Use of the Asthma Control Questionnaire to predict future risk of asthma exacerbation

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Background: Direct correlation of assessments of a validated composite measure such as the Asthma Control Questionnaire (ACQ) and risk of exacerbation has not been previously demonstrated in a randomized controlled trial.
Objective: To evaluate the ability of the ACQ score over time to predict risk of a future asthma exacerbation.
Methods: This analysis included data from a 12-week placebo-controlled trial (N = 292) of AMG 317, an IL-4 receptor α antagonist, in patients with moderate to severe atopic asthma. At baseline, patients had an ACQ score ≥1.5. Exacerbations were defined as requirement for systemic corticosteroids. A Cox proportional hazards model was used, with ACQ score as the time-dependent covariate. The analysis was repeated for individual components of the ACQ.
Results: Each 1-point increase in ACQ was associated with a 50% increased risk of exacerbation (hazard ratio, 1.50; 95% CI, 1.03-2.20) for the following 2-week period. Evaluation of individual ACQ components also demonstrated a similar trend, though each to a lesser degree than the full composite ACQ.
Conclusion: Although based on a retrospective analysis, with small number of exacerbations, these findings support the utility of the composite ACQ score measurement to predict risk of future exacerbation in clinical trials and clinical practice. The composite ACQ score measurement was found to be a better predictor of future risk than individual ACQ components. (J Allergy Clin Immunol 2011;127:167-72.)

Key words: *Asthma exacerbation, ACQ score, asthma control, prediction, IL-4 receptor α, antagonist*

Asthma is a chronic inflammatory disorder of the airways that affects over 300 million people worldwide.[1] Many patients with asthma experience ongoing symptoms that interrupt daily activities, cause overall poor quality of life, and may subsequently lead to lower productivity and greater health care costs.[2] In a recently published cross-section survey of 2500 patients with asthma, the percentage who needed acute care for asthma in the past 12 months has not changed significantly in 2009 versus 1998 (34% vs 36%).[3,4] Several large community-based asthma surveys have also shown that the majority of patients have a high rate of symptoms and impairment from their disease.[4-6] Recent community-based surveys have shown that 51% to 59% of patients have uncontrolled asthma even with the use of standard asthma medications.[7-9] The Gaining Optimal Asthma Control (GOAL) clinical trial found that <45% of patients achieved total asthma control (ie, no daytime symptoms, use of bronchodilators, or exacerbations, and morning peak expiratory flow ≥80% in 7 of 8 weeks) despite intensive therapy and dose escalation based on existing treatment guidelines.[10]

The importance of asthma control has been emphasized by the recent disease management guidelines, including the Global Initiative for Asthma guidelines and the National Asthma Education and Prevention Program.[11,12] Control of asthma is monitored by level of current control (impairment) and risk for long-term effects on exacerbations, progressive impairment of lung function, and medication side effects.[11,12] Achieving adequate asthma control and minimizing future risk of exacerbations are the primary goals in the management of the disease.

Level of asthma control may be examined by a single clinical feature of asthma such as FEV_1. However, the American Thoracic Society/European Respiratory Society statement on endpoints for asthma clinical trials recommends considering use of a validated composite measure, such as the Asthma Control Questionnaire (ACQ), in clinical trials to assess asthma control.[13] The utility of composite measures to predict long-term risk, particularly exacerbations, remains poorly studied. Although measurements such as variation in peak expiratory flow rate (PEFR) and low

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Abbreviations used
ACQ: Asthma Control Questionnaire
HR: Hazard ratio
MID: Minimal important difference
PEFR: Peak expiratory flow rate

FEV_1 have been associated with risk of exacerbations,[14] it is conceivable that a composite measure such as the ACQ,[15] which assesses the adequacy of asthma control by using symptoms, activity limitation, use of rescue medications, and lung function, may better capture different aspects of asthma control and prediction of risk.

Direct correlation of sequential measurements of asthma control over time and risk of exacerbation has not been previously reported in a randomized clinical trial. The purpose of this study was to examine the association between the ACQ score and the risk of future exacerbation within a randomized controlled trial of patients with moderate to severe asthma. Individual components of the ACQ as well as the ACQ 6-item (ACQ-6) and 5-item (ACQ-5) versions were also examined for their association with the risk of exacerbation.

METHODS

Patients

A *post hoc* analysis of data from a 12-week multicenter, double-blind, randomized, placebo-controlled clinical trial[16] was conducted to assess the association between the ACQ and asthma exacerbation. Patients with moderate to severe atopic asthma were enrolled in a dose-ranging phase 2 study to assess the safety and efficacy of AMG 317, an IL-4 receptor α antagonist. Patients were randomly assigned in a 1:1:1:1 ratio to receive 1 of 3 doses of the IL-4 receptor α antagonist or placebo administered once weekly for 12 weeks.

