

Original Article

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

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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.

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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 (FEV₁/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. © 2016 The Authors. Published by Elsevier Inc. on behalf of the American Academy of

*Abbreviations used**BUD/FM- Budesonide/formoterol**DPI- Dry-powder inhaler**FAO- Fixed airflow obstruction**FEV₁/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*

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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 (FEV₁/FVC) below a postbronchodilator threshold of 0.70,¹¹ whereas others have used an FEV₁/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 $\geq 12\%$ and ≥ 0.20 L FEV₁ 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 FEV₁ % predicted value of $\geq 45\%$ to $\leq 85\%$ 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 μ g and as-needed rescue albuterol (2-4 inhalations [90 μ g per inhalation]). Patients were randomized to receive one of the following treatments twice daily: BUD/FM pMDI 320/9 μ g as 160/4.5 μ g $\times$ 2 inhalations; BUD pMDI 320 μ g as 160 μ g $\times$ 2 inhalations + FM dry-powder inhaler (DPI) 9 μ g as 4.5 μ g $\times$ 2 inhalations (not presented in this analysis); BUD pMDI 320 μ g as 160 μ g $\times$ 2 inhalations; FM DPI 9 μ g as 4.5 μ g $\times$ 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.

Assessments

Patient disposition has been detailed previously.¹⁷ Treatment outcomes were assessed based on the mean changes from baseline to the mean during the randomized treatment period for pulmonary function variables (predose FEV₁ [L]) and daily diary-derived variables. Baseline FEV₁ was defined as the predose FEV₁ value measured on the day of randomization. Baseline for all diary variables was defined as the mean of all run-in diary data excluding the day of randomization. Study withdrawal because of a predefined asthma event was assessed based on predefined criteria for worsening asthma including a decrease in morning predose FEV₁ of $\geq 20\%$ from the value at randomization or a decrease to $<40\%$ of predicted normal; use of ≥ 12 inhalations of albuterol per day on ≥ 3 days within any 7 consecutive days after randomization; a decrease in morning peak expiratory flow of $\geq 20\%$ from baseline (defined as the mean of all values from the 7-day period immediately preceding randomization) on ≥ 3 days within any period of 7 consecutive days after randomization; nighttime awakening due to asthma requiring the use of rescue medication on ≥ 2 nights within any period of 7 consecutive days after randomization; or clinical exacerbation requiring emergency treatment, hospitalization, or use of asthma medication not allowed in the protocol.

Patients who experienced any of the predefined criteria for worsening asthma were automatically withdrawn from the study, with the exception of patients who reported ≥ 2 nights with an awakening due to asthma for whom withdrawal was at the investigator's discretion. The analysis of patient withdrawals includes only patients who withdrew based on predefined asthma-related events after week 2. All other non-asthma-related patient withdrawals after week 2 were considered censored events.

Secondary efficacy variables captured via electronic diary included overall daily rescue medication use (the sum of the number of daytime and nighttime inhalations of rescue medication from the same calendar day) and asthma control days (a composite variable defined as a symptom-free day that was also free from daytime or nighttime use of rescue medication).¹⁷

FAO assessments

The presence of FAO (FAO+) was defined as postbronchodilator FEV₁/FVC $<$ LLN, and the absence of FAO (FAO-) was defined as FEV₁/FVC $\geq$ LLN.^{13,15} LLN was based on gender- and race/ethnicity-specific regression equations developed from the third National Health and Nutrition Examination Survey (NHANES III), which included males and females in 3 major racial and/or ethnic groups (white, African Americans, and Mexican Americans) with an age range of 8-80 years.¹⁴ Patients who were not in these 3 major racial and/or ethnic groups were not included in this analysis. The equations were extrapolated for the 1 patient aged more than 80 years.

FAO status during the treatment period was assigned based on whether FEV₁/FVC was $<$ LLN or $\geq$ LLN (FAO+ and FAO-, respectively) approximately 15-30 minutes after albuterol (2-4 inhalations [90 μ g/inhalation] or up to 2.5 mg nebulized albuterol) at screening, and 120 minutes after study drug at weeks 2, 6, and 12. At each visit, patients were classified as either FAO+ or FAO-. "Persistent FAO+" describes patients who were FAO+ at screening and remained FAO+ at each study visit as defined above. "Persistent FAO-" describes patients who were FAO- at screening and remained FAO- at each study visit as defined above. If at any visit, the FAO status was different from the FAO status at screening, the patient was classified as inconsistent FAO.

