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TENOR Revisited

Reynold A. Panettieri Jr., MD[a], **Geoffrey Chupp, MD**[b]

[a]Rutgers Institute for Translational Medicine and Science, Rutgers University, New Brunswick, NJ

[b]Yale Center for Asthma and Airways Disease, Yale University, New Haven, CT

Asthma remains a challenging global cause of morbidity and mortality. Despite substantial improvements in our understanding of airway inflammation and pathogenesis, the rates of hospitalizations and emergency department visits for asthma exacerbations have changed little since the 1970s.[1] Asthma care costs are disproportionately allocated to those with severe disease, representing approximately 5% to 10% of all patients with asthma. A seminal observation on severe asthma was reported in 2004: The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study characterized the natural history of asthma over a 3-year period.[2–4] In this issue, Haselkorn et al[5] revisited the TENOR cohort, which is still one of the largest, prospective natural history studies ever conducted of severe, difficult-to-manage asthma or very poorly controlled (VPC) asthma.

A nostalgic look at VPC asthma through the lens of TENOR described a 3-year, multicenter, observational cohort study of 4756 patients (n = 3489 adults ≥18 years of age, n = 497 adolescents 13–17 years of age, and n = 770 children 6–12 years of age) with severe or difficult-to-treat asthma. The primary objective of the study was to characterize the natural history of asthma. Uncontrolled asthma, as defined by 2007 National Institutes of Health guidelines, was highly prevalent. A wealth of studies derived from the cohort revealed that regardless of age, patients with severe or difficult-to-treat asthma demonstrated high rates of health care use and substantial asthma burden despite receiving multiple long-term controller medications. Exacerbation history was the best predictor of future asthma exacerbations. Collectively, the TENOR findings suggested these attributes identified high-risk patients and that IgE and allergen sensitization played a role in the majority of severe or difficult-to-treat participants with asthma.

Haselkorn et al[5] narrow the gap in our understanding of the longitudinal incidence and clinical manifestations of VPC asthma. From 2013 to 2014, TENOR II, a multicenter, observational study of patients with severe/difficult-to-treat asthma who were enrolled in TENOR, was restudied at least 10 years after TENOR. Of the original 283 sites that conducted TENOR, 59 sites participated in TENOR II, enrolling 341 subjects with VPC asthma who represented 28% of their original cohort. Interestingly, 10 years after TENOR, approximately 48% of TENOR II met the criteria for VPC asthma. Comorbidities, asthma triggers by self-report, and geometric mean IgE levels were higher in patients with VPC asthma, compared with those without VPC asthma. Differences in pulmonary function

Corresponding author: Reynold A. Panettieri, Jr., MD, Rutgers Institute for Translational Medicine and Science, 89 French Street, Suite 4211, New Brunswick, NJ 08901. Rp856@rbhs.rutgers.edu.

tests also existed and showed that patients with VPC asthma manifested lower forced expiratory volume in 1 second (FEV1) and greater bronchodilator (BD) reversibility than those with non-VPC asthma. Racial differences (black vs other), allergic trigger count, oral corticosteroid use, and post-BD FEV1 correlated with a persistent VPC asthma phenotype. In addition, there were substantially more patients with VPC asthma who were “ever” smokers (34%), compared with patients with non-VPC asthma (17%). This demonstrates that after 10 years a large percentage of patients have a sustained phenotype of VPC asthma characterized by atopy, reversible airway obstruction, and a significant smoking history.

Haselkorn et al provide interesting observations into the natural history of VPC asthma. Over a decade since TENOR, 48% of patients met the criteria for VPC asthma while there had been substantial advancements in therapeutic agents over the decade, including the approval of the first biologic for asthma, omalizumab. Given that the TENOR cohort manifested significant atopy, it is likely that many patients were treated with omalizumab. During the period of time between TENOR and TENOR II, there was also the increased use of combination inhaled corticosteroids and long-acting bronchodilators that might have improved outcomes. Therefore, many patients’ VPC asthma remains uncontrolled despite these advances. Alternatively, the results could also be explained by the notion that the natural history of VPC asthma waxes and wanes with most patients improving over time. Looking forward, with the approval of other biologics, the incidence of VPC asthma may continue to decrease over the next decade. These circumstances are worthy of further study.

The finding that “ever” smokers were more likely to manifest a sustained VPC asthma phenotype agrees with evidence to suggest that environmental tobacco smoke exposure (ETS) renders asthma subjects more susceptible to severe disease. The concept that asthma/COPD overlap syndrome is also consistent with the findings of Haselkorn et al suggests that ETS modulates responsiveness to current therapies. With a lens on the expanding landscape of tetrahydrocannabinol and nicotine delivery devices, how vaping and nicotine inhalation alters the incidence of VPC asthma will be an important research question.

The observation that bronchomotor lability predicts VPC asthma is fascinating. It is not surprising that patients with lower FEV1 measurements were more likely to manifest a sustained VPC asthma phenotype. However, the observation that those with the greatest change in bronchodilator responsiveness were more likely to have VPC asthma is somewhat counter-intuitive. One struggles to reconcile how airway remodeling due to persistent inflammation, which renders the airway irreversibly obstructive, can explain the findings of Haselkorn et al. It is plausible that those without VPC asthma with better lung function at baseline are incapable of manifesting a BD response and therefore have less bronchomotor lability. Further research is necessary to understand the molecular mechanisms of bronchodilation associated with VPC asthma.

Despite the important observations of Haselkorn et al, the study has some limitations. The limited enrollment across the TENOR sites may have resulted in a sampling bias that impacts the study’s relevance to all patients with VPC asthma. Most patients enrolled in TENOR II were obtained from allergists’ practices (71%) rather than those of pulmonologists (29%). Accordingly, these patients will likely manifest an atopic status

and are more likely to receive omalizumab. Because allergists may refer to pulmonologists patients who have irreversible airway obstruction and are unresponsive to current therapies, one may expect that such patients are more likely to be prescribed systemic corticosteroids. Such bias may have affected the relevance of TENOR II to a general population of patients with VPC asthma.

Taken together, Haselkorn et al provide important insights into the natural history of VPC asthma. The suggestion that less than 50% of patients manifest VPC asthma after a decade of observation is both encouraging and highlights unmet needs. The results show that the heterogeneous prognosis of VPC asthma remains a problem despite improved therapeutics and understanding of asthma pathobiology. Importantly, Haselkorn et al provide a continued mandate to further exploration on how to improve outcomes for those with VPC asthma.

Conflicts of interest:

R. A. Panettieri has received research support from, served as a speaker for, and is on the advisory board for AstraZeneca; has received research support from and is on the advisory board for MedImmune, RIFM, and Equillium; has received research support from and served as a speaker for Genentech; is on the advisory boards for Theravance and Avillion; has served as a speaker for Sanofi/Regeneron; and received research support from OncoArendi and Metera. G. Chupp has served on the advisory boards and speakers' bureaus and has received research support from Genentech, Astrazeneca, Boeringer-Ingelheim, GlaxoSmithKline, Sanofi-Genzyme, and Regeneron; has served as an advisory board member for Teva.

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