

Development of the Asthma Control Composite outcome measure to predict omalizumab response

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Background: Previous assessments of response to omalizumab were based on diary-based data rather than standard validated instruments. A composite instrument that translates diary-based data into standard validated asthma control measures would characterize patient response to treatment in terms of current asthma control definitions.

Objective: To develop the Asthma Control Composite (ACC) tool, using real-time diary-based data to predict treatment response in terms of asthma control.

Methods: The ACC tool was derived retrospectively using pooled data from two phase 3 studies in patients with moderate to severe allergic asthma. Patients were randomized to receive subcutaneous omalizumab or placebo for 16 weeks plus stable beclomethasone dipropionate therapy, followed by a 3-month corticosteroid reduction period and 5-month double-blind safety extension. Control was assessed as “complete,” “good,” or “not controlled,” based on a composite score of 4 elements: rescue medication (puffs/day), total asthma symptom score, average number of awakening nights/28 days, and activity limitation.

Results: The ACC was mapped to standard validated measures of patient-reported outcomes, with results consistent with clinical outcomes. The proportion of patients with baseline uncontrolled asthma achieving “good” or “complete” asthma control was 48% with omalizumab and 32% with placebo at approximately 4 months. The mean composite score also was improved with omalizumab (3.52) vs placebo (2.56) at approximately 4 months.

Conclusions: The ACC tool accurately reflects asthma control in moderate to severe asthma patients eligible for biological therapy. Unlike the ACT, which has not been validated in this patient population, the ACC shows promise as an asthma control assessment tool in patients with moderate to severe asthma.

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INTRODUCTION

The primary goal of asthma therapy is to achieve and maintain control of disease, as defined by a global assessment of symptoms, reliever use, lung function, and the frequency/severity of exacerbations. Recently, the National Asthma Education and Prevention Program Expert Panel 3 report introduced guidelines for management of asthma based on disease control.¹ Signs of poor asthma control include waking at night with asthma symptoms, trips to the hospital, and the need for quick-relief medication such as albuterol more than twice per week for asthma symptoms.¹

Currently the approval of most asthma drugs is based on a single parameter of control—lung function as measured by forced expiratory volume in 1 second (FEV₁). However, the American Thoracic Society/European Respiratory Society Task Force on Asthma Control and Exacerbations has concluded that no single outcome measure can adequately assess

asthma control, and for clinicians, an unmet need remains for a practical, validated method for measurement of asthma control for use in their daily practice. Thus, assessment in clinical trials and in clinical practice should include components relevant not just to achievement of best possible clinical control but also to reduction of future risk of adverse outcomes.²

Omalizumab (Xolair; Genentech, Inc, South San Francisco, California) is an anti-immunoglobulin E (IgE) therapy that reduces exacerbation frequency in patients with moderate to severe persistent allergic asthma^{3–9} and is approved by the Food and Drug Administration for this indication in patients 12 years of age and older. Earlier clinical trials of omalizumab^{10–12} did not use the standard measures of asthma outcomes—Asthma Control Test (ACT),¹³ Asthma Control Questionnaire (ACQ),¹⁴ and Asthma Therapy Assessment Questionnaire (ATAQ)¹⁵—because they were unavailable at the time of the trials, having been introduced only in recent years, and validated in mild asthma but not in severe disease. Instead, diaries were used in the omalizumab trials to collect patient asthma symptom data. Earlier analyses of asthma control also included the Global Evaluation of Treatment Effectiveness (GETE) (defined in the online supplement). In brief, the GETE is a 5-point scale describing the assessment of the patient’s asthma symptoms; a score of 1 indicates excellent or complete control of asthma, and a score of 5

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indicates worsening of asthma.¹⁶ In the pivotal trials, the GETE was assessed independently by both the patient and the investigator at week 28.

Therefore, to define response to omalizumab in terms of standard measures of asthma control, developing a composite measure of asthma control modeled on the validated instruments (ACT, ACQ, and ATAQ), but using the diary-based data that had been collected in 2 large clinical trials of omalizumab, was necessary. The Asthma Control Composite (ACC) is a research tool designed to recognize measures of control, understand how the diary-based omalizumab data map to ACT, ACQ, and ATAQ parameters, and determine which measures have the greatest impact on asthma control.