Statistical analysis

Formal statistics were not performed in this post hoc analysis. Data were stratified by FAO category based on the LLN definition using descriptive statistics only. Kaplan-Meier was used for estimating the probability of not having a withdrawal event.

RESULTS

Patient demographics and FAO status

Of 596 randomized patients, a total of 386 were included in this post hoc analysis. Patients excluded from the analysis included those for whom spirometry data at all evaluation times were not available, patients who withdrew from the study within the first 2 weeks for any reason, and patients for whom race was not known or standard reference values were not available for LLN categorization. In 268 of the 386 patients (69%), FAO status was stable throughout the study as either persistent FAO- (n = 155; 40%) or persistent FAO+ (n = 113; 29%). The remaining 118 patients (31%) had inconsistent FAO, having changed FAO status at least once during the course of the study (Table 1).

Patient demographics, disease characteristics, and FAO status at screening are shown in Table 1. Patients with persistent FAO+ had a greater percentage of males and longer duration of asthma than patients with persistent FAO- or inconsistent FAO. FEV₁ % predicted was lower for patients with persistent FAO+ than for patients with persistent FAO- or inconsistent FAO. Use of rescue medication at baseline was higher in the patients with persistent FAO+ and inconsistent FAO than in the patients with persistent FAO-.

A greater percentage of patients remained FAO- throughout the treatment period when treated with BUD/FM versus any other treatments (Figure 1). The placebo group had the lowest percentage of patients remaining FAO- throughout the treatment period. Of the patients with inconsistent FAO, 84 were reclassified from FAO- at baseline to FAO+ during the treatment period, and 34 from FAO+ to FAO-. Of the 84 patients who were reclassified from FAO- to FAO+, 33% received placebo, 24% received FM, 30% received BUD, and the lowest percentage (13%) received BUD/FM. Of the 34 patients who were reclassified from FAO+ to FAO-, more patients received BUD/FM (41%) than BUD (24%), FM (24%), or placebo (12%). Sample sizes between treatment groups were different due to premature withdrawals, and therefore data points were not available to define FAO status over the entire course of the 12-week trial for all patients.

Withdrawal due to predefined events and FAO status

Probability of withdrawal due to predefined asthma events according to FAO status is shown in Figure 2. When combining patients across treatment arms, patients with persistent FAO- had the fewest number of withdrawals due to predefined asthma events (Figure 2, A) compared with patients with persistent FAO+ (Figure 2, B) or inconsistent FAO (Figure 2, C).

Over the course of the study, the percentage of withdrawals was greater for FM alone (33 of 98 [34%]) and placebo (34 of 89 [38%]) compared with BUD/FM (9 of 107 [8%]) and BUD alone (16 of 92 [17%]). Withdrawals in patients with persistent FAO+ were fewest with BUD/FM versus the other treatments (Figure 2, B). During the first 6 weeks of the study, the majority of withdrawals occurred among patients with persistent FAO+

TABLE I. Patient demographic and screening disease characteristics by FAO category (LLN definition)

	Persistent FAO – (n = 155)	Persistent FAO + (n = 113)	Inconsistent FAO (n = 118)	Total (N = 386)
Age, y	42.6 (16.5)	41.7 (15.2)	40.7 (14.8)	41.8 (15.6)
Sex, n (%)				
Male	50 (32.3)	49 (43.4)	41 (34.7)	140 (36.3)
Female	105 (67.7)	64 (56.6)	77 (65.3)	246 (63.7)
BMI, kg/m ²	30.5 (8.6)	29.0 (6.6)	29.7 (7.0)	29.8 (7.6)
Duration of asthma, y	19.2 (16.0)	28.4 (15.6)	21.6 (13.9)	22.6 (15.7)
% Reversibility	21.7 (14.5)	23.1 (12.0)	22.6 (11.5)	22.4 (12.9)
Predose FEV ₁ (L)*	2.3 (0.6)	2.1 (0.7)	2.2 (0.7)	2.2 (0.7)
FEV ₁ % predicted ^{†,‡}	72.7 (9.1)	62.8 (10.3)	67.9 (10.6)	68.3 (10.7)
Predose FVC (L)*	3.1 (0.9)	3.5 (1.1)	3.3 (1.0)	3.3 (1.0)
FVC % predicted ^{†,‡}	81.6 (12.0)	85.9 (12.8)	85.5 (13.1)	84.0 (12.7)
Baseline ICS dose, n (%)				
Moderate§	118 (30.6)	76 (19.7)	87 (22.5)	281 (72.8)
High	37 (9.6)	37 (9.6)	31 (8.0)	105 (27.2)
Rescue medication use, inh/d¶	2.0 (2.1)	2.9 (2.6)	2.4 (2.4)	2.4 (2.4)
% Asthma control days¶, #	6.5 (14.9)	8.6 (18.6)	8.3 (18.4)	7.7 (17.1)

