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PII: S1081-1206(21)00563-9
DOI: <https://doi.org/10.1016/j.anai.2021.08.005>
Reference: ANAI 3683



To appear in: *Annals of Allergy, Asthma Immunology*

Received date: 6 April 2021
Revised date: 27 July 2021
Accepted date: 2 August 2021

Please cite this article as: Tmirah Haselkorn PhD , David Mink MS , Farid Kianifard PhD , Benjamin Ortiz MD , Brandee Paknis PharmD , Jason Lecocq MD , Bradley E. Chipps MD , Eugene R. Bleecker MD , Predominance of Atopic Asthma in Patients with Severe or Difficult-to-Treat Asthma in the TENOR-II Cohort, *Annals of Allergy, Asthma Immunology* (2021), doi: <https://doi.org/10.1016/j.anai.2021.08.005>

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Predominance of Atopic Asthma in Patients with Severe or Difficult-to-Treat Asthma in the TENOR-II Cohort

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Study design: T Haselkorn, B Ortiz, B Paknis, J Lecocq, BE Chipps and ER Bleecker; data collection: T Haselkorn, B Ortiz, BE Chipps and ER Bleecker; data analysis: D Mink and F Kianifard; data interpretation: all authors; writing of the manuscript: all authors; reviewing of the manuscript: all authors; final approval of the manuscript: all authors

Conflict of Interest

TH is a former consultant to Novartis Pharmaceuticals Corp. BO is former employee and stockholder of Novartis Pharmaceuticals Corporation. DM is an employee of ICON Clinical Research, a company that receives research funding from Genentech, Novartis, and other pharmaceutical companies. BK, FK and JL are employees of Novartis Pharmaceuticals Corporation. ERB reports he has undertaken clinical trials through his employer, Wake Forest School of Medicine and University of Arizona, for AstraZeneca, MedImmune, Boehringer Ingelheim, Genentech, Novartis, Regeneron, and Sanofi Genzyme, personal fees from ERB has also served as a paid consultant for ALK-Abello, AstraZeneca, MedImmune, Glaxo Smith Kline, Novartis, Regeneron, Sanofi Genzyme, and TEVA, outside the submitted work.

Funding Source

Novartis Pharmaceuticals Corporation, East Hanover NJ and Genentech Inc., San Francisco, CA

Clinical Trial Registration

Not applicable

Keywords

Severe asthma; difficult-to-treat asthma; atopic asthma; predominance; observational study

Abbreviations

ATS: American Thoracic Society

CI: Confidence interval

FeNO: Fraction of exhaled nitric oxide

IgE: immunoglobulin E

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

TENOR: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens

VPC: Very poorly controlled

Atopy, the genetic propensity to produce immunoglobulin E (IgE) against common environmental allergens is a known risk factor for asthma.¹ In 2001, the TENOR I observational study (NCT00091767) was initiated to understand the natural history of disease in patients with severe or difficult-to-treat asthma.² TENOR II was a multicenter, observational study conducted over 10 years later using cross-sectional follow-up assessment of patients from TENOR I.² As the “difficult-to-treat” asthma phenotype remains poorly defined, we sought to determine prevalence of atopy in TENOR II and describe demographic and clinical differences between atopic and non-atopic asthma patients.

Fifty-nine specialty sites participated in TENOR II, representing 1230 original TENOR I patients. Of these, 341 (27.7%) adult patients (aged ≥ 18 years) were subsequently enrolled into

TENOR II. Specific IgE concentrations were determined using the ImmunoCAP[®] or HYCOR[®] using a threshold of 0.35 kU/L for positive reading.³ Atopic asthma was defined as positive specific-IgE test to at least one of ten commonly tested allergens. Allergic rhinitis was self-reported in the medical history questionnaire (“Have you ever had a problem with sneezing or runny/blocked nose when you did not have a cold?”). Percentage of patients with very poorly controlled (VPC), not well-controlled, and well-controlled asthma was assessed using National Heart, Lung, and Blood Institute guidelines impairment domain as described previously.² Self-reported healthcare utilization in three months prior to TENOR II visit was collected, as well as ATS severe exacerbations.²

Analyses were performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement,⁴ where descriptive statistical analyses only are reported for demographic and clinical characteristics (item 14(a) of STROBE statement), and inferential statistical analyses for outcome measures are limited to reporting confidence intervals for differences between two subgroups.