METHODS

The ACC asthma control outcome measure uses data collected in diary format to predict response to omalizumab, reflecting a real-time assessment. The tool was derived retrospectively with pooled data from 2 almost identically designed double-blind placebo-controlled phase 3 studies (Studies 008 and 009), which are considered pivotal for documenting the efficacy and safety of omalizumab in allergic asthma.^{3–8} Both studies were approved by institutional review boards at each test site, and each patient provided written informed consent.

Patient population

The population for studies 008 and 009 consisted of patients aged 12 to 75 years with moderate to severe allergic asthma for 1 year or longer. Other inclusion criteria were positive response to a skin prick test for at least 1 common allergen, total serum IgE ≥ 30 IU/mL to ≤ 700 IU/mL, FEV₁ reversibility of 12% or greater within 30 minutes after administration of albuterol (90–180 μ g), baseline FEV₁ $\geq 40\%$ and $\leq 80\%$ of predicted; and treatment with 420 to 840 μ g/day beclomethasone dipropionate (BDP) or an equivalent inhaled corticosteroid for less than 3 months before randomization. Exclusion criteria are further described in the original report.³

Study design and dosage regimens

In studies 008 and 009, patients were randomized to receive subcutaneous omalizumab (≥ 0.016 mg/kg/IgE [IU/mL] every 4 weeks, based on the patient's body weight and serum IgE levels) or matching placebo every 2 or 4 weeks for 16 weeks in addition to stable BDP therapy. This was followed by a 3-month period during which the corticosteroid dose was reduced gradually, maintaining asthma control, and a 5-month double-blind safety extension, in which patients were maintained on the optimum corticosteroid dose from the taper period that in the investigator's clinical judgment was required for appropriate asthma control.

Asthma symptoms, rescue medication use, and impact on activities

Patients recorded asthma symptoms in a diary twice daily using a questionnaire designed to obtain symptom scores

(e-Table 1). Patients were to assess nocturnal asthma symptoms, which included the use of rescue medication, morning asthma symptoms, and daytime asthma symptoms.

Description of the ACC

The ACC defines control by 3 categories: complete control, good control, and not controlled (Table 1). Control definitions are composite measures that include 4 asthma assessment categories, each scored as shown in Table 1. Each asthma assessment category is scored with points determined by the level of control the symptoms reflect. For example, a patient using 0 or 1 puff/day of rescue medication would be considered as having “complete control” for the rescue medication category and would receive 2 points. If the patient had indicated a need of 2 or 3 puffs/day, then the rescue medication category would be considered as “good control” and a score of 1 point would be assigned, and so on. With all 4

Table 1. Asthma Control Parameters of the Asthma Control Composite (ACC)^a

Assessment categories	Control level (points assigned for fitting assessment criteria)		
	Complete control (2 points)	Good control (1 point)	Not controlled (0 points)
Rescue medication use (puffs/day)	0 or 1	2 or 3	>3
Total asthma symptom score ^b (composite score)	0 to 1.5	>1.5 to 3	>3
Average number of awakening nights per 28 days	0	1 or 2	≥ 3
Activity limitation (AQLQ question 32) ^c	6 or 7	5	1, 2, 3, or 4

^a The range of scores for each of the 4 individual categories is 0–2; the range of total composite scores is 0–8. A patient is considered a responder if s/he has a score of 1 or 2 for *each* of the 4 assessments; eg, scoring a “0” in any of the 4 assessments will qualify the patient as a nonresponder. Responders were defined based on achieving control, either complete or good, depending on the graph/analysis, and this was prospectively defined in the construct of the ACC.

^b The total asthma symptom score includes the nocturnal asthma score (up to 4), and morning and daytime asthma symptom scores (up to 1 and 4, respectively): shortness of breath, chest discomfort, wheezing, and cough, and is combined with activity restrictions. (For individual subscore components of the asthma symptom score, see eTable 1 in the online supplement.) The maximum possible total score is 9.

^c For questions on the Asthma Quality of Life Questionnaire (AQLQ), a response of “9” indicates that the subject did not answer the question. Therefore, responses of “9” were treated as “NA.” The standardized version of the AQLQ includes 5 generic activity questions, which replace patient-specific activities in the original AQLQ. These include strenuous activities, moderate activities, social activities, work-related activities, and sleeping.

assessments completed, a composite score for each patient was obtained by adding the 4 scores. The overall level of asthma control and range of possible scores were determined by matching the composite score to scores shown in Table 2.

