
Effects of fluticasone propionate and salmeterol hydrofluoroalkane inhalation aerosol on asthma-related quality of life

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Background: Current asthma guidelines emphasize domains of impairment and risk for assessing severity and control, noting the need to consider separately the effects of asthma on asthma quality of life and functional capacity. Proper treatment to control asthma should result in improvements in patient well-being and functional status.

Objective: To assess asthma-related quality of life after treatment with combination fluticasone propionate and salmeterol delivered via hydrofluoroalkane 134a metered-dose inhaler compared with the individual components alone.

Methods: Asthma-related quality of life was assessed as part of two 12-week, randomized, double-blind, placebo-controlled clinical trials comparing the fluticasone propionate–salmeterol combination administered via a single metered-dose inhaler with salmeterol, fluticasone propionate, and placebo administered via traditional chlorofluorocarbon metered-dose inhaler. The Asthma Quality of Life Questionnaire was completed at baseline and end point. Score changes, overall and for the 4 separate domains, were compared within and among the treatment groups.

Results: A total of 720 of 725 patients completed a baseline Asthma Quality of Life Questionnaire and were included in the analyses. In both studies, all mean scores improved significantly from baseline with the fluticasone propionate–salmeterol combination, with significantly greater improvement in the overall score compared with salmeterol alone, fluticasone propionate alone, and placebo groups. Improvements with the combination were also clinically meaningful compared with changes with salmeterol and placebo in both studies and with fluticasone propionate in study 1.

Conclusions: Treatment with combination fluticasone propionate and salmeterol delivered via hydrofluoroalkane metered-dose inhaler resulted in significantly greater improvements in asthma-related quality of life compared with individual components and placebo administered via traditional chlorofluorocarbon metered-dose inhaler.

Ann Allergy Asthma Immunol. 2009;102:323–327.

INTRODUCTION

Diagnosing asthma is only the first step in reducing the symptoms, functional limitations, impairment in quality of life, and risk of adverse events that are associated with the disease. The ultimate goal of treatment is to enable a patient to live with none of these manifestations of asthma, and an initial evaluation of the severity of the disease allows an estimate of the type and intensity of treatment needed.¹ Although evaluation of lung function and other clinical measures of asthma control (eg, asthma symptoms and rescue medication use) remains central to the clinical evaluation and management of asthma, the importance of patients' perceptions of asthma, its effects, and its treatment on day-to-day living is now also well recognized. Changes in physiologic measures, such as lung function, may result in little if any perceptible change in patient functioning or well-being. On the other hand, measures of asthma-related quality of life (QoL) can offer useful information that is not revealed

through spirometry or symptom assessments, providing further insight into assessing the overall burden of asthma and best course of treatment for individual patients.²

Previous studies have shown that individually the inhaled corticosteroid (ICS) fluticasone propionate and the inhaled long-acting β_2 -agonist (LABA) salmeterol each improve asthma-related QoL.^{3–6} In addition, numerous studies have shown the clinical benefits of an ICS plus a LABA compared with the individual components alone.^{7–10} The studies reported here demonstrate that improvements in asthma-related QoL are also greater when fluticasone propionate and salmeterol are administered together in a single device.

METHODS

Study Design

Asthma-related QoL was evaluated as part of 2 large, multicenter, 12-week, randomized, placebo-controlled clinical trials comparing the fluticasone propionate–salmeterol combination of 44/21 μ g (study 1 = SAS30003) and the fluticasone propionate–salmeterol combination of 110/21 μ g (study 2 = SAS30004), delivered as 2 inhalations twice daily via hydrofluoroalkane metered-dose inhaler (MDI), with the individual components of fluticasone propionate, 44 μ g, or fluticasone propionate, 110 μ g, and salmeterol, 21 μ g, delivered

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Disclosures: Authors have nothing to disclose.

Funding Sources: This research was funded by GlaxoSmithKline.