Of 317 patients with an available specific IgE measure, majority (n = 231; 72.9%) had atopic asthma; 86 (27.1%) had non-atopic asthma. Atopic patients were younger than non-atopic patients at enrollment (56.2 (16.6) and 61.7 (14.7) years, respectively), and at asthma diagnosis (17.9 (17.4) vs. 27.9 (17.2) years, respectively; **Table 1**). Both groups had more female patients, and a greater proportion of non-atopic patients were prior smokers (32.1% vs. 21.7%). Rates of allergic rhinitis were comparably high between atopic (82.2%) and non-atopic patients (72.9%). Lung function was similar between two subgroups. Total IgE geometric mean was higher in atopic patients (130.7 IU/mL vs 14.1 IU/mL, respectively). Mean blood eosinophil counts were similar. Mean FeNO levels were slightly higher in atopic patients. The three most common

sensitizations for atopic patients were perennial aeroallergens cat dander (59.7%), dog dander (53.7%) and *Dermatophagoides farinae* (43.7%). Self-reported asthma triggers were more frequent in atopic than non-atopic patients, with exception of taking aspirin. Triggers included breathing-dust (79.2% vs 65.1% respectively [95% CI for difference: 2.8%, 25.5%]), pollen (74.0% vs 59.3% respectively [95% CI: 2.9%, 26.5%]) and being near animals (57.6% vs 33.7% respectively [95% CI: 12.0%, 35.7%]). Similar proportions of atopic and non-atopic patients had cats (19.6% vs 25.0%, 95% CI: -16.0%, 5.1%) and dogs (42.2% vs 39.3%, 95% CI: -9.4%, 15.1%) at home. Over half (53%) of patients exposed to cats were allergic to cats, while 42% not exposed to cats were allergic to cats, and 46% exposed to dogs were allergic to dogs, while 36% not exposed were allergic to dogs.

About a quarter of both atopic and non-atopic patients had ≥ 1 asthma exacerbation in the prior three months (24.7% vs 26.7%; Table 1). Non-atopic patients were more likely to require hospitalization/emergency department visits versus atopic patients (8.1% vs 4.8%). Severe exacerbations in prior three months were more frequent in non-atopic than atopic patients (7.0% vs 2.6%). Majority of patients in both groups had VPC asthma. Combined inhaled corticosteroid and long-acting β_2 -agonist use was reported in 73.8% and 67.4% of atopic and non-atopic patients, respectively; 13.8% and 4.7% used omalizumab, respectively.

Prevalence of atopic asthma in TENOR II (73%) is higher than that from the Third National Health and Nutrition Examination Survey, which indicated approximately half of current asthma cases in the US population are atopic.⁵ Studies have reported existence of an allergic phenotype in patients with early-onset asthma. Such patients have increased airway reactivity to perennial aeroallergens but similar, or better, lung function to non-atopic patients.⁶ In current analyses, atopic patients had an earlier onset asthma versus non-atopic patients, however percent predicted

pre- and post-bronchodilator FEV₁ were similar. Although total IgE levels were higher in atopic than non-atopic patients, blood eosinophil counts were similar. Recently, approximately 19% of severe asthma population was shown to be characterized by high IgE (>75 kU/L)/low eosinophil ($\leq 400 \mu\text{L}$) combination.⁷

Exposure to cats and dogs in early life may be protective or a risk factor for development of atopic asthma.⁸ Studies suggest that an abundant number of bacterial microbiota in house dust correlate with concentrations of indoor allergens and are associated with asthma risk.⁹ In this analysis, perennial aeroallergens were the most common allergens among atopic patients. Patient-reported allergic triggers including pollen, breathing-dust, and being near animals, were more frequent among atopic than non-atopic patients. These results are consistent with previously published reports on commonly observed allergic triggers in asthmatics.¹ High rates of exacerbations in both subgroups and an increased rate of severe exacerbations in non-atopic patients, coupled with medication data from TENOR II, suggest less than optimal adherence to asthma guidelines.² Study limitations include self-reported nature of several variables, and inclusion of one observation time point. The sample size could pose other limitations, although sensitivity analyses demonstrated representativeness of TENOR II to TENOR I cohort.² Strengths include using a robust approach for confirming atopic disease in this older cohort of patients with severe asthma, and characterizing them using a broad array of variables. Findings from this 10-year, real-world, follow-up of patients with severe/difficult-to-treat asthma indicate that allergic asthma and VPC asthma are highly prevalent despite standard-of-care. Use of improved management strategies, adherence to asthma guidelines, reducing exposure to pet dander, and avoiding smoking may reduce burden of severe asthma, particularly in those who may be less responsive to corticosteroids.²

Acknowledgments

We thank Chiranjit Ghosh, PhD and Rahul Lad, PhD (Novartis) for providing medical writing support for this manuscript. We thank Dr. Larry Borish, University of Virginia Health System, Charlottesville, VA, USA, and Dr. Scott T. Weiss, Channing Division of Network Services, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA, for their contributions to the original analysis.