RESULTS

Mapping the tool

With the exception of morning symptoms and wheezing, which are not assessed in the ATAQ, the ACC, ACT, ACQ, and ATAQ tools assess very similar components of control (Table 3). The greatest difference between the tools is that the ACC data are collected daily in a diary format, which reflects real-time assessment, in contrast to the ACT, ACQ, and ATAQ, which rely on recall of symptoms over the previous 2 to 4 weeks.

Patient demographics and baseline characteristics

The pooled patient population of adults and adolescents with allergic asthma ($N = 1,070$) were randomized to treatment with either omalizumab ($n = 542$) or placebo ($n = 528$); all patients also received stable BDP therapy. The 2 treatment groups were well balanced in terms of baseline demographics and asthma characteristics (Table 4).

Omalizumab response by composite tool

Previous reports of the 2 clinical trials indicated improvement in asthma symptoms for patients treated with omalizumab compared with patients treated with placebo, as measured by a reduced frequency of exacerbations and requirement for inhaled corticosteroids.^{3-6,8} Analysis of the patient diary data utilizing the components of the ACC also indicates improved asthma symptoms for patients in the omalizumab treatment group. Because of entry criteria, none of the patients were classified as “complete control” at baseline (visit 3). At both weeks 16 and 28 (visits 7 and 13, respectively), 9% of omalizumab recipients had achieved “complete control” compared with 4% of placebo recipients (Fig 1A). The “good control” asthma category included 9% of patients at baseline in both the omalizumab and placebo treatment groups. At week 16, 39% of patients treated with omalizumab achieved “good control” compared with 28% of placebo recipients (Fig 1B). The percentage of patients achieving “good control” was maintained through week 28 with 40% and 29% of patients treated with omalizumab and placebo, respectively, classified in the “good control” category. At baseline, 91% of patients in each treatment group were classified as “not controlled.” At week 16, only 52% of omalizumab-treated patients remained in the “not controlled” category, compared with 68%

of placebo-treated patients (Fig 1C). At week 28, 51% of omalizumab-treated patients remained uncontrolled compared with 66% of placebo-treated patients.

At baseline, the mean composite scores were similar, 1.33 and 1.29 for omalizumab and placebo groups, respectively, and indicated an overall asthma classification of “not controlled” for each treatment group (Fig 2). At week 16, the mean composite scores were improved to 3.47 and 2.57 in omalizumab-treated and placebo-treated patients, respectively, and to 3.52 and 2.56 at week 28. The scores indicate an improvement in overall asthma classification to “good control” for omalizumab-treated patients, whereas placebo-treated patients remained as “not controlled.”

DISCUSSION

We present a new asthma control outcome measure, the ACC, to evaluate response to omalizumab. The ACC does not rely on lung function for assessment of asthma control but incorporates 4 independent components: sleep impairment, asthma symptoms, impact on activities and function, and use of rescue medication. We have mapped these measures of asthma control to demonstrate analogy to those that make up the clinically validated ACT, ACQ, and ATAQ tools. Importantly, whereas the ACT, ACQ, and ATAQ tools rely on recall of asthma symptoms for up to 4 past weeks, the ACC uses data collected daily in diary format, reflecting “real-time” assessment.

Application of this tool to retrospectively analyze pooled data from 2 clinical trials agrees with the earlier findings that omalizumab improved control of asthma symptoms compared with placebo.^{3,6} The proportion of patients with initially uncontrolled asthma at baseline who achieved “good” or “complete” asthma control was higher for patients treated with omalizumab than for patients treated with placebo (49% vs 34%) approximately 4 months after baseline. Similarly, the mean composite score improved more for patients treated with omalizumab than for patients treated with placebo assessed up to 4 months after baseline.

