved by a central institutional review board, and when necessary, by the institutional review board at each site.

The TENOR study population comprised subjects 6 years of age or older 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). Subjects had to be receiving care from their physician/provider for at least 1 year and had to have evidence of either high use of the healthcare system or medications, or both. Subjects were excluded if they were heavy smokers ($\geq$30 pack-years) or had a diagnosis of cystic fibrosis. All participants supplied written informed consent.

Subjects 12 years of age or older at baseline with a history of a positive skin test and a total serum IgE level between $\geq$30 to $\leq$700 IU/mL were included in this analysis. Among subjects 12 years of age or older at baseline with a positive skin test ($n = 2,656$), 474 (18%) females and 93 (4%) males had a total serum IgE level less than 30 IU/mL and 155 (6%) females and 151 (6%) males had a total serum IgE more than 700 IU/mL and were, therefore, excluded from the analysis. The IgE levels chosen for this analysis are based on the therapeutic range currently available for anti-IgE monoclonal antibody therapy, allowing the opportunity to better characterize the population that is eligible for such treatment.

Demographic and Clinical Assessments

Data for this analysis were based on the baseline assessment. In addition to assessing each subject's asthma severity, physicians reported whether their patient's asthma was considered difficult-to-treat based on specified parameters (i.e., complex treatment regimen, multiple drugs required, unable to avoid triggers, frequent exacerbations, severe exacerbations, and/or unresponsive to therapy).

Demographic (age, gender, race, height, and weight) and clinical data (spirometry, total serum IgE, healthcare utilization, medication use, smoking history) were collected by study coordinator interview and evaluation. Data on targeted comorbid conditions (allergic rhinitis, atopic dermatitis) were also collected.

Asthma Medications and Healthcare Utilization (HCU)

Patients reported current asthma control medications, including long-term controller and quick-relief medications. At study entry, and at each 6-month visit, patients reported asthma-related HCU during the previous 3 months. A history of intubation was recorded at study entry.

Asthma Control and Asthma-Related Quality of Life

Patients self-reported asthma control and management using the Asthma Therapy Assessment Questionnaire (ATAQ) (14). Scores ranged from 0 (no control problems) to 4 (maximum number of control problems). The Juniper Mini Asthma Quality of Life Questionnaire (MiniAQLQ) (15) was used to measure the functional impairments that are most troublesome to patients with asthma. Overall scores range from 1 to 7, with a higher score indicating a better asthma-related quality of life.

Skin Test, Asthma Triggers, and IgE Data

Skin test results and asthma triggers were self-reported. Asthma triggers were selected from a list of common exposures (e.g., animals, dust, mold, cigarette smoke).

Total serum IgE levels (IU/mL) were measured at baseline by each study site using any commercially available assay. All total serum IgE assay tests used in TENOR received 510 (k) Food and Drug Administration approval and were considered substantially equivalent in accuracy and precision. In addition, all total serum IgE assays were calibrated to the World Health Organization's second International Reference Preparation for Human Serum IgE, World Health Organization IRP 75/502 (16).

Statistical Analysis

The Student's *t* test for continuous variables or chi-square tests for categorical variables were used to obtain *p* values for comparing males and females. Logistic regression, adjusting for age, was performed to assess the risk of HCU and medication use in males and females. All analyses were performed using SAS Version 9.1 for Windows (SAS Institute, Cary, NC).

RESULTS

A total of 4,756 subjects were enrolled into TENOR by 283 U.S. study sites between January and October of 2001. Of those subjects 12 years or older at baseline with an IgE measure and who were skin tested ($n = 2,843$), 1,783 (63%) had a history of a positive skin test (ST+) and an IgE level between $\geq$30 to $\leq$700 IU/mL. The majority of subjects were female (65%). Subjects were further compared by gender using baseline demographic and clinical characteristics (Table 1). Female subjects were older (46.0 ± 16.4 *vs* 40.0 ± 20.2 year; $p < 0.0001$) and had a higher mean BMI (30.3 ± 8.1 *vs* 28.2 ± 6.6 kg/m^2; $p < 0.0001$) than males. There were no differences between female and male subjects in terms of duration of asthma, race/ethnicity, or smoking history.