Received for publication October 10, 2008; Received in revised form November 20, 2008; Accepted for publication December 5, 2008.

as 2 inhalations twice daily via chlorofluorocarbon MDI, and placebo hydrofluoroalkane MDI. Safety and efficacy data from these studies have been reported previously.^{9,10}

To be eligible to participate, patients were at least 12 years of age with a medical history of asthma (as defined by the American Thoracic Society), required asthma pharmacotherapy for the 6 months before screening, had a forced expiratory volume in 1 second (FEV₁) of 40% to 85% of predicted, and had 15% or greater reversibility after 2 puffs of albuterol. Study 1 included 360 symptomatic patients previously treated with a low dose of ICS, fluticasone propionate inhalation powder, 200 µg/d or equivalent (n = 134), or inhaled β₂-agonists, including as-needed short-acting β₂-agonists (n = 142) or salmeterol (n = 84; note that the study was conducted before guideline recommendation for the use of LABAs in conjunction with ICSs). Study 2 included 365 patients who were symptomatic and previously treated with medium-dose ICSs, specifically fluticasone propionate inhalation powder, 400 to 600 µg/d or equivalent. The study protocols were approved by the appropriate investigational review boards, and all patients provided written informed consent.

Asthma Quality of Life Questionnaire

Patients completed the Asthma Quality of Life Questionnaire (AQLQ) at baseline (randomization) and at end point (last clinic visit). The AQLQ is a 32-item disease-specific questionnaire that assesses QoL (during the previous 2-week period) in 4 domains: activity limitation, asthma symptoms, emotional function, and environmental exposure. Patients answer each question using a 7-point Likert scale, with 1 indicating total impairment (all of the time) and 7 indicating no impairment (none of the time). An overall AQLQ score is obtained by averaging scores for all 32 items, and a higher score indicates better asthma-related QoL.

The AQLQ^{11–13} has been used extensively in clinical trials because it has been shown to be valid, reliable, and responsive; these are important components to effectively analyze

patient well-being and function (ie, effects of intervention). Unlike most other QoL questionnaires, the AQLQ has, in addition to an overall score and individual domain scores, a criterion for determining what constitutes a minimally important (ie, clinically meaningful) change in score resulting from asthma treatment. The minimal clinically important change is defined as “the smallest difference in score ... which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patients management.”¹⁴ The availability of such a criterion makes interpretation of changes in asthma-related QoL more meaningful for clinicians. For the AQLQ, a change in score of 0.5 point or more is considered a minimally important change, whereas 1.0 is considered a moderate change and 1.5 is considered a large change.¹⁵

Statistical Analysis

Overall AQLQ and individual domain scores were calculated. Mean changes within treatment groups from baseline at end point (last on-treatment data) were evaluated using *t* tests on the hypothesis of no change from baseline. Mean changes among the treatment groups from baseline at end point were analyzed using analysis of covariance, with baseline score as a covariate, and included terms for treatment, investigator cluster, and stratum (study 1 only). *P* values were 2-sided and statistically significant at ≤.05. *P* values for the individual domains were only used for statistical inference if change in the overall AQLQ score was statistically significant. An intragroup or intergroup change in mean AQLQ score of 0.5 point or more was considered clinically meaningful.

RESULTS

A total of 720 of the 725 patients (99%) completed the AQLQ at baseline and were included in these analyses. Baseline patient demographics are given in Table 1. Patients in study 1 were primarily white (80%), female (52%), and 34 years old, with a mean FEV₁ of 2.27 L and 67.4% predicted.