The pivotal trials included an additional parameter of asthma control, the GETE, assessed independently by both the patient and the investigator at week 28. Because GETE was evaluated at only 1 visit in the pivotal trials, it was not included in the development of the ACC. However, in other studies in which GETE was assessed at the same time points as the other parameters of asthma control, it could be included in the composite score for ACC and was mapped as follows: a score of “1” would map as “complete control”; a score of “2” would map as “good control”; and a score of “3,” “4,” or “5” would map as “not controlled.” Although the GETE has been used in past omalizumab analyses as an overall assessment of asthma control,¹⁶ it was collected in a manner that can be expressed only as a “change from baseline.” The intention with the ACC was to provide an assessment at both baseline and a given follow-up point in time, to mirror other asthma control instruments. Thus the GETE was

Table 2. Asthma Control Composite Score Classification

Score	Overall asthma classification
8	Complete control
4, 5, 6, or 7	Good control
0, 1, 2, or 3	Not controlled

Table 3. Mapping of Asthma Control Composite (ACC) to ACQ/ACT/ATAQ

Components of control	Questionnaires			
	ACC (Daily recall)	ACQ (2 weeks recall; past week)	ACT (4 weeks recall)	ATAQ (4 weeks recall)
Nocturnal awakening	Average number of awakening nights per 28 days	How often were you woken by your asthma during the night?	How often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness, or pain) wake you up at night or earlier than usual in the morning?	Wake up at night because of asthma?
Morning symptoms	Total asthma symptom score ^a	How bad were your asthma symptoms when you woke up in the morning?	How often have you had shortness of breath?	–
Wheeze		How much of the time did you wheeze?	How much of the time did your asthma keep you from getting as much done at work, school, or at home?	–
Impact on daily functioning/activity limitations	Activity limitations (AQLQ question 32)	How limited were you in your activities because of your asthma?	How often have you used your rescue inhaler or nebulizer (3 or more times per day; 1 or 2 times per day; 2 or 3 times per week; once a week or less; not at all)?	Miss any work, school, or normal daily activity because of your asthma?
Rescue medication use	Rescue medication (puffs/day)	How many puffs of short-acting bronchodilator have you used each day? (Response: puffs most days)		What was the highest number of puffs in 1 day you took of the inhaler?

Abbreviations: ACT, Asthma Control Test; ACQ, Asthma Control Questionnaire; ATAQ, Asthma Therapy Assessment Questionnaire; AQLQ, Asthma Quality of Life Questionnaire.

^a The total asthma symptom score includes the nocturnal asthma score, and morning and daytime asthma symptom scores: shortness of breath, chest discomfort, wheezing, and cough, and is combined with activity restrictions.

Table 4. Patient Demographics and Baseline Characteristics for the Pooled Patient Population^a

	Omalizumab (n = 542) n (%)	Placebo (n = 528) n (%)
Mean age, yr (range)	39.7 (12–76)	39.0 (12–74)
Sex (female/male), n	297/245	290/238
Mean BDP dose, μ g/day (range)	724 (500–1,600)	726 (200–2,000)
Rescue albuterol use, puffs/day (range)	4.7 (0–14.6)	4.7 (0–18.1)
Mean serum total IgE, IU/mL (range)	198 (20–860)	196 (21–814)
History of atopic dermatitis, n (%)	36 (6.6)	55 (10.5)
No. of positive allergens (range)	2.72 (0–5)	2.67 (0–5)
Mean duration of asthma, yr (range)	20.5 (1–68)	20.8 (1–63)
Total symptom score (0–9) (range)	4.11 (0–8.36)	4.14 (0–8.64)
Nocturnal symptom score (0–4) (range)	1.2 (0–3.7)	1.2 (0–4)
In the past year		
No. of visits to a doctor's office for urgent asthma treatment (range)	0.94 (0–15)	1.01 (0–24)
Overnight hospital admission for asthma, n (%)	17 (3.3)	31 (6.3)
No. of emergency department (ED) visits for asthma treatment (range)	0.20 (0–12)	0.25 (0–20)
Asthma treatment in an ICU, n (%)	6 (1.1)	5 (0.9)
History of an emergency asthma treatment, ^a n (%)	216 (41.5)	201 (41.4)
FEV ₁		
Absolute value, mL (range)	2,426 (650–5,120)	2,441 (640–5,050)
% predicted	69 (30–112)	69 (22–111)
≤65% predicted, n (%)	118 (21.8)	112 (21.2)
Mean FVC, mL (range)	3,489 (1,370–7,760)	3,481 (380–7,480)
Mean FEF _{25–75%} , mL/s (range)	1,832 (250–6,860)	1,825 (220–4,980)
Mean morning PEF, L/min (range)	347 (114–618)	354 (145–656)

Abbreviations: BDP, beclomethasone dipropionate; ED, emergency department; FEV₁, forced expiratory volume in 1 s; FEF_{25–75%}, forced expiratory flow from 25–75% of vital capacity; FVC, forced vital capacity; ICU, intensive care unit; IgE, immunoglobulin E; PEF, peak expiratory flow.