References

1. Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? *Thorax*.1999;54(3):268-72.
2. Chipps BE, Haselkorn T, Paknis B, et al. More Than a Decade Follow-Up in Patients With Severe or Difficult-To-Treat Asthma: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) II. *J Allergy Clin Immunol*.2018 May;141(5):1590-1597.
3. Szeffler SJ, Wenzel S, Brown R, et al. Asthma outcomes: biomarkers. *J Allergy Clin Immunol*.2012;129(3 Suppl):S9-23.
4. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. *Ann Intern Med*.2007;147(8):W163-94.

5. Arbes SJ, Jr., Gergen PJ, Vaughn B, Zeldin DC. Asthma cases attributable to atopy: results from the Third National Health and Nutrition Examination Survey. *J Allergy Clin Immunol.*2007;120(5):1139-45.
6. Miranda C, Busacker A, Balzar S, Trudeau J, Wenzel SE. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. *J Allergy Clin Immunol.*2004;113(1):101-8.
7. Haughney J, Morice A, Blyth KG, et al. A retrospective cohort study in severe asthma describing commonly measured biomarkers: Eosinophil count and IgE levels. *Respir Med.* 2018;134:117-123
8. Apter AJ. Early exposure to allergen: is this the cat's meow, or are we barking up the wrong tree?. *J Allergy Clin Immunol.*2003;111(5):938-46.
9. O'Connor GT, Lynch SV, Bloomberg GR, et al. Early-life home environment and risk of asthma among inner-city children. *J Allergy Clin Immunol.*2018;141:1468-1475.

Table 1. Baseline demographics and clinical characteristics and outcome measures of atopic* and non-atopic patients in the TENOR II cohort (N = 317)

Characteristic	Atopic* n = 231	Non-atopic n = 86
Demographics		

Age at TENOR II enrollment, years, mean (SD)	56.2 (16.6)	61.7 (14.7)
Age at asthma diagnosis, years, mean (SD)	17.9 (17.4)	27.9 (17.2)
Sex, n (%)		
Male	84 (36.4)	27 (31.4)
Female	147 (63.6)	59 (68.6)
Race, n (%)		
White	180 (77.9)	73 (84.9)
Black	26 (11.3)	10 (11.6)
Hispanic	17 (7.4)	3 (3.5)
Asian or Pacific Islander	4 (1.7)	0 (0)
Other	4 (1.7)	0 (0)
Smoking status, n (%)		
Ever smoked	50 (21.7)	27 (32.1)
Current	7 (14.0)	1 (3.7)
Atopic dermatitis, n (%)	60 (26.1)	23 (27.1)

Allergic rhinitis, n (%)	189 (82.2)	62 (72.9)	
<i>Lung function</i>			
Pre-bronch FEV ₁ % predicted, mean (SD)	72.2 (22.1)	73.3 (21.4)	
Post-bronch FEV ₁ % predicted, mean (SD)	78.0 (21.5)	78.8 (20.0)	
Site speciality, n (%)			
Pulmonologist	57 (26.1)	13 (15.9)	
Allergist	161 (73.9)	69 (84.1)	
<i>Laboratory measures</i>			
Total IgE (IU/mL)			Difference (95% CI)
Geometric mean (95% CI)	130.7 (107.9, 158.1)	14.1 (8.70, 23.0)	Ratio (95% CI for ratio): 9.24 (6.00, 14.24)
Median (interquartile range)	114.9 (274.7)	16.0 (43.7)	
Eosinophils (cells/ μ L), mean (SD)	201 (143)	198 (147)	3 (-33, 39)

Median (interquartile range)	200 (200)	200 (100)	
FeNO (ppb), mean (SD)	30.12 (32.10)	26.85 (18.43)	3.27 (-6.36, 12.91)
Median (interquartile range)	22.25 (20)	21.00 (17.5)	
<i>Exacerbation in the prior 3 months</i>			
Any exacerbation, n (%)	57 (24.7)	23 (26.7)	-2.1% (-13.0%, 8.8%)
ED/Hospital, n (%)	11 (4.8)	7 (8.1)	-3.4% (-9.8%, 3.0%)
Severe exacerbation, n (%)	6 (2.6)	6 (7.0)	-4.4% (-10.1%, 1.4%)
<i>NHLBI impairment category</i>			
Very poorly controlled asthma, n (%)	142 (61.7)	51 (59.3)	2.4% (-9.7%, 14.6%)
Not well controlled asthma, n (%)	71 (30.9)	30 (34.9)	-4.0% (-15.7%, 7.7%)
Well controlled asthma, n (%)	17 (7.4)	5 (5.8)	1.6% (-4.4%, 7.6%)

*Atopic patients defined as having at least one positive specific IgE reading using threshold of 0.35 kU/L;

FEV₁, forced expiratory volume in 1 second; NHLBI, National Heart, Lung, and Blood Institute; SD, standard deviation.

For total IgE, this is the geometric mean ratio (atopic / non-atopic) and 95% confidence interval for the ratio.

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outcome measures are limited to reporting confidence intervals for differences between the two subgroups.

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