Females had a higher prevalence of comorbid allergic conditions than males (Figure 1). The prevalence of allergic rhinitis was 80% in female subjects and 74% in male subjects ($p < 0.05$). Atopic dermatitis was reported in 14% of females and 11% of males ($p < 0.05$). In addition, a significantly greater proportion of female subjects than male subjects reported their asthma being triggered by dust (82% *vs* 78%; $p < 0.05$), mold (69% *vs* 54%; $p < 0.0001$), and pet dander (61% *vs* 53%; $p < 0.01$) (Figure 1). A significantly greater proportion of female subject than male subjects (43% *vs* 38%; $p < 0.05$) were unable to avoid asthma triggers, as suggested by physician assessment of treatment difficulty. Despite this allergic history, female subjects had significantly lower geometric mean total serum IgE levels compared with males (128.5 IU/mL *vs* 159.5 IU/mL; $p < 0.0001$).

In terms of asthma-related quality of life, females reported a significantly lower MiniAQLQ overall score than males (4.6 ± 1.3 *vs* 5.2 ± 1.2; $p < 0.0001$); the difference also

TABLE 1.—Demographic and clinical characteristics of female and male ST+ subjects ≥12 years at baseline with total serum IgE ≥30 and ≤700 IU/mL in TENOR

	Female	Male	*p* value
All patients, *n* (%)	1,156 (65)	627 (35)	
Age at baseline, mean ±SD (yr)	46.0 ± 16.4	40.0 ± 20.2	<0.0001
Body mass index, mean ±SD (kg/m^2)	30.3± 8.1	28.2 ± 6.6	<0.0001
Race/ethnicity, *n* (%)			
White	922 (80)	507 (81)	NS
Non-white	234 (20)	120 (19)	
Total serum IgE, geometric mean, IU/mL (95% CI)	128.5 (122.3–134.9)	159.5 (149.4–170.3)	<0.0001
Physician-assessed asthma severity, *n* (%)			
Mild	26 (2)	20 (3)	NS
Moderate	560 (48)	275 (44)	
Severe	570 (49)	332 (53)	
Smoking history for subjects ≥18 yr, n (%)			
Never smoked	729 (68)	292 (64)	NS
Past smoker	308 (29)	155 (34)	
Current smoker	31 (3)	10 (2)	
Duration of asthma, mean ± SD (yr)	23.2 ± 16.2	22.1 ± 15.8	NS
% Predicted post-bronchodilator FEV_1, n (%)			
≥80	594 (56)	270 (47)	<0.01
>60 to <80	285 (27)	197 (34)	
≤60	187 (17)	105 (18)	
Actual post-bronchodilator FEV_1/FVC ratio, mean ± SD	73.9 ± 11.7	71.2 ± 12.1	<0.0001
MiniAQLQ overall score, mean ± SD	4.6 ± 1.3	5.2 ± 1.2	<0.0001

NS, not significant. All data are from baseline visit.

met the established threshold for a minimal clinically meaningful difference (0.5) (17, 18). Healthcare utilization was also significantly greater in females compared with males (Figure 2), based on the use of steroid bursts in past 3 months