To be eligible for the study, patients had to meet the following inclusion criteria: (1) age 18 to 65 years, (2) FEV_1% predicted ≥50% to ≤80%, (3) at least 12% reversibility over baseline FEV_1 with β-agonist inhalation, (4) inhaled corticosteroid ≥200 and ≤1000 μg/d fluticasone propionate or equivalent, (5) positive to skin prick test or RAST to at least 2 allergens, and (6) ongoing asthma symptoms with ACQ score at screening and baseline ≥1.5. Subjects who received oral or parenteral corticosteroids within 6 weeks before the first run-in visit were excluded from the study. Details for this clinical trial have been previously published.[16]

Before enrollment into the study, the institutional review board for each site provided written approval of the protocol, and patients provided informed consent to participate in the study.

ACQ

Eligible patients completed the ACQ weekly for 2 weeks before treatment initiation and every 2 weeks for 16 weeks after treatment initiation. The ACQ is a validated 7-item questionnaire that measures asthma control and is increasingly being used in clinical practice and research.[15,17,18] Patients are asked to recall their symptoms during the previous week and to respond to the first 6 questions (nighttime waking, symptoms on waking, activity limitation, shortness of breath, wheeze, and rescue short-acting medication use) on a 7-point scale from 0 (no impairment) to 6 (maximum impairment). Clinicians score the percent predicted prebronchodilator FEV_1 (the seventh question) on a similar 7-point scale as the other ACQ questions. The items are equally weighted, and the ACQ score is the mean of the 7 items, with scores between 0 (totally controlled) and 6 (severely uncontrolled). The minimal important difference (MID) is 0.5, representing the smallest change that is considered clinically meaningful.[17] An ACQ score of 1.5 has been identified as the best discriminator between patients with asthma who are well controlled and those who are not well controlled.[19]

Shorter versions of the ACQ have been validated, including the ACQ-6, which excludes lung function, and ACQ-5, which excludes lung function and rescue medication use.[17,18]

Asthma exacerbation

Asthma exacerbation was defined as "requirement for systemic corticosteroids." An alternative definition, "requirement for systemic corticosteroids or doubling of inhaled corticosteroid dose," was also separately evaluated. Both definitions were prespecified in the study protocol and analysis plan.

Time to event for asthma exacerbation was defined as the time to the first exacerbation after treatment initiation for patients with at least 1 exacerbation. For patients with no exacerbations through 12 weeks of study, the time to event was considered censored and was thus observed from randomization to either week 12 or their last follow-up date, whichever date occurred first.

Other assessments

Spirometry assessments were performed at screening and every 2 weeks for 16 weeks. Rescue medication use was defined as the number of puffs per day of short-acting β-agonist use and was recorded daily in an electronic diary (eDiary). Patients recorded daily peak flows and asthma symptoms in the morning and evening using the eDiary. The nighttime symptom score was rated on a 0 to 3 scale with 0 meaning "no symptoms," 1 meaning "mild, awoke wheezing at least once but returned to sleep," 2 meaning "moderate, awakened more than once and remained awake for >1 hour," and 3 meaning "severe, awake most of the night."

Statistical analysis

The association between baseline ACQ score and exacerbation was assessed by using a Cox proportional hazards model adjusting for treatment assignment. A second Cox proportional hazards model used all ACQ scores before exacerbation as time-dependent covariates.[20] The time-dependent model was selected to enable the use of all the ACQ scores over time before the exacerbation occurred, rather than the single baseline or the last ACQ score. The association between the last ACQ score before exacerbation and the risk of exacerbation was also assessed by using a logistic regression model. The linearity assumption between ACQ and odds of asthma exacerbation was assessed by plotting the log of the odds and mean ACQ in 5 ACQ categories (≦1, >1 and ≤2, >2 and ≤3, >3 and ≤4, >4).

To identify a threshold ACQ score that would predict future asthma exacerbation, the sensitivity and specificity for the prediction at a given ACQ score were calculated for all ACQ scores measured immediately before exacerbation.

Individual components of ACQ, ACQ-6, and ACQ-5 were also evaluated for their association with risk of exacerbation.

The eDiary measures were recorded daily and summarized weekly as an independent measure from the ACQ. Effects of asthma measures, such as night-time symptom score from eDiary and lung function on the risk of exacerbation, were assessed to evaluate whether the effects of these asthma measures were similar to the effects of those components in ACQ.

RESULTS

Patients

A total of 292 patients with moderate to severe asthma were included in the analysis. The study population was 71% white, 18% black, 58% women, and had a mean age of 41 years (Table I). At baseline, patients had a mean FEV_1 of 68.3% and mean ACQ score of 2.54. Baseline characteristics were similar between patients with and without an exacerbation. All baseline