BMI, Body mass index; FAO, fixed airflow obstruction; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; inh/d, inhalations per day; ICS, inhaled corticosteroid; LLN, lower limit of normal; NHANES III, third National Health and Nutrition Examination Survey.

Values shown are mean (SD) unless otherwise noted.

*Baseline is defined as the predose FEV₁ or FVC measured on the day of randomization.

[†]NHANES III.

[‡]Prebronchodilator, visit 2 (day of randomization).

§Moderate ICS dose: beclomethasone dipropionate (chlorofluorocarbon [CFC]) 504-840 µg/d, beclomethasone dipropionate (hydrofluoroalkane [HFA]) 160-280 µg/d, budesonide 400-600 µg/d, flunisolide 1000-1999 µg/d, fluticasone (CFC) 264-440 µg/d, fluticasone (Diskus) 300-500 µg/d, or triamcinolone acetonide 800-1999 µg/d.

||High ICS dose: beclomethasone dipropionate (HFA) >280 µg/d, budesonide >600 µg/d, flunisolide >2000 µg/d, fluticasone (CFC) >440 µg/d, fluticasone (Diskus) >500 µg/d, or triamcinolone acetonide >2000 µg/d.

¶Baseline is defined as the mean of all values obtained during the run-in period.

#Asthma control days are defined as a composite measure of symptom-free days that were also free from daytime or nighttime use of rescue medication.

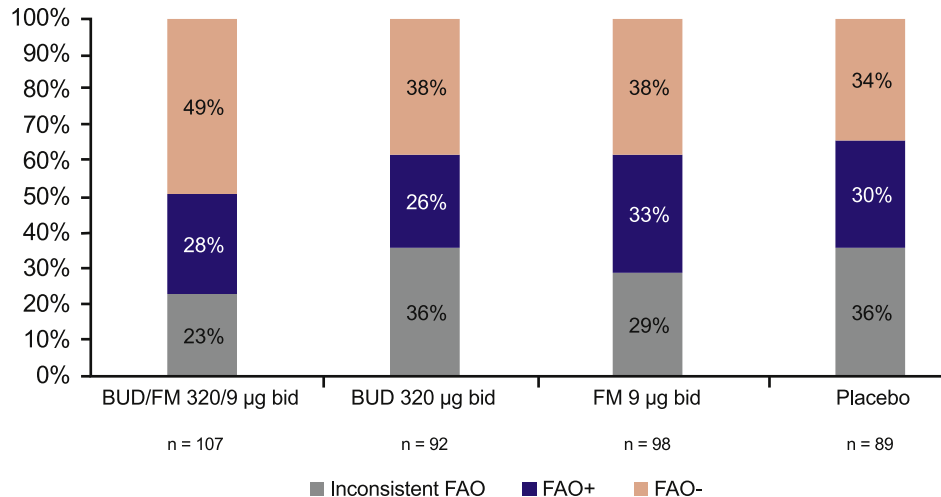


FIGURE 1. Distribution of FAO status throughout the treatment period: (A) numbers of patients and (B) percentage of total. BUD, Budesonide; FAO, fixed airflow obstruction; FM, formoterol.

treated with FM or placebo (Figure 2, B). Among patients with inconsistent FAO, the fewest withdrawals were observed in the BUD/FM and BUD treatment arms; however, the percentage of patients with inconsistent FAO withdrawing in both of these arms (Figure 2, C) was greater than the percentages seen with either the persistent FAO+ (Figure 2, B) or FAO– (Figure 2, A) groups.