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^a A composite variable based on history in the last year of at least 1 of the following: overnight hospital admission or treatment in an ICU for asthma, or at least one ED or doctor's office visit for urgent asthma treatment.

not used in the version of ACC taken forward for further exploratory analyses.

The ACC tool is limited in that not all components of the asthma symptom score map directly to ACT, ACQ, or ATAQ components. For example, the total asthma symptom score determined from patient diaries does not directly map to assessments in the ACT or ACQ but does assess some of the daily symptoms (shortness of breath, chest discomfort, wheezing, and cough) recorded in these measures; additionally, the ATAQ does not include an assessment for daily symptoms of asthma.

Importantly, the FEV₁ is not a component of the ACC, ACT, or ATAQ tools, despite the importance placed on this measurement in clinical practice. We excluded FEV₁ as a component of this ACC tool given that numerous studies have found a discordance between FEV₁ and patient-assessed asthma control level.¹⁷ The conclusion of the American Thoracic Society/European Respiratory Society Task Force on Asthma Control and Exacerbations that “no single outcome measure can adequately assess asthma control”² supports the use of the clinically validated assessment tools that assess numerous components of the asthma disease process.

Similar to the ACC, National Institutes of Health guidelines classify asthma control into 3 categories, “well con-

trolled,” “not well controlled,” or “very poorly controlled.”¹¹ The assessment categories described in the NIH guidelines involve more measurements than those in the ACC and include incidence of symptoms and night-time awakening, interference with normal activity, requirement for rescue medication, FEV₁ or peak flow measurements, validated questionnaire scores, and frequency of exacerbations.

Studies of guideline-based definitions of asthma control indicate a clear need for a standard definition of asthma control and understanding of the implications that these definitions may have on clinical practice and future research.¹⁸ The consequence of differences among definitions of asthma control is that they may lead to divergent research conclusions or treatment practices.

Measurements of patient response to treatment by assessment of asthma control are becoming more accepted for management of asthma. Investigators in the Gaining Optimal Asthma Control study examined the association between guideline-derived asthma control and health-related quality of life assessed using the Asthma Quality of Life Questionnaire (AQLQ) in patients with uncontrolled asthma whose treatment was directed toward achieving the highest possible level of control.^{19,20} Gaining Optimal Asthma Control investigators observed that the treatment aimed at controlling asthma im-

