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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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.

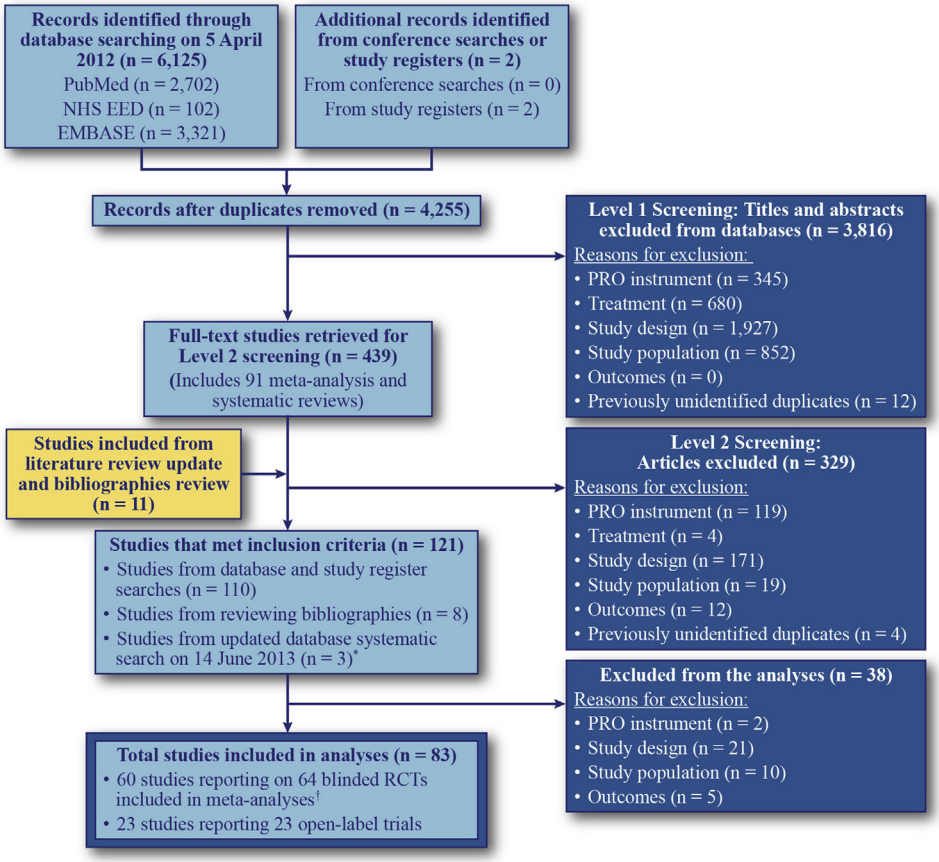

FIG 1. Flow diagram of study selection. *The update of the database systematic search was conducted from March 26, 2012, to June 14, 2013, with the objective of capturing additional blind RCTs. †Only blind RCTs identified in this search were included in the meta-analysis. *NHS EED,* National Health Service Economic Evaluation Database.

TABLE I. Summary of baseline characteristics

Treatment	No. of studies	No. of patients	Mean age (y)	Mean body mass index (kg/m^2)	Reversibility* (%)	Female (%)	White (%)	Never smoked (%)	Baseline mean FEV_1 (L)
ICS	33	8,525	40.3	26.6	23.0	59.0	77.0	80.9	2.32
LABA	17	4,811	40.2	NA	22.0	57.8	81.6	NA	2.31
ICS + LABA	25	14,988	41.2	27.7	23.6	60.2	54.9	81.6	2.21
LTRA	19	5,336	37.5	NA	17.8	56.6	78.3	74.4	2.43
SABA	5	1,763	41.6	NA	23.3	59.1	NA	NA	2.18
Omalizumab	6	1,407	41.5	NA	24.6	58.5	80.4	76.2	2.58
Theophylline	1	161	41.0	NA	NA	75.0	60.0	NA	NA
Placebo	33	5,536	39.1	NA	25.0	57.0	78.8	79.5	2.40
All treatments	64	42,527	40.2	26.7	22.9	58.8	73.5	80.3	2.3

NA, Data not available; *SABA*, short-acting β-agonist.
*Reversibility as the mean percentage increase in FEV_1 after β_2-agonist inhalation at baseline or screening.

Sensitivity analyses were performed to assess the effect of data imputation for the SE and the effect of including in the analysis studies that compared treatments within the same treatment classes. Inconsistency of the network was also evaluated.[19-21] A test result was declared significant if the *P* value was .05 or less.

RESULTS

Systematic review and summary of included trials

Sixty articles reporting on 64 RCTs (42,527 patients) were identified (see Fig 1 and the Results section in this article's Online Repository at www.jacionline.org for details).

Table I presents a weighted average of the baseline characteristics by treatment. In general, baseline characteristics were similar across treatments.

