Original Article

Assessment of Consistency of Fixed Airflow Obstruction Status during Budesonide/Formoterol Treatment and Its Effects on Treatment Outcomes in Patients with Asthma

Donald P. Tashkin, MD[a], Gary E. Moore, MS[b], Frank Trudo, MD[c], Michael DePietro, MD[c], and Bradley E. Chipps, MD[d]
Los Angeles, Calif; Little Rock, Ark; Wilmington, Del; and Sacramento, Calif

What is already known about this topic? The demographics and responses to treatment of patients with asthma with fixed airflow obstruction (FAO) have been characterized; however, the consistency of postbronchodilator airflow limitation and response to treatment for patients with inconsistent postbronchodilator airflow limitation are unknown.

What does this article add to our knowledge? Approximately one third of patients in this study with moderate-to-severe asthma have persistent fixed airflow obstruction (FAO+), 40% persistent fully reversible airflow obstruction (FAO−), and approximately one third inconsistent airflow limitation; the treatment responses of the latter are most similar to those of patients with FAO+.

How does this study impact current management guidelines? Irrespective of FAO status, patients with moderate-to-severe asthma who received budesonide/formoterol benefitted from greater percentage of asthma control days, fewer withdrawals due to worsening asthma, and greater reduction of rescue medication use compared with budesonide or formoterol alone.

BACKGROUND: The consistency of fixed airflow limitation status during treatment in patients with asthma is unknown.
OBJECTIVE: The objective of this study was to determine the consistency of fixed airflow obstruction (FAO) status during treatment and effects on treatment response.

METHODS: This post hoc analysis from a 12-week study (NCT00652002) assessed patients aged 12 years or more with moderate-to-severe asthma randomized to twice-daily budesonide/formoterol (BUD/FM) via pressurized metered-dose inhaler (pMDI) 320/9 μg, BUD pMDI 320 μg, FM 9 μg via dry-powder inhaler, or placebo. FAO status was assessed post-bronchodilator at screening and after study drug administration at weeks 2, 6, and 12 via the forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) ratio < lower limit of normal (LLN) (FAO+) or ≥ LLN (FAO−). Patients with persistent FAO− and FAO+ retained their screening FAO status at all visits. Patients with inconsistent FAO changed categories at least once during the study. Assessments included early withdrawal due to predefined worsening asthma events (PAEs), lung function, and symptoms.

RESULTS: Of 386 patients, 29% had persistent FAO+, 31% inconsistent FAO, and 40% persistent FAO−. PAEs were lowest in the FAO− group overall and with BUD/FM treatment in patients with FAO+ and inconsistent FAO. Baseline demographics and treatment responses of the inconsistent FAO group were most similar to the FAO+ group. The greatest improvements in asthma control days and use of rescue medications were seen with BUD/FM treatment, regardless of FAO status.

CONCLUSIONS: Approximately one third of patients with moderate-to-severe asthma in this study had inconsistent FAO, and their treatment responses were most similar to patients with FAO+. Regardless of FAO status, patients treated with BUD/FM experienced the most improved treatment responses and fewest withdrawals due to PAEs.

[a]Department of Medicine, University of California, Los Angeles, Calif
[b]Moore Computing Services, Inc., Little Rock, Ark
[c]AstraZeneca LP - Respiratory, Wilmington, Del
[d]Capital Allergy and Respiratory Disease Center, Sacramento, Calif

This study was supported by AstraZeneca LP (Wilmington, Del). F.T. and M.D. are employees of AstraZeneca LP and own stock/stock options. All authors participated in study design, analysis, and interpretation of data, writing of this report, and the decision to submit this article for publication. Medical writing assistance was provided by Sean Sheffler-Collins, PhD, of Scientific Connexions, an Ashfield Company, part of UDG Healthcare plc (Lyndhurst, NJ) and funded by AstraZeneca LP (Wilmington, Del).

Conflicts of interest: D.P. Tashkin received writing assistance in kind and statistical analysis support; is on the board for and has received consultancy and lecture fees and research support from AstraZeneca. G. E. Moore has received consultancy fees from AstraZeneca (contract work prior to co-author, after co-author all work has been pro bono). F. Trudo and M. DePietro are employed by and have stock in AstraZeneca. B. E. Chipps is on the boards for and has received consultancy and lecture fees from AstraZeneca, Boehringer Ingelheim, Genentech, Meda, Merck, and Novartis.

Received for publication August 28, 2015; revised February 10, 2016; accepted for publication February 26, 2016.
Available online ■■

Corresponding author: Donald P. Tashkin, MD, David Geffen School of Medicine at UCLA, 10833 Le Conte Ave., Los Angeles, CA 90095-1690. E-mail: DTashkin@mednet.ucla.edu.