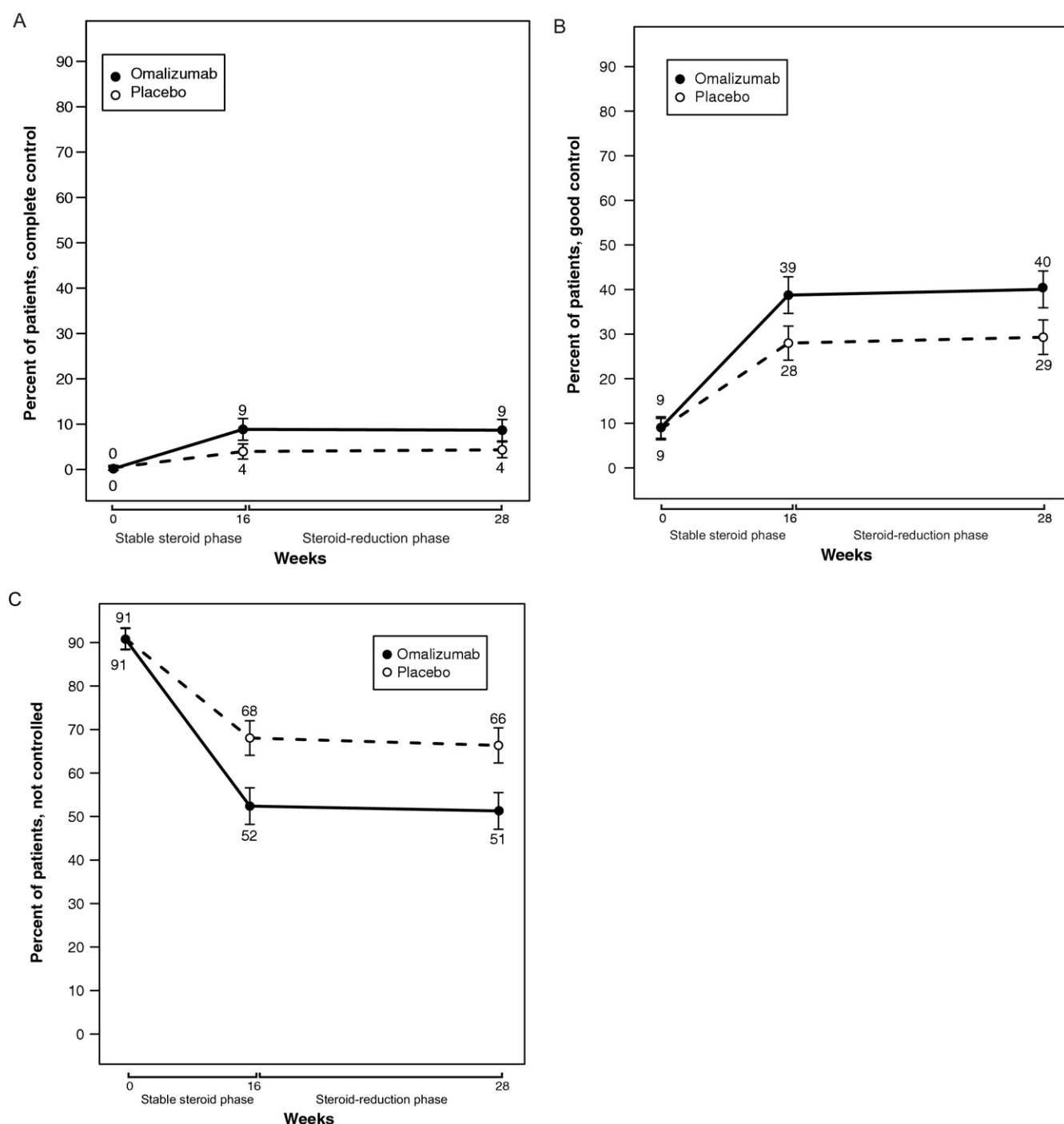


Figure 1. Categorical response to omalizumab as defined by the ACC tool (complete control, good control, not controlled) at baseline, weeks 12–16 (end of the steroid stabilization period), and weeks 26–28 (end of the steroid reduction phase). Percentage of total patients ($N = 1,070$) assessed in the 2 studies. *Closed symbols, solid lines* = omalizumab patients; *open symbols, dashed lines* = placebo patients. *Vertical bars* indicate 95% confidence intervals. A, Percentage of patients scoring as “complete control.” B, Percentage of patients scoring as “good control.” C, Percentage of patients scoring as “not controlled.”

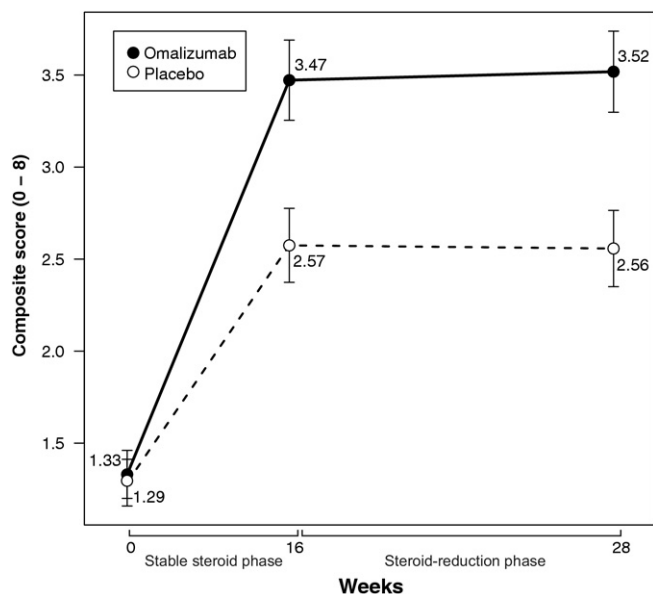


Figure 2. Response to omalizumab expressed as the numeric composite score obtained by applying the ACC tool at baseline, end of the stabilization period, and end of the steroid reduction phase for the pooled patient population ($N = 1,070$). Closed symbols, solid lines = omalizumab patients; open symbols, dashed lines = placebo patients. Vertical bars indicate 95% confidence intervals.