Lung function and FAO status

Overall, BUD/FM treatment resulted in a numerically greater improvement in mean change from baseline in predose FEV₁

versus FM or BUD alone in the persistent FAO– and persistent FAO+ groups (Figure 3). Over the course of the study, the FM and placebo arms in the persistent FAO+ and inconsistent FAO groups demonstrated a decline in mean predose FEV₁ not seen in the persistent FAO– group.

Patient-reported outcomes and FAO status

A decrease in rescue medication use, measured as ≥ 0.5 inhalations per day, was observed in patients in all treatment arms (Figure 4). Regardless of FAO status, a numerically greater

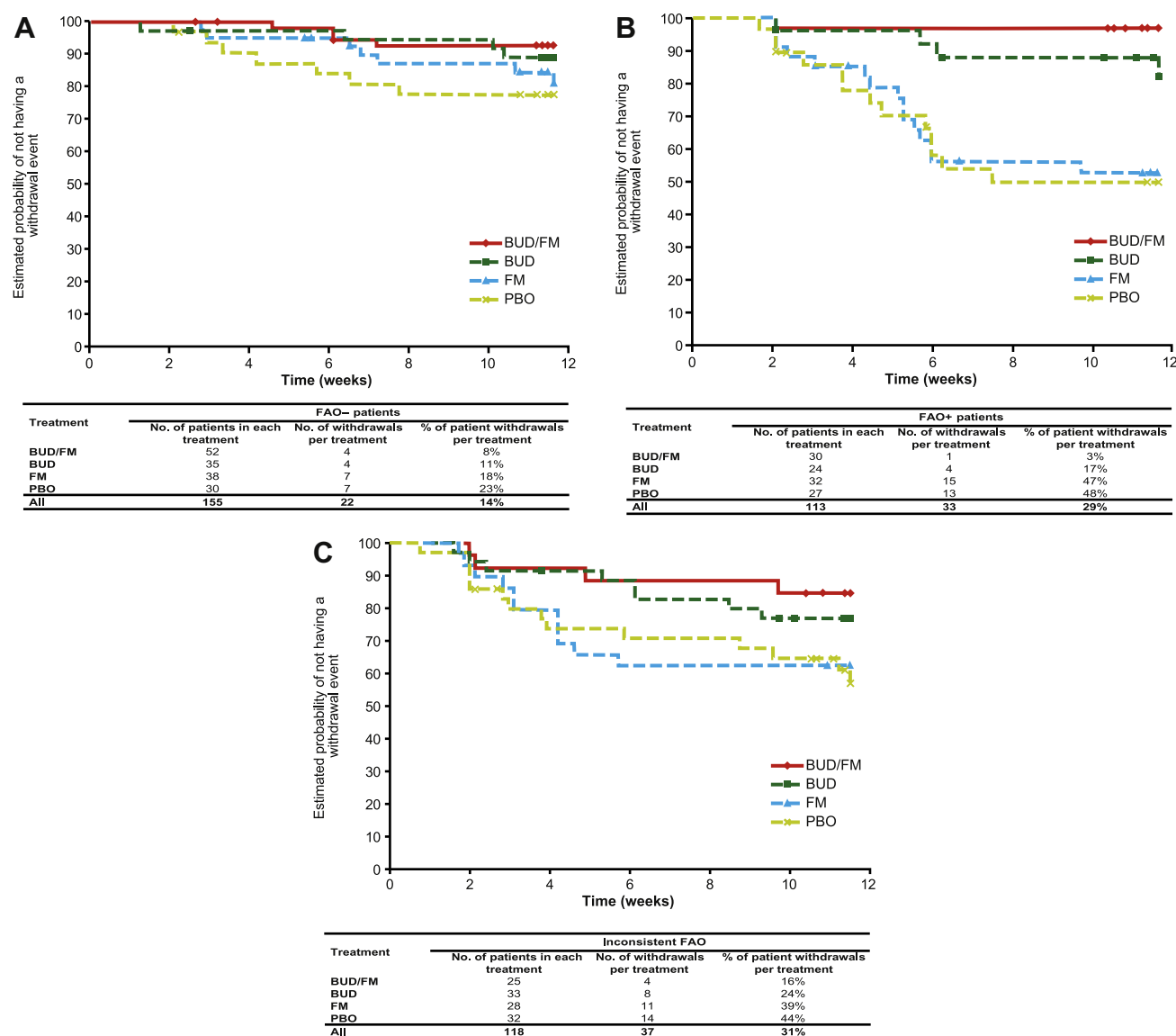


FIGURE 2. Withdrawals due to PAEs in patients with (A) persistent FAO-, (B) persistent FAO+, and (C) inconsistent FAO. *BUD*, Budesonide; *FAO*, fixed airflow obstruction; *FM*, formoterol; *PAEs*, predefined worsening asthma events; *PBO*, placebo.