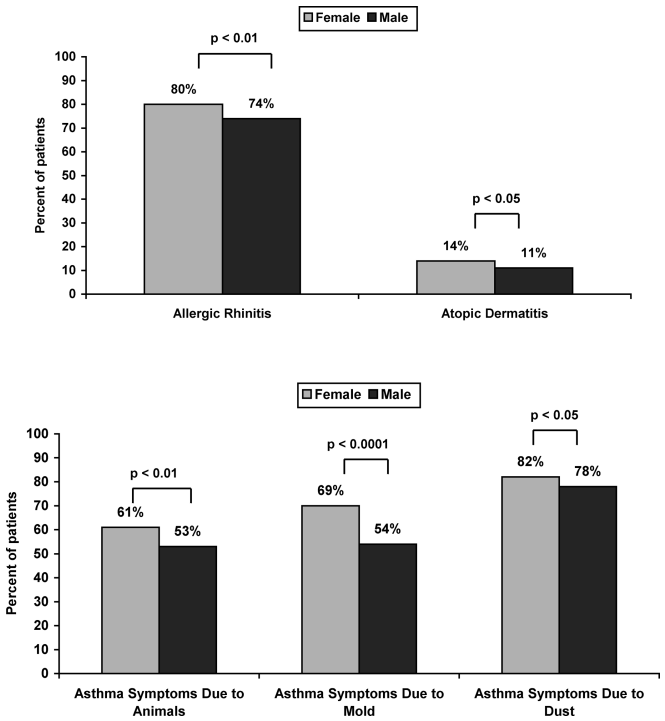
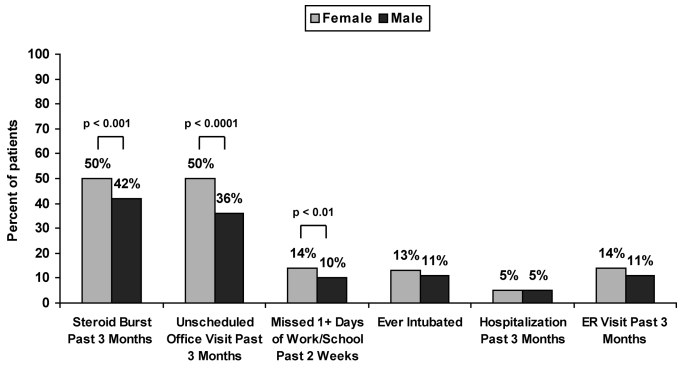


FIGURE 1.—History of allergic comorbidities and asthma triggers in female and male ST+ subjects ≥12 years at baseline with total serum IgE between ≥30 to ≤700 IU/mL in TENOR.



*Data adjusted for age

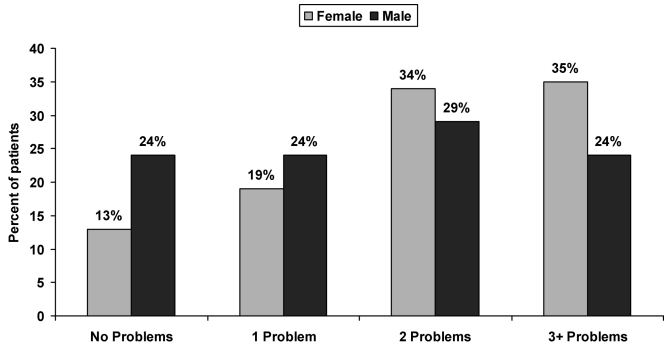
FIGURE 2.—Asthma-related healthcare utilization in female and male ST+ subjects ≥12 years at baseline with total serum IgE ≥ 30 to ≤700 IU/mL in TENOR. *Data are from the baseline visit.

(50% *vs* 42%; $p < 0.001$), unscheduled office contact in past 3 months (50% *vs* 36%; $p < 0.0001$), and missing 1 or more days of work/school in past 2 weeks (14% *vs* 10%; $p < 0.01$).

Females reported more problems controlling their asthma compared to males (Figure 3). For example, 35% of females compared with 24% of males reported 3 or more asthma control problems. Females were more likely to report missed activities and being awakened at night due to their asthma (data not shown).

Female subjects, however, had significantly ($p < 0.01$) better lung function compared with males based on % predicted post-bronchodilator FEV_1. As shown in Table 1, more female subjects than male subjects had predicted FEV_1 greater than or equal to 80% (56% *vs*. 47%) and fewer female subjects than male subjects had predicted values greater than 60%, but less than 80% (27% *vs* 34%). Similar proportions of female and male subjects had predicted FEV_1 less than or equal to 60% (17% *vs* 18%). The actual post-bronchodilator FEV_1/FVC ratio was significantly higher in females than in males (73.9 ± 11.7 *vs* 71.2 ± 12.1; $p < 0.0001$).