proves health-related quality of life to levels approaching normal. These results emphasize the importance of asthma control as an outcome of clinical trials. The Characterization of Allergic Asthma: A Chart Review In Moderate-to-Severe Disease to Assess Asthma Control, Allergies, Patient Outcomes and Treatment (CHARIOT) study²¹ was a retrospective analysis of patient charts to determine the proportion of patients in community practice with uncontrolled asthma. The CHARIOT study involved the National Asthma Education and Prevention Program guidelines for assessment of control and determined that more than 80% of patients studied were classified as uncontrolled by fitting the definition of “very poorly controlled.”

The development of the “Control of Allergic Rhinitis and Asthma Test” (CARAT) questionnaire to measure the degree of control of allergic rhinitis and asthma (ARA) in adult patients with a previous medical diagnosis of ARA has been described recently.²² CARAT involves 17 questions in a brief self-administered tool and simultaneously addresses the control of upper and lower respiratory disease, and it does not include a quantitative measure of lung function. Domains similar to the ACC include assessment of lower airway symptoms (wheezing, cough), effect of ARA on activities, sleep impairment, and treatment (rescue medication). CARAT also addresses nasal and ocular symptoms and exacerbations.

In summary, we have clinically validated the ACC tool as a new research tool to study asthma control in a moderate to

severe asthma population eligible for biologic treatment, such as the patient population studied in the omalizumab clinical trials. Unlike the ACT, which has not been validated in this asthma patient population, the ACC shows promise as a tool for asthma control assessment. Its potential utility as an assessment tool in clinical practice merits further study.

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SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.anai.2011.06.005.

REFERENCES

1. National Heart, Lung and Blood Institute. *National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Full Report*. 2007. Bethesda, MD: National Institutes of Health.
2. Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med*. 2009;180:59–99.
3. Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol*. 2001;108:184–190.
4. Lanier BQ, Corren J, Lumry W, Liu J, Fowler-Taylor A, Gupta N. Omalizumab is effective in the long-term control of severe allergic asthma. *Ann Allergy Asthma Immunol*. 2003;91:154–159.
5. Buhl R, Soler M, Matz J, et al. Omalizumab provides long-term control in patients with moderate-to-severe allergic asthma. *Eur Respir J*. 2002;20:73–78.
6. Soler M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J*. 2001;18:254–261.
7. Finn A, Gross G, van Bavel J, et al. Omalizumab improves asthma-related quality of life in patients with severe allergic asthma. *J Allergy Clin Immunol*. 2003;111:278–284.
8. Corren J, Casale T, Deniz Y, Ashby M. Omalizumab, a recombinant humanized anti-IgE antibody, reduces asthma-related emergency room visits and hospitalizations in patients with allergic asthma. *J Allergy Clin Immunol*. 2003;111:87–90.
9. Bousquet J, Wenzel S, Holgate S, Lumry W, Freeman P, Fox H. Predicting response to omalizumab, an anti-IgE antibody, in patients with allergic asthma. *Chest*. 2004;125:1378–1386.
10. Milgrom H, Berger W, Nayak A, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). *Pediatrics*. 2001;108:E36.
11. Silkoff PE, Romero FA, Gupta N, Townley RG, Milgrom H. Exhaled nitric oxide in children with asthma receiving Xolair (omalizumab), a monoclonal anti-immunoglobulin E antibody. *Pediatrics*. 2004;113:e308–e312.
12. Bousquet J, Cabrera P, Berkman N, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy*. 2005;60:302–308.
13. Nathan RA, Sorkness CA, Kosinski M, et al. Development of the asthma control test: a survey for assessing asthma control. *J Allergy Clin Immunol*. 2004;113:59–65.
14. Juniper EF, O’Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J*. 1999;14:902–907.