percentage of patients with a decrease in rescue medication use of ≥ 0.5 inhalations per day were seen in the BUD/FM treatment arm compared with all other treatments. Similarly, the greatest increase in the percentage of asthma control days was reached in the BUD/FM treatment arm compared with all other treatment arms, regardless of FAO status (Figure 5). The BUD treatment arm had similar mean changes from baseline in the percentage of asthma control days compared with placebo for patients with persistent FAO+ and inconsistent FAO.

DISCUSSION

Previous analyses of patients with asthma with FAO determined their status at screening only, and did not account for the possibility of FAO inconsistency during the course of a study.¹⁵ The present post hoc analysis evaluated FAO status at screening as well as at weeks 2, 6, and 12 of the study. These analyses identified an inconsistent FAO group that is in many ways similar to the

persistent FAO+ group, including a poor response to FM alone. The prevalence of persistent FAO+ and inconsistent FAO in this cohort of patients with moderate-to-severe stable asthma was 60%, which is similar to the prevalence of FAO+ asthma (range, 49%-60%) reported in other studies of adult patients with severe or difficult-to-treat asthma.^{2,19} In contrast, reports in patients with mild-to-moderate asthma using LLN criteria at screening found only 24% of patients to be FAO+. These data are consistent with the increased incidence of an irreversible component of airflow obstruction observed as the severity of asthma increases.³ Patients with persistent FAO+ had a longer history of asthma compared with patients with persistent FAO- or inconsistent FAO, a finding also observed in the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study analysis of risk factors seen for persistent airflow limitation.¹⁹ Patients with FAO- in the BUD/FM arm were the most stable group and least likely to change status to FAO+.

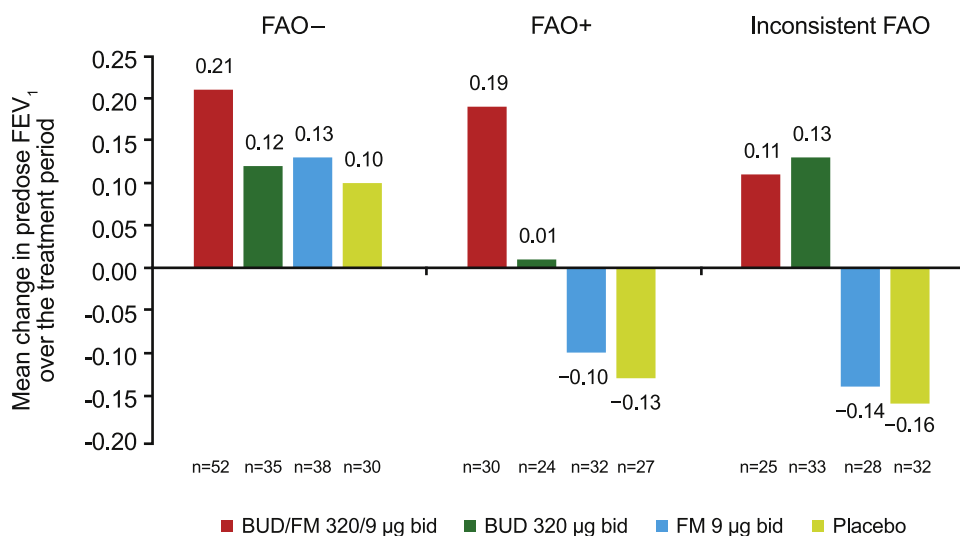


FIGURE 3. Predose FEV₁ improvements in L by treatment and FAO status. Baseline was defined as the predose FEV₁ value measured on the day of randomization (visit 2) or the screening predose value, if no value was available at visit 2. *bid*, Twice daily; *BUD*, budesonide; *FAO*, fixed airflow obstruction; *FEV₁*, forced expiratory volume (L) in 1 second; *FM*, formoterol.