There were no significant differences between males and females in terms of medication use, physician-assessed



* $p < 0.0001$ for overall comparison by gender

FIGURE 3.—Results of the Asthma Therapy Assessment Questionnaire (ATAQ), control domain (range 0–4), in female and male ST+ subjects ≥12 years at baseline with total serum IgE ≥30 to ≤700 IU/mL in TENOR.* Data are from the baseline visit.

asthma severity (Table 1) or overall physician evaluation of treatment difficulty.

Discussion

TENOR is a cohort of subjects with severe or difficult-to-treat asthma. The current analysis focuses on gender differences in a subgroup of subjects 12 years of age or older with IgE–mediated allergic asthma, based on skin test positivity and total serum IgE levels between $\geq$30 to $\leq$700 IU/mL. Results showed that females appeared to fare worse on a number of objective and subjective clinical measures of disease severity, including quality of life, healthcare utilization, and asthma control. Compared with male subjects, female subjects were also significantly more likely to report allergic comorbidities, such as allergic rhinitis and atopic dermatitis, were more susceptible to asthma triggering, and were unable to avoid asthma triggers, as suggested by physician assessment of treatment difficulty. By these markers of asthma severity, females with IgE–mediated allergic asthma in TENOR appear to have more severe disease. At the same time, however, they demonstrated better lung function, had similar treatment patterns, and showed no differences in physician-assessed asthma severity compared with males.

One possible reason for more severe disease in female subjects with IgE–mediated allergic asthma in TENOR may be related to allergen sensitivity. Females reported a greater prevalence of allergic comorbidities, such as allergic rhinitis and atopic dermatitis compared with male subjects. In general, data from large epidemiologic studies indicate that the prevalence of allergic rhinitis is more common in women than in men (19, 20). In addition, factors in the home environment, such as unvented gas appliances, may increase allergic asthma symptoms more in atopic women than in atopic men (21). The role of aeroallergens in the worse outcomes in female subjects in this analysis is further supported by gender differences in triggering. Female subjects appeared to be more susceptible to asthma triggering than male subjects. A significantly greater proportion of female subjects than male subjects reported their asthma being triggered by dust, mold, and pet dander. This suggests that women may be exposed to indoor allergens more often than men. In addition, more females were unable to avoid asthma triggers compared to males, as suggested by physician assessment of treatment difficulty. It is possible, however, that the gender differences in allergen sensitivity seen in TENOR may be related to differences in respiratory symptom perception and reporting (2, 22).

It is also possible that females do not respond as well to their asthma medications as males. In TENOR, female subjects with IgE–mediated allergic asthma used the same number of long-term control medications as male subjects, despite their reporting more asthma control problems. There were also no differences between male and female subjects in physician-assessment of treatment difficulty, based on the need for multiple drugs or the use of complex drug regimens to control symptoms. In addition, the type of drugs used, including long-term inhaled and high-dose inhaled corticosteroids, long-acting beta-agonists, leukotriene modifiers, methylxanthines, and cromones, was also similar between genders. These data suggest that either female patients with asthma are under-treated, or their symptoms (but not lung function) do not respond as well to their medications as males. Indeed, evidence in the literature suggests that gender differences exist in the response of immunologic diseases, like asthma, to glucocorticosteroid treatment (23–26). For example, in one 6-week randomized, double-blind, placebo-controlled trial of inhaled fluticasone in previously untreated adult subjects (20–50 years of age) recruited from an epidemiologic study (27), the magnitude of the treatment effect, based on the dose of methacholine causing a 20% reduction in FEV_1, was significantly greater in men than in women.

