Magnitude of effect of asthma treatments on Asthma Quality of Life Questionnaire and Asthma Control Questionnaire scores: Systematic review and network meta-analysis

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Background: The Asthma Quality of Life Questionnaire (AQLQ) and the Asthma Control Questionnaire (ACQ) are widely used in asthma research; however, in studies of newer asthma treatments, mean improvements in these measures compared with placebo arms do not exceed the minimal important difference (MID), particularly when a new treatment is added to current treatment.

Objective: We performed a systematic review and network meta-analysis to examine the magnitude of AQLQ and ACQ responses achieved with commonly used asthma drugs and factors influencing these end points in clinical trials.

Methods: A systematic literature search was conducted to identify blinded randomized controlled trials reporting AQLQ or ACQ results. Mixed treatment comparisons, combined with meta-regression, were then performed.

Results: Of the 64 randomized controlled trials (42,527 patients) identified, 54 included the AQLQ and 11 included the ACQ as end points. The presence of a run-in period, the nature of treatment during the run-in period, concurrent treatment during the treatment period, and instrument version significantly influenced the change in AQLQ score from baseline and whether it exceeded the MID. When compared with placebo, only inhaled corticosteroids (ICSs), with or without a long-acting β-agonist, achieved the MID. The ACQ results were comparable with those of the AQLQ: no differences from placebo exceeded the MID, and ICS-based treatments provided the greatest improvements.

Conclusion: The established within-patient MID for the ACQ and AQLQ is not achievable as a group-wise efficacy threshold between treatment arms in clinical studies in which controllers are added to ICS treatment. Thus in addition to reporting mean changes of the instruments, other measurement criteria should be considered, including responder analyses. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Asthma, asthma control, quality of life, network meta-analysis, questionnaire*

The step-wise approach to pharmacotherapy in patients with asthma involves addition of therapy with the goal of achieving both symptom control and prevention of exacerbations.[1] However, evaluating the efficacy of adding 1 or more controllers to inhaled corticosteroids (ICSs) at step 3 and beyond in the treatment guidelines is challenging for several reasons. Generally, the incremental benefit achieved with each addition is likely to diminish as more treatments are added. Furthermore, because treatments differ in their effect on different asthma end points, improvement might be limited to some, but not all, end points. Demonstrating improvement in patient-reported outcomes (PROs), such as symptom control and health status, is particularly challenging because these outcomes are subjective and can vary widely among subjects. Consequently, their measurement involves the use of complex tools for semiquantitative assessment of symptoms and impairment. Health authorities might require evidence of improvement in 1 or more patient-reported end points for registration, reimbursement, or both of new asthma treatments. Widely used PROs in clinical trials are the Asthma Control Questionnaire (ACQ)[2,3] and the Asthma Quality of Life Questionnaire (AQLQ).[4] For both instruments, the accepted minimal important difference (MID) is 0.5 units,[5,6] which is the "smallest difference in score … which patients perceive as beneficial and which would mandate a change in the patient's management."[5] The MID is a measure of within-person change but in clinical trials is used as a threshold value for between-group comparisons.[7]

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Supported by Boehringer Ingelheim, Ingelheim am Rhein, Germany.

Disclosure of potential conflict of interest: This study was funded by Boehringer Ingelheim. E. D. Bateman has received consultancy fees from Actelion, Almirall, ALK-Abello, AstraZeneca, Boehringer Ingelheim, Cephalon, Hoffmann La Roche, and Navigant Consulting; he has received compensation for serving on the advisory boards for Almirall, AstraZeneca, Boehringer Ingelheim, Forest, GlaxoSmithKline, ICON, Merck, Novartis, Pfizer, and Takeda; he has received lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Pfizer and Takeda; and his institution has received compensation for participation in clinical trials sponsored by Actelion, Aeras, Almirall, AstraZeneca, Boehringer Ingelheim, Cephalon, Chiesi, GlaxoSmithKline, Hoffmann La Roche, Merck, Novartis, Sanofi-Aventis, Takeda, and Teva. P. Moroni-Zentgraf is an employee of Boehringer Ingelheim, as is D. Esser and A. Fowler. J. M. FitzGerald has received compensation for attending advisory boards and delivering lectures from Boehringer Ingelheim. C. Chirila and M. Fernandez have declared that their institution (RTI Health Solutions) received funding from Boehringer Ingelheim for the literature review, statistical analysis, and preparation of this manuscript.

Received for publication October 21, 2014; revised March 20, 2015; accepted for publication March 25, 2015.

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0091-6749

http://dx.doi.org/10.1016/j.jaci.2015.03.023

Abbreviations used
ACQ: Asthma Control Questionnaire
AQLQ: Asthma Quality of Life Questionnaire
ICS: Inhaled corticosteroid
LABA: Long-acting β-agonist
LTRA: Leukotriene receptor antagonist
MID: Minimal important difference
MTC: Mixed treatment comparison
PRO: Patient-reported outcome
RCT: Randomized controlled trial