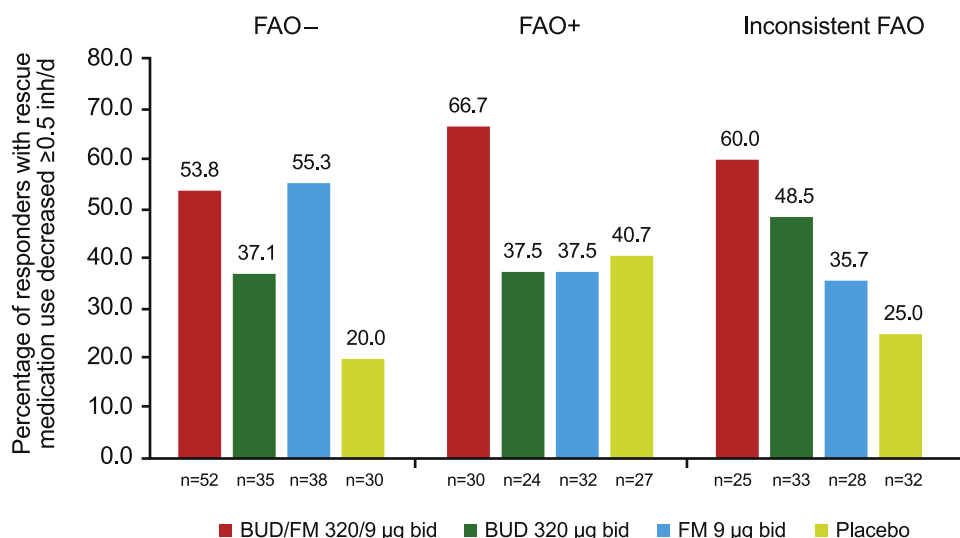


FIGURE 4. Percentage of responders with a ≥ 0.5 inh/d decrease in rescue medication use by treatment and FAO status. A decrease in rescue medication use was defined as the change from baseline (mean of all values during the run-in period) to mean value during the treatment period. *bid*, Twice daily; *BUD*, budesonide; *FAO*, fixed airflow obstruction; *FM*, formoterol; *inh/d*, inhalations per day.

The presence of FAO (as defined by either $FEV_1/FVC \leq 0.70$ ¹⁹ or $<75\%$ ² predicted) has been generally associated with greater disease burden, poorer prognosis, and more severe asthma.^{19,20} In addition, the results of a 17-year study in patients with asthma with chronic airflow limitation (defined as $FEV_1 < 80\%$ predicted) showed an increased risk of mortality,¹⁶ and the findings of a 5-year follow-up study in patients with FAO due to either asthma or chronic obstructive pulmonary disease (defined by $FEV_1/FVC < 0.70$) found an increased rate of decline in FEV₁ and an increased frequency of exacerbations in those patients with FAO versus asthma controls without FAO.²¹ Our data support the impact of FAO on greater disease burden, with the greatest number of patient withdrawals due to worsening asthma-related

events occurring in patients with persistent FAO+ and inconsistent FAO and the fewest patient withdrawals occurring in patients with persistent FAO-. Patients who had inconsistent FAO behaved most like those patients who had persistent FAO+, with a similar number of withdrawals due to worsening asthma-related events. Patients treated with BUD/FM compared with the other study treatments had the fewest withdrawals in the FAO+ and inconsistent FAO groups, suggesting additional benefits in preventing worsening asthma-related events for more severely obstructed patients. Consistent with the greater disease burden seen with persistent airflow obstruction, a level of deterioration of predose FEV₁ roughly similar to that in the placebo treatment arm occurred in the patients with persistent FAO+ and inconsistent