In line with their greater symptomatology, females with IgE–mediated allergic asthma also reported greater functional impairment due to their asthma, as evidenced by their significantly lower overall scores on the MiniAQLQ compared with males. Results from the ATAQ also showed that females had more problems controlling their asthma compared with males and were more likely to miss activities and be awakened at night due to their asthma, findings similar to those reported by Osborne et al. (28). Furthermore, females exhibited a higher rate of HCU in terms of requiring a steroid burst in the previous 3 months, having an unscheduled office visit in previous 3 months, and missing 1+ days of work/school in past 2 weeks. There was also a suggestion of more severe exacerbations in females than males, as evidenced by the higher proportion of female subjects with ER visits in the previous 3 months ($p = 0.06$). These results are similar to a prospective cohort study in which almost twice as many adult females as adult males presented to the ER with acute asthma (29). Interestingly, in that study as well, women with asthma had better pulmonary function than men.

Hormonal factors may also contribute to the immunological and inflammatory processes underlying allergies and asthma and, hence, differences in clinical presentation between males and females. Studies suggest that some female sex steroids are proinflammatory and increase susceptibility to atopy (1, 30). In addition, approximately 30% to 40% of female asthmatics report worsening of asthma symptoms during the perimenstrual period (30), and evidence suggests that menstruation may trigger severe asthma attacks in women with unstable asthma (31).

In our analysis of subjects with IgE–mediated asthma, BMI was statistically significantly different between genders, with females having a somewhat higher mean BMI compared to males (30.3 ± 8.1 *vs* 28.2 ± 6.6). Other investigators have reported a dose-effect relationship between the incidence of current asthma and BMI in adult women, but not adult men (5, 32). Moreover, asthma severity has been shown to increase with BMI in women but not men, an association that remained after adjustment for age, FEV_1, smoking status, and BMI-adjusted dyspnea (33).

Despite the worse health outcomes in female subjects with IgE-mediated allergic asthma, the current TENOR analysis showed better lung function in female subjects than in male subjects. These data are consistent with a prospective cohort study that showed that adult females presenting to the ER with acute asthma had better pulmonary function than their male counterparts (29). This apparent disassociation between lung function and other measures of asthma severity, including

HCU, suggests that lung function alone may underestimate asthma severity (34, 35).

Despite the greater degree of allergic symptoms (and similar history of skin test reactivity) IgE levels in females were significantly lower compared with males in this analysis. This observation raises interesting hypotheses regarding the relationships between total and specific IgE, IgE-mediated allergic asthma symptoms, and lung function. Lower total serum IgE levels in females appear to be associated with less airway obstruction but more asthma and allergic symptoms. The disconnect between the high total IgE levels and relatively lower allergic asthma symptomatology in males compared with females seen in this TENOR analysis suggests these symptoms are more closely related to specific IgE levels, as measured with radioallergosorbent test (RAST) or skin testing, rather than with total serum levels. Whether these specific IgE antibodies are also somehow protective against decline in lung function requires further study.

It should be noted that skin test data and allergic comorbidities in TENOR relied on subject self-report, introducing the possibility for error or misclassification in these data. However, the consistently higher prevalence of allergic comorbidities and asthma triggers in females compared to males suggests that these data adequately capture allergic reactivity and other measures of allergic sensitivity in TENOR patients. In addition, nearly 500 patients reported that they had never been skin tested for allergies and were therefore not included in this analysis. Other TENOR analyses have demonstrated that patients not tested for allergies show a similar clinical profile to skin test positive patients than to skin test negative patients, suggesting that if tested, these patients would likely test positive (36).

Conclusions

The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens is a large cohort of subjects with severe or difficult-to-treat asthma. In the current analysis of TENOR subjects 12 years of age or older with IgE-mediated allergic asthma (skin test positive with an IgE level $\geq$30 to $\leq$700 IU/mL), important gender differences were observed in clinical measures of disease severity, including quality of life, HCU, and asthma control. In addition, female subjects were significantly more likely to report allergic rhinitis and atopic dermatitis, were more susceptible to asthma triggering, and were unable to avoid asthma triggers. The reasons for these gender differences in subjects with IgE-mediated allergic asthma require further study, but results from the analysis presented suggest detailed evaluations of asthma patients, including symptom-related questions and asthma-related HCU, are needed to accurately assess asthma severity and control.

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