Table 1. Baseline Demographics^a

Demographics	Study 1				Study 2			
	Placebo	Fluticasone propionate-salmeterol, 88/42 µg	Salmeterol, 42 µg	Fluticasone propionate, 88 µg	Placebo	Fluticasone propionate-salmeterol, 220/42 µg	Salmeterol, 42 µg	Fluticasone propionate, 220 µg
No. of patients	87	92	92	89	89	94	91	91
Age, y	33.2	32.8	34.4	34.7	41.1	38.8	37.5	39.1
Female, %	53	57	46	52	56	61	62	63
White, %	84	73	80	83	87	78	88	82
FEV ₁ , L	2.27	2.29	2.33	2.20	2.17	2.23	2.22	2.18
FEV ₁ , % predicted	66.7	68.1	67.8	67.1	67.5	68.3	68.5	69.0
Baseline overall AQLQ score	4.92	4.55	4.85	4.81	4.85	4.89	4.81	5.05

Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; FEV₁, forced expiratory volume in 1 second.

^a Data (other than No. of patients) are expressed as means.

Patients in study 2 were also primarily white (83.8%), female (60.5%), and 39 years old, with a mean FEV₁ of 2.2 L and 68.3% predicted. The mean overall AQLQ scores at baseline were 4.78 in study 1 and 4.90 in study 2, indicating moderate impairment in asthma-related QoL.

Overall AQLQ Scores

In both studies, patients treated with fluticasone propionate–salmeterol hydrofluoroalkane demonstrated statistically significant ($P < .006$) and clinically meaningful (≥ 0.5) improvements in mean overall AQLQ scores from baseline at end point (Table 2). Improvements with fluticasone propionate–salmeterol hydrofluoroalkane in both studies were significantly greater ($P < .005$) compared with placebo, salmeterol, and fluticasone propionate (Table 3). Furthermore, the differences were clinically meaningful (≥ 0.5) for fluticasone propionate–salmeterol hydrofluoroalkane compared with placebo and salmeterol in studies 1 and 2 and compared with fluticasone propionate in study 1.

AQLQ Domain Scores

In both studies, patients treated with fluticasone propionate–salmeterol hydrofluoroalkane demonstrated statistically significant ($P < .05$) and clinically meaningful improvements in all 4 AQLQ domain scores from baseline at end point (Table 2). In study 1, improvements in all 4 domains were significantly greater for fluticasone propionate–salmeterol hydrofluoroalkane compared with placebo ($P < .001$) and salmeterol ($P < .045$) and in 3 of the 4 domain scores (ie, activity limitation, asthma symptoms, and emotional function but not environmental exposure) compared with fluticasone propionate ($P < .01$; Table 3). Likewise, in study 2, improvements in all 4 domain scores were significantly greater compared with placebo ($P < .001$) and in 3 of the 4 domain scores (ie, activity limitation, asthma symptoms, and emotional function but not environmental exposure) compared with salmeterol ($P < .001$) and fluticasone propionate ($P < .02$; Table 3).

Additional Analyses

Because AQLQ scores cannot exceed 7, patients with higher baseline overall QoL scores have less potential for improve-

ment from baseline relative to patients with lower baseline scores. Higher baseline overall QoL scores can limit the range of improvements that occur in response to treatment and thus the range of differences among treatment groups that can be achieved. In a recent study, the developer of the AQLQ identified a plateau in mean overall AQLQ score of approximately 5.8.¹⁶ For this reason, patients with baseline overall AQLQ scores of 5.8 or less were defined a priori for analysis.

Fifty-five patients (15%) from study 1 and 63 patients (18%) from study 2 with baseline overall AQLQ scores greater than 5.8 were excluded from the secondary analyses. Results from the secondary analysis of the reduced population were similar to the results from the intent-to-treat population.

DISCUSSION

The purpose of periodic asthma evaluation and ongoing monitoring is to determine whether the goals of asthma therapy are being achieved and asthma is controlled. When asthma is not controlled, it is associated with significant asthma burden¹⁷ and decreased QoL and increased health care use.¹⁸ The level of asthma control translates in the degree to which both dimensions of the manifestations of asthma, impairment, and risk are reduced by therapeutic intervention.