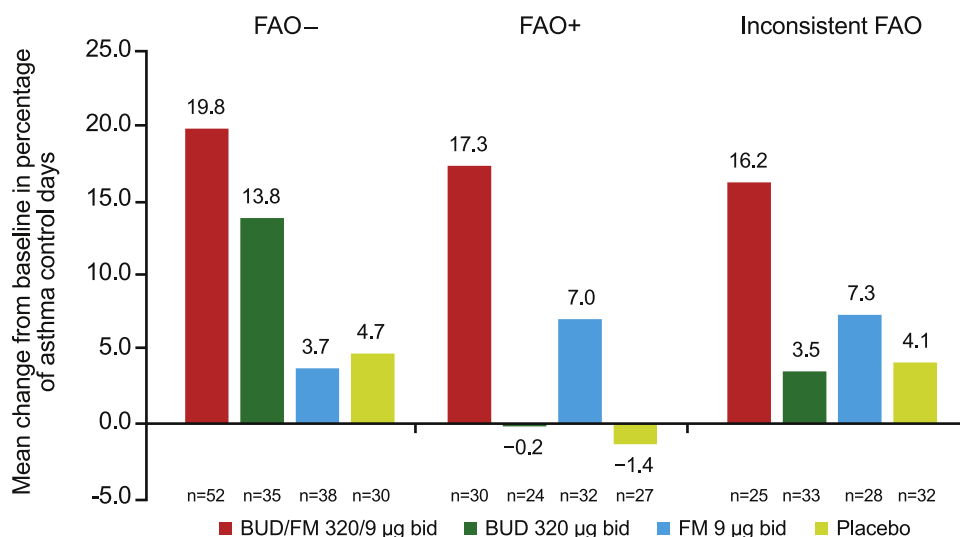


FIGURE 5. Mean change in percentage of asthma control days by treatment and FAO status. An increase in the percentage of asthma control days was defined as the mean change from baseline (mean of all run-in period values) over the double-blind treatment period. *bid*, Twice daily; *BUD*, budesonide; *FAO*, fixed airflow obstruction; *FM*, formoterol.

FAO treated with FM alone. This finding sharply contrasts with patients with persistent FAO-, who had improved responses with all treatments.

BUD/FM has been shown to reduce the need for rescue medications in patients with moderate-to-severe asthma,¹⁷ a benefit confirmed by this analysis irrespective of FAO status. Despite a higher use of rescue medications at baseline for patients with persistent FAO+ and inconsistent FAO versus patients with FAO-, large differences were observed between BUD/FM treatment and placebo in the percentage of patients with a decrease in rescue medication use of ≥ 0.5 inhalations per day for all 3 FAO groups (between-group differences of 26.0%, 35.0%, and 33.8%, respectively). Although pulmonary function and symptoms do not always improve in parallel, patients improved in both categories with BUD/FM treatment compared with placebo regardless of FAO status. As a composite variable, improvements in asthma control days capture the improvements in days with no symptoms plus freedom from daytime or nighttime use of rescue medication. Therefore, compared with rescue medication use, the marked increase in the percentage of asthma control days reflects an impact on a broader parameter of symptomatology, and implies a broader benefit.

Limitations of the analysis are the post hoc nature, the relatively small subgroups, use of descriptive statistics, and the study duration of 12 weeks. It is difficult to establish a clear cause-and-effect relationship between FAO status and treatment responses and vice versa, and correlations are hypothetical. It may take longer than 12 weeks to reach the maximum corticosteroid effect, and it is also possible that maximal bronchodilation was not achieved in patients at screening and the week 2, 6, and 12 testing intervals, which could have misidentified FAO status. Considering the short study duration, interpretation of our findings assessing the effect of inconsistent postbronchodilator airflow limitation on exacerbations is limited. Finally, because FAO status was based on posttreatment spirometry at weeks 2, 6, and 12, there was a limited expected bronchodilatory response for patients receiving placebo or BUD. In addition, the findings

from this analysis may not be generalized to all patients with asthma. Patients were required to show bronchodilator reversibility for entry into the study, active smokers were excluded, and pack-year history was less than 10. Thus, the data presented in this article are valid only for certain subsets of patients with asthma. The findings presented here could serve as a foundation for future analyses in other subsets of patients with asthma.

CONCLUSION

The patient group identified as inconsistent FAO had baseline demographic and disease state characteristics and responses to treatment that were more similar to those of patients with persistent FAO+ than patients with persistent FAO-. Adult and adolescent patients with moderate-to-severe asthma who had persistent FAO- had favorable clinical responses to FM monotherapy not observed with patients who had persistent FAO+ or inconsistent FAO. Patients with asthma treated with BUD/FM combination therapy were most likely to retain persistent FAO- and least likely to develop inconsistent FAO. Irrespective of FAO status, the BUD/FM treatment arms experienced the lowest percentage of patient withdrawals due to asthma-worsening events, the largest change in percentage of asthma control days, and numerically a greater percentage of responders with a decrease in rescue medication use.