2213-2198

http://dx.doi.org/10.1016/j.jaip.2016.02.014

Abbreviations used
BUD/FM- Budesonide/formoterol
DPI- Dry-powder inhaler
FAO- Fixed airflow obstruction
FEV_1/FVC- Ratio of forced expiratory volume in 1 second to forced vital capacity
LLN- Lower limit of normal
PAEs- Predefined worsening asthma events
pMDI- Pressurized metered-dose inhaler

 (J Allergy Clin Immunol Pract 2016;■:■-■)

Key words: *Asthma; Airflow limitation; Fixed airflow obstruction; Budesonide; Formoterol; Lung function*

Asthma is a chronic inflammatory disorder associated with bronchial hyperresponsiveness, which leads to variable and recurring episodes of wheezing, breathlessness, chest tightening, and coughing.[1] Some patients, often those with severe asthma, demonstrate an expiratory airflow obstruction that is not completely reversible despite optimal treatment.[1-3] The presence of not fully reversible or fixed airflow obstruction (FAO) is generally attributed to airway inflammation resulting in remodeling,[1] which encompasses structural changes including increased smooth muscle mass, loss of epithelial integrity, basement membrane thickening, subepithelial fibrosis, submucosal gland hyperplasia, decreased cartilage integrity, and increased airway vascularity.[4-7]

Remodeling is associated with greater disease burden and poorer clinical outcomes.[6] Proposed causes of FAO in asthma include insufficient treatment, persistence of inflammation, active smoking, neutrophilic inflammation that may be less responsive to treatment, and the potential development of steroid resistance.[7-9] Clinical factors that have been associated with FAO in asthma include the presence of eosinophilia, elevated immunoglobulin E, history of smoking, asthma onset more than 25 years of age, duration of asthma, aging, and the degree of airway hyperresponsiveness.[2,10]

There is no accepted definition of FAO in asthma. Persistent airflow limitation in chronic obstructive pulmonary disease is defined as the ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) below a postbronchodilator threshold of 0.70,[11] whereas others have used an FEV_1/FVC that is lower than the lower limit of normal (LLN) after optimal treatment.[12] The LLN definition is derived from reference equations specific to the population under study, which take into account age, gender, and ethnicity.[13,14] A previous descriptive analysis characterized FAO using the LLN-based definition in patients with mild-to-moderate or moderate-to-severe asthma.[15] In that analysis, patients with FAO had greater impairment than patients without FAO overall, and they appeared to have an enhanced response to budesonide/formoterol (BUD/FM) combination therapy; however, interpretation was limited because FAO status was assessed only on a single occasion at screening.[15] Although the presence of FAO is widely recognized by practicing clinicians and asthma researchers, little is known about the stability of FAO status over time except that progressive airflow obstruction has been linked with an increased risk of mortality.[16] Despite the fact that variable airflow limitation is a hallmark of asthma,[1] inconsistent FAO status is not defined.

Here, we present a post hoc analysis of the stability of FAO status during a 12-week study of adults and adolescents with moderate-to-severe asthma.[15] The objectives of this analysis were to characterize the consistency of baseline FAO status during the 12-week treatment period and to determine whether patients with persistent FAO, inconsistent FAO, or absence of FAO responded differently to treatment.[15] In particular, we assessed the association between FAO status and early study withdrawal due to predefined worsening asthma events, pulmonary function, rescue medication use, and percentage of asthma control days.

METHODS

Patients, study design, and treatments

This post hoc analysis includes data from a previously reported double-blind, double-dummy, placebo-controlled, randomized, 12-week study conducted in patients aged 12 years or more with moderate-to-severe, inhaled corticosteroid-dependent asthma who were not active smokers and, if a former smoker, had a smoking history of ≤10 pack-years.[15,17] At screening, patients must have demonstrated reversibility of ≥12% and ≥0.20 L FEV_1 from the baseline value within 15-30 minutes after the administration of a standard dose of short-acting bronchodilator.[17]

Asthma was defined according to American Thoracic Society criteria.[18] Patients were required to have used moderate- to high-dose inhaled corticosteroids either alone or in combination with other asthma maintenance medications and to have a prebronchodilator FEV_1 % predicted value of ≥45% to ≤85% measured ≥6 hours after the last dose of inhaled short-acting β_2 agonist and ≥24 hours after taking a long-acting β_2 agonist.[17] The study included a 2-week run-in period during which patients received twice-daily BUD pressurized metered-dose inhaler (pMDI) 160 μg and as-needed rescue albuterol (2-4 inhalations [90 μg per inhalation]). Patients were randomized to receive one of the following treatments twice daily: BUD/FM pMDI 320/9 μg as 160/4.5 μg × 2 inhalations; BUD pMDI 320 μg as 160 μg × 2 inhalations + FM dry-powder inhaler (DPI) 9 μg as 4.5 μg × 2 inhalations (not presented in this analysis); BUD pMDI 320 μg as 160 μg × 2 inhalations; FM DPI 9 μg as 4.5 μg × 2 inhalations; or placebo.[17]

To maintain blinding, patients in all treatment groups received both a pMDI and a DPI containing either active treatment or placebo. Patients were eligible for randomization if they had documented daytime or nighttime asthma symptom scores >0 (where 0 indicates no symptoms and 3 indicates severe symptoms) on ≥3 of 7 consecutive days during the run-in period.[17] Patients received peak flow meters and hand-held electronic diaries at screening, and were instructed to use the electronic diary twice daily to record peak expiratory flow, asthma symptoms, nighttime awakenings as a result of asthma, and rescue medication use.[17]

Study protocols were approved by an institutional review board for each of the clinical sites and conducted in conformance with guidelines for the ethical treatment of human subjects, Good Clinical Practice, and applicable local regulations. Patients provided written informed consent and written assent as appropriate, before study procedures were begun.[17] The study was performed in accordance with ethical principles based on the Declaration of Helsinki and consistent with the International Conference on Harmonization/Good Clinical Practice and applicable regulatory requirements.