Studies have shown that both fluticasone propionate and salmeterol individually improve asthma-related QoL,^{3–6} and the 2 agents administered together in a single Diskus device improve activity limitations and strenuous activities.¹⁹ With the need to phase out chlorofluorocarbons as propellants in MDIs, hydrofluoroalkane propellants have been introduced as a safer, environmentally friendly alternative. Clinical trials have demonstrated that hydrofluoroalkane MDI is an acceptable clinical alternative for the chlorofluorocarbon MDI with similar safety and efficacy.^{20–22} Thus, the use of 2 types of propellants in this study should have no impact on the evaluation of the overall outcomes.

This report demonstrates the overall QoL effects of these agents administered together via a hydrofluoroalkane MDI

Table 2. Mean Change From Baseline at End Point in AQLQ Domain Scores

AQLQ domain	Study 1				Study 2			
	Placebo	Fluticasone propionate–salmeterol, 88/42 µg	Salmeterol, 42 µg	Fluticasone propionate, 88 µg	Placebo	Fluticasone propionate–salmeterol, 220/42 µg	Salmeterol, 42 µg	Fluticasone propionate, 220 µg
Activity limitation	0.30	1.33 ^{a,b}	0.49 ^a	0.85 ^{a,b}	−0.09	0.85 ^{a,b}	0.37 ^a	0.49 ^a
Asthma symptoms	0.17	1.44 ^{a,b}	0.41 ^a	0.81 ^{a,b}	−0.37 ^a	0.93 ^{a,b}	0.32 ^a	0.38 ^a
Emotional function	0.13	1.40 ^{a,b}	0.33 ^a	0.75 ^{a,b}	−0.24	0.89 ^{a,b}	0.23	0.39 ^a
Environmental exposure	0.12	1.07 ^{a,b}	0.58 ^{a,b}	0.80 ^{a,b}	−0.10	0.74 ^{a,b}	0.53 ^{a,b}	0.35 ^a
Overall	0.20	1.34 ^{a,b}	0.45 ^a	0.81 ^{a,b}	−0.22 ^a	0.89 ^{a,b}	0.34 ^a	0.43 ^a

Abbreviation: AQLQ, Asthma Quality of Life Questionnaire.

^a Statistically significant difference, $P \leq .05$.

^b Clinically meaningful difference, ≥ 0.5 .

Table 3. Mean Differences Among Treatment Groups in AQLQ Domain Scores

AQLQ domain	Study 1			Study 2		
	Fluticasone propionate–salmeterol, 88/42 μ g, vs placebo	Fluticasone propionate–salmeterol, 88/42 μ g, vs salmeterol, 42 μ g	Fluticasone propionate–salmeterol, 88/42 μ g, vs fluticasone propionate, 88 μ g	Fluticasone propionate–salmeterol, 220/42 μ g, vs placebo	Fluticasone propionate–salmeterol, 220/42 μ g, vs salmeterol, 42 μ g	Fluticasone propionate–salmeterol, 220/42 μ g, vs fluticasone propionate, 88 μ g
Activity limitation	1.03 ^{a,b}	0.84 ^{a,b}	0.48 ^a	0.94 ^{a,b}	0.48 ^a	0.36 ^a
Asthma symptoms	1.27 ^{a,b}	1.03 ^{a,b}	0.63 ^{a,b}	1.30 ^{a,b}	0.61 ^{a,b}	0.55 ^{a,b}
Emotional function	1.27 ^{a,b}	1.07 ^{a,b}	0.65 ^{a,b}	1.13 ^{a,b}	0.66 ^{a,b}	0.50 ^{a,b}
Environmental exposure	0.95 ^{a,b}	0.49 ^a	0.27	0.84 ^{a,b}	0.21	0.39
Overall	1.14 ^{a,b}	0.89 ^{a,b}	0.53 ^b	1.11 ^{a,b}	0.55 ^{a,b}	0.46

Abbreviation: AQLQ, Asthma Quality of Life Questionnaire.