Assessment of recent placebo-controlled studies of new controller treatments in patients with severe asthma (eg, omalizumab and tiotropium) reveals that improvements in AQLQ and ACQ responses are smaller than might be expected.[8,9] For example, in trials of tiotropium in patients whose symptoms are uncontrolled with at least an ICS and a long-acting β-agonist (LABA), group mean differences in AQLQ and ACQ scores compared with placebo did not exceed the MID for either instrument. These observations call into question the performance of these instruments and the interpretation of results obtained with them, particularly when multiple treatments are being used.[9] It is worth noting that both the AQLQ and the ACQ were developed and their reliability, validity, and responsiveness were assessed in a patient population that was largely steroid naive or receiving ICSs alone.[4,5,10,11]

The MID for clinical outcomes is estimated by means of a process of triangulation that compares the outcome of interest with changes in other measures to arrive at the smallest difference that might represent benefit.[12] At both the group and individual levels, the MID might depend on the clinical context and patient management decision at hand, the baseline from which the patient starts, and whether the patient's symptoms are improving or deteriorating.[13] The initial derivation of the MID for both the AQLQ and the ACQ was based largely on the physician's judgment of change in patients whose symptoms improved on monotherapy with an ICS, with placebo as a control. To the authors' knowledge, the MID has not been correlated with other important measures of interest in asthma, such as exacerbations or the frequency of hospitalization. Furthermore, to date, there has been no critical review of the extent to which the MID is achievable when treatments are added to highly effective medications, such as ICSs or ICS plus LABA combinations.

We report here a systematic review and meta-analysis of clinical trials in patients with asthma in which the AQLQ, ACQ, or both was used to examine the achievability of between-group mean differences of 0.5 or more with established asthma treatments.

METHODS

Search strategy

A systematic literature search using PubMed, Embase, and the National Health Service Economic Evaluation Database was conducted on April 5, 2012, and updated on June 14, 2013 (details are provided in the Methods section and Table E1 in this article's Online Repository at www.jacionline.org). In addition, the bibliographies of existing literature reviews and meta-analyses, the clinicaltrials.gov study register, and the 2011 and 2012 conference Web sites of the American Thoracic Society and European Respiratory Society were searched. No limits regarding publication date or language were applied.

Inclusion criteria and selection of studies

Using predefined inclusion and exclusion criteria, 2 reviewers (C.C. and M.F.) independently scanned titles and abstracts of the identified studies at level 1 screening to evaluate potential study relevance; full texts of studies selected at level 1 were reviewed at level 2 screening (see the Methods section in this article's Online Repository for full details). Discrepancies were reconciled between the 2 reviewers or by a third reviewer (D.E.), if necessary.

Double-blind randomized controlled trials (RCTs) of adolescent and adult patients with uncontrolled, symptomatic, or persistent asthma at baseline were included if the overall score changes from baseline values for the AQLQ, ACQ, or both were reported after patients received 1 or more of the following treatments: an ICS, a LABA, a leukotriene receptor antagonist (LTRA), a short-acting β-agonist, omalizumab, or theophylline. Data from all the instrument versions of the AQLQ, such as the Standardized AQLQ and the MiniAQLQ,[10,11] and of the ACQ, such as the 5-item and 6-item versions (ACQ-5 and ACQ-6),[6] were collected.

Data extraction and assessment of risk of bias

Data from the original studies were extracted by using a standardized abstraction form developed in Microsoft Excel (see the Methods section in this article's Online Repository for details), which included study design information. To consistently capture key study differences, run-in and background treatments were defined as stable comedications if they were taken by at least 50% of patients in addition to the study medication before randomization, after randomization, or both. Data were independently checked for accuracy by 2 reviewers (C.C. and M.F.); the risk of bias of individual studies was assessed at the study and outcome level by using the quality criteria presented in the National Institute for Health and Care Excellence single technology appraisal guidance[14] and the Centre for Reviews and Dissemination's guidance (see the Methods section in this article's Online Repository for details).[15]

Outcome measures

The meta-analysis assessed AQLQ and ACQ score changes from baseline, where baseline was defined as the last visit before the start of the treatment phase. The extracted assessments were based on the time point of the study primary end point, as designated in the publication, or the latest available time point (if no time point was designated as primary).

Statistical methods

For each outcome, a mixed treatment comparison (MTC) combined with meta-regression was performed. Linear mixed models with the SE of mean change from baseline in the instrument used as a weighting variable and trials as random effects were constructed by using the PROC MIXED procedure in SAS (version 9.3; SAS Institute, Cary, NC). If the SE was not available, it was either derived or imputed (see the Methods section in this article's Online Repository for details). Adjusted least-squares means for each treatment and adjusted mean differences between any 2 treatments, along with 95% CIs, were estimated. Multiple covariates were assessed, both individually and in combination, for inclusion in the MTC model to address heterogeneity[16] and reduce inconsistency between treatment comparisons (see the Methods section in this article's Online Repository for details).[17] Covariates with *P* values of .05 or less were included in the model.

By comparing the estimated mean changes from baseline and their CIs with the MID,[18] the size of the treatment responses were further classified as follows:

- *no effect* if the point estimate did not reach the MID and the 95% CI included zero;
- *no clinically significant effect* if the point estimate did not reach the MID and the 95% CI was between zero and the MID;
- *not significantly less than the MID* if the point estimate did not reach the MID and the 95% CI was greater than zero but contained the MID;
- *probable clinically significant effect* if the point estimate exceeded the MID but the 95% CI contained the MID; and
- *large clinically significant effect* if the point estimate exceeded the MID and the 95% CI exceeded the MID.