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REFERENCES

- GINA. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2015. Available from: <http://www.ginasthma.org/>. Accessed May 11, 2015.
- ten Brinke A, Zwinderman AH, Sterk PJ, Rabe KF, Bel EH. Factors associated with persistent airflow limitation in severe asthma. *Am J Respir Crit Care Med* 2001;164:744-8.

3. Pascual RM, Peters SP. The irreversible component of persistent asthma. *J Allergy Clin Immunol* 2009;124:883-90. quiz 891-2.
4. Grainge CL, Lau LC, Ward JA, Dulay V, Lahiff G, Wilson S, et al. Effect of bronchoconstriction on airway remodeling in asthma. *N Engl J Med* 2011;364:2006-15.
5. Jarjour NN, Erzurum SC, Bleecker ER, Calhoun WJ, Castro M, Comhair SA, et al. Severe asthma: lessons learned from the National Heart, Lung, and Blood Institute Severe Asthma Research Program. *Am J Respir Crit Care Med* 2012;185:356-62.
6. Bergeron C, Al-Ramil W, Hamid Q. Remodeling in asthma. *Proc Am Thorac Soc* 2009;6:301-5.
7. Boulet LP. Irreversible airway obstruction in asthma. *Curr Allergy Asthma Rep* 2009;9:168-73.
8. Choi JS, Jang AS, Park JS, Park SW, Paik SH, Park JS, et al. Role of neutrophils in persistent airway obstruction due to refractory asthma. *Respirology* 2012;17:322-9.
9. Perret JL, Dharmage SC, Matheson MC, Johns DP, Gurrin LC, Burgess JA, et al. The interplay between the effects of lifetime asthma, smoking, and atopy on fixed airflow obstruction in middle age. *Am J Respir Crit Care Med* 2013;187:42-8.
10. Guerra S, Sherrill DL, Kurzius-Spencer M, Venker C, Halonen M, Quan SF, et al. The course of persistent airflow limitation in subjects with and without asthma. *Respir Med* 2008;102:1473-82.
11. Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2015. Available from: <http://www.goldcopd.org/>. Accessed May 11, 2015.
12. van Dijk WD, Gupta N, Tan WC, Bourbeau J. Clinical relevance of diagnosing COPD by fixed ratio or lower limit of normal: a systematic review. *COPD* 2014;11:113-20.
13. Swanney MP, Ruppel G, Enright PL, Pedersen OF, Crapo RO, Miller MR, et al. Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruction. *Thorax* 2008;63:1046-51.
14. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. *Am J Respir Crit Care Med* 1999;159:179-87.
15. Tashkin DP, Chipps BE, Trudo F, Zangrilli JG. Fixed airflow obstruction in asthma: a descriptive study of patient profiles and effect. *J Asthma* 2014;51:603-9.
16. Panizza JA, James AL, Ryan G, De Klerk N, Finucane KE. Mortality and airflow obstruction in asthma: a 17-year follow-up study. *Int Med J* 2006;36:773-80.
17. Noonan M, Rosenwasser LJ, Martin P, O'Brien CD, O'Dowd L. Efficacy and safety of budesonide and formoterol in one pressurised metered-dose inhaler in adults and adolescents with moderate to severe asthma: a randomized clinical trial. *Drugs* 2006;66:2235-54.
18. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. *Am Rev Respir Dis* 1987;136:225-44.
19. Lee JH, Haselkorn T, Borish L, Rasouliyan L, Chipps BE, Wenzel SE. Risk factors associated with persistent airflow limitation in severe or difficult-to-treat asthma: insights from the TENOR study. *Chest* 2007;132:1882-9.
20. ten Brinke A. Risk factors associated with irreversible airflow limitation in asthma. *Curr Opin Allergy Clin Immunol* 2008;8:63-9.
21. Contoli M, Baraldo S, Marku B, Casolari P, Marwick JA, Turato G, et al. Fixed airflow obstruction due to asthma or chronic obstructive pulmonary disease: 5-year follow-up. *J Allergy Clin Immunol* 2010;125:830-7.