^a Statistically significant difference, $P \leq .05$.

^b Clinically meaningful difference, ≥ 0.5 .

device. In patients previously treated with short-acting β_2 -agonists alone, salmeterol, or a low-dose ICS (study 1), overall asthma-related QoL improvements were significantly greater and clinically meaningful compared with baseline for fluticasone propionate–salmeterol hydrofluoroalkane. In addition, these improvements were 3 times greater for patients treated with fluticasone propionate–salmeterol, 44/21 μ g, than for those treated with salmeterol, 21 μ g, and almost twice as large as improvements for patients treated with fluticasone propionate, 44 μ g. Similarly, in patients previously treated with moderate doses of ICS (study 2), overall asthma-related QoL improvements were significantly greater and clinically meaningful compared with baseline for fluticasone propionate–salmeterol. In addition, these improvements were more than twice as great for patients treated with fluticasone propionate–salmeterol, 110/21 μ g, than for patients treated with salmeterol, 21 μ g, or fluticasone propionate, 110 μ g.

The results of these 2 large-scale, controlled, clinical trials not only establish the beneficial effects of fluticasone propionate–salmeterol hydrofluoroalkane MDI on overall asthma-related QoL but also show that patients who received fluticasone propionate–salmeterol had significantly greater improvements in activity limitation, asthma symptoms, and emotional function than those who received the individual components alone. In addition, these changes in asthma-related QoL, with only a few exceptions, were clinically meaningful (ie, the patient would be expected to perceive the change, according to the criterion established by the developer of the AQLQ).¹⁵

In a recent publication by Schatz and colleagues,²³ patients were identified as being at increased risk of acute asthma episodes based on asthma-specific QoL and a history of episodes requiring unscheduled visits in the past year. Low QoL (based on data-derived optimal cut-point scores) and prior acute episodes each independently increased the risk of requiring emergency care nearly 4-fold. The study showed

that an optimal cut-point score for predicting subsequent exacerbations varies, depending on whether the patient has a history of recent exacerbations. The optimal cut-point score in patients with a history of prior exacerbations (4.3) was lower than the optimal cut-point score in patients without acute episodes requiring unscheduled care in the prior year (4.7).²³ This study underscores the importance of assessing QoL and its predictive value for future asthma episodes. In our study the beneficial changes in asthma-related QoL with fluticasone propionate–salmeterol hydrofluoroalkane occurred in conjunction with significant improvements in markers of asthma control (ie, FEV₁ and peak expiratory flow),^{9,10} indicating that fluticasone propionate–salmeterol hydrofluoroalkane improves not only lung function but also daily function and well-being in a wide range of patients with asthma.

As noted by Fuhlbrigge and colleagues,¹⁷ the use of daytime or nighttime symptoms to define the burden of asthma likely “underestimates the burden of asthma and may lead to inadequate treatment of asthma based on national guideline recommendations.” Ascertaining patient burden using instruments such as the AQLQ provides additional information to assist in the management and control of asthma. Current asthma guidelines recommend the evaluation of asthma control based on current pulmonary function and the patient’s recall of symptoms, physical activity, QoL, and need for short-acting β_2 -agonists for quick relief of symptoms during the previous 2 to 4 weeks. The ultimate goal of assessing asthma control is to estimate the type and intensity of treatment needed.¹

In summary, treatment with fluticasone propionate–salmeterol delivered via hydrofluoroalkane MDI resulted in significantly greater improvements in asthma-related QoL compared with its individual components and placebo administered via chlorofluorocarbon MDI. One of the major goals of asthma treatment is to improve the functioning and well-being of the patient; thus, AQLQ evaluation is an important measure of the effectiveness of a treatment regimen

and should be incorporated in a patient's evaluation regularly. These findings demonstrate the value of patient-reported outcomes and the contribution of fluticasone propionate-salmeterol hydrofluoroalkane as controller therapy in achieving the goals of asthma therapy.

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