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15. Skinner EA, Diette GB, Algatt-Bergstrom PJ, et al. The Asthma Therapy Assessment Questionnaire (ATAQ) for children and adolescents. *Dis Manag.* 2004;7:305–313.
 16. Bousquet J, Rabe K, Humbert M, et al. Predicting and evaluating response to omalizumab in patients with severe allergic asthma. *Respir Med.* 2007;101:1483–1492.
 17. Bukstein D, Kraft M, Liu AH, Peters SP. Asthma end points and outcomes: what have we learned? *J Allergy Clin Immunol.* 2006;118: S1–15.
 18. Campbell, JD, Blough DK, Sullivan SD. Comparison of guideline-based control definitions and associations with outcomes in severe or difficult-to-treat asthma. *Ann Allergy Asthma Immunol.* 2008;101:474–481.
 19. Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med.* 2004;170:836–844.
 20. Bateman ED. Severity and control of severe asthma. *J Allergy Clin Immunol.* 2006;117:519–521.
 21. Marcus P, Arnold RJ, Ekins S, et al. A retrospective randomized study of asthma control in the US: results of the CHARIOT study. *Curr Med Res Opin.* 2008;24:3443–3452.
 22. Nogueira-Silva L, Martins SV, Cruz-Correia R, et al. Control of allergic rhinitis and asthma test: a formal approach to the development of a measuring tool. *Respir Res* 2009;10:52.
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e-Table 1. Diary Questionnaire: Evaluation of Asthma Symptoms, Peak Expiratory Flow Rates, and Rescue Medication Use

During the run-in period and the double-blind treatment period, patients maintained a daily diary to record asthma symptom scores, peak expiratory flow rates (PEFR), and number of puffs of rescue medication used during the day and night. The asthma symptom scores and PEFR were recorded as follows:

Nocturnal asthma score

Each morning, on awakening, the patient recorded the answer to the following question in the Patient Diary:

How did you sleep last night?

0 = I did not wake up because of any breathing problems.

1 = I awoke once because of my breathing problems but did not use my rescue medication.

2 = I awoke once because of my breathing problems, but my rescue medication controlled my symptoms.

3 = I awoke more than once because of my breathing problems, but my rescue medication controlled my symptoms.

4 = I had difficulty sleeping because of my breathing problems even though I used my rescue medication.

Morning asthma symptoms

Each morning, on awakening, the patient recorded the answer to the following question in the Patient Diary:

Did you have asthma symptoms on arising in the morning?

0 = No

1 = Yes

Daytime asthma symptom scores

Each evening, before bedtime, the patient performed an evaluation on his or her asthma symptoms over the preceding 24-hour period.

This evaluation included an overall assessment of the following symptoms: shortness of breath (breathlessness), chest discomfort (tightness), wheezing, and cough.

The following scale was used to record these combined symptoms:

0 = No symptoms at all; unrestricted activity.

1 = Symptoms caused little or no discomfort; unrestricted activity.

2 = Symptoms caused some discomfort, at times limiting strenuous activity.

3 = Symptoms caused moderate discomfort and sometimes limited routine activity.

4 = Symptoms occurred at rest, caused marked discomfort, and usually limited routine activity.

Peak expiratory flow rate (PEFR)

PEFR was measured twice daily in the morning and evening during the run-in period and once daily in the morning during the double-blind treatment period. The measurements were performed using a Mini-Wright peak flow meter (given to patients at visit 1) within 15 minutes on awakening in the morning and at 5 PM ($\pm 1/2$ hour) in the evening. For each sampling time point, patients performed 3 consecutive efforts within 10 minutes and recorded the best value on the diary card.

Evaluation of injection site local symptoms/signs

After study-drug administrations (weeks 0–16), patients recorded local symptoms/signs at each injection site as follows: onset date and time, duration of reaction, and severity (3-point scale; mild, moderate, severe) of burning, itching, warmth, bruising, redness, hive formation, and any other local reaction were recorded individually; the maximum size of the reaction was noted using the following scale:

0 = Unable to assess

1 = Less than a dime

2 = A dime

3 = A nickel

4 = A quarter

5 = A half-dollar or larger

GETE (Global Evaluation of Treatment Effectiveness)

At the end of the steroid-reduction period (weeks 26–28), a global evaluation of the treatment effectiveness was performed by the investigator and the patient, using the following scale:

1. Excellent (complete control of asthma)

2. Good (marked improvement of asthma)

3. Moderate (discernible but limited improvement in asthma)

4. Poor (no appreciable change in asthma)

5. Worsening of asthma