Overall, the quality of the studies was good (see Table E2 in this article's Online Repository at www.jacionline.org). Most studies reported the differences in dropouts between the treatment groups and the reasons for patient withdrawal, although reporting of randomization methods, concealment allocation, and blinding of participants was not clear in many of the studies. The risk of bias in the analyses was not clear in several studies because the conduct of intention-to-treat analyses was poorly described and

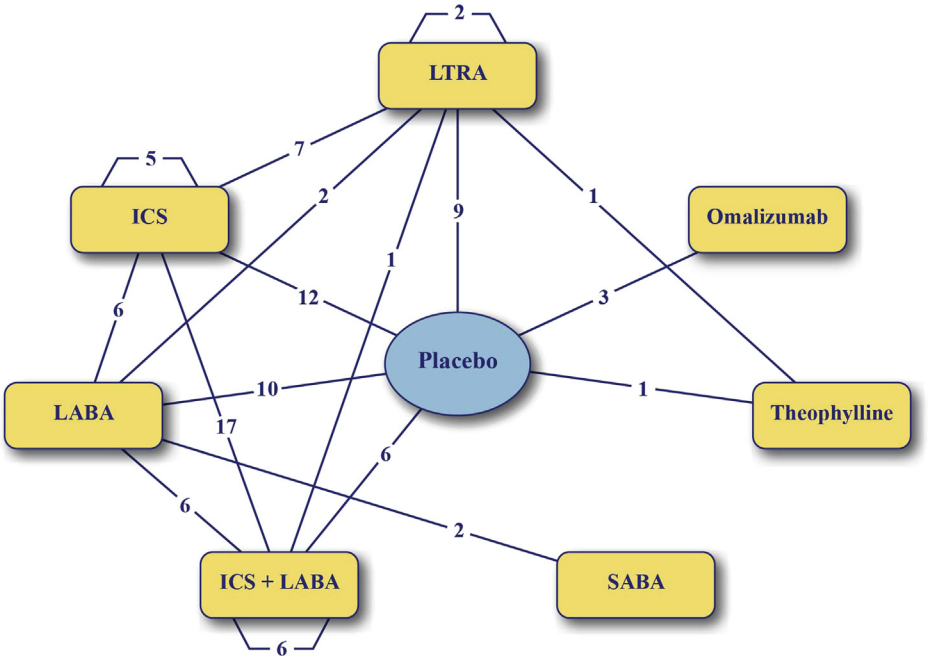

FIG 2. AQLQ network of evidence. Numbers indicate the number of studies with comparisons of AQLQ score changes between treatments (which could include different drugs in the same class) in RCTs of patients with asthma. See Table E3 in this article's Online Repository for the list of studies included in this network. *SABA,* Short-acting β-agonist.

applied. For example, the number of patients used in the calculations of health-related quality of life often was not clearly reported.

MTC of AQLQ results

The AQLQ was included as an end point in 54 of the 64 blinded RCTs. Fig 2 shows the AQLQ network diagram; numbered lines indicate the number of studies included in the comparison (see Table E3 in this article's Online Repository at www.jacionline.org for more detailed information on the individual studies). Higher AQLQ scores indicate better health-related quality of life, such that increases from baseline are considered favorable.

During the run-in period, subjects in 9 (17%) RCTs had no medication (or no run-in period), in 9 (17%) RCTs they received placebo, and in 36 (66%) RCTs they received an ICS. During the treatment phase, subjects in 38 (72%) RCTs had no background treatment, and in 15 (28%) RCTs they continued ICS use as background treatment. Overall, 41 (76%) RCTs used the original AQLQ instrument, whereas 13 (24%) RCTs used alternate versions (Standardized AQLQ [20%] or MiniAQLQ [4%]).

Study treatment, run-in treatment (none [or no run-in period], placebo, or ICS), background treatment (none or ICS), AQLQ type (original or other), and study treatment by background treatment were statistically significant covariates included in the final MTC multivariable model for the AQLQ.

Changes in AQLQ scores from baseline (within-treatment comparisons)

Adjusted AQLQ estimates of change from baseline for pooled treatment groups in trials with or without background medication or with different run-in treatments and type of AQLQ are presented in detail in Table E4 in this article's Online Repository at www.jacionline.org. Fig 3 shows AQLQ score changes from baseline for situations considered representative of asthma clinical studies by using the AQLQ original version and various combinations of run-in period and background treatment (ie, no run-in treatment and no ICS background, placebo run-in period and no ICS background, ICS run-in period and ICS background).

In trials with no run-in period and no concurrent (background) controller treatment during the treatment period, the estimated AQLQ changes from baseline achieved in the ICS plus LABA, ICS, LTRA, and LABA treatment groups were all greater than 0.5 and categorized as large and clinically significant. However, placebo also achieved a mean improvement greater than 0.5 units (0.553; 95% CI, 0.367-0.739), which was categorized as probably clinically significant.

When a run-in period was present during which placebo was used and there was no concurrent therapy during the active phase of the trials, the estimated AQLQ change from baseline was large and clinically significant only for the ICS plus LABA (0.919; 95% CI, 0.734-1.104) and ICS (0.729; 95% CI, 0.549-0.909) treatment groups. For LTRA (0.504; 95% CI, 0.324-0.685), the increase exceeded 0.5 and was of probable clinical significance, but LABA treatment alone (0.419; 95% CI, 0.223-0.616) did not exceed the MID threshold and thus was not clinically significant.

When an ICS formed part of the treatment during the run-in period and was used as background treatment, the estimated AQLQ improvements from baseline for the LABA, LTRA, and omalizumab groups were large and clinically significant; however, those for theophylline, short-acting β-agonist, and placebo were also greater than 0.5 units but only fulfilled the criteria for probable clinical significance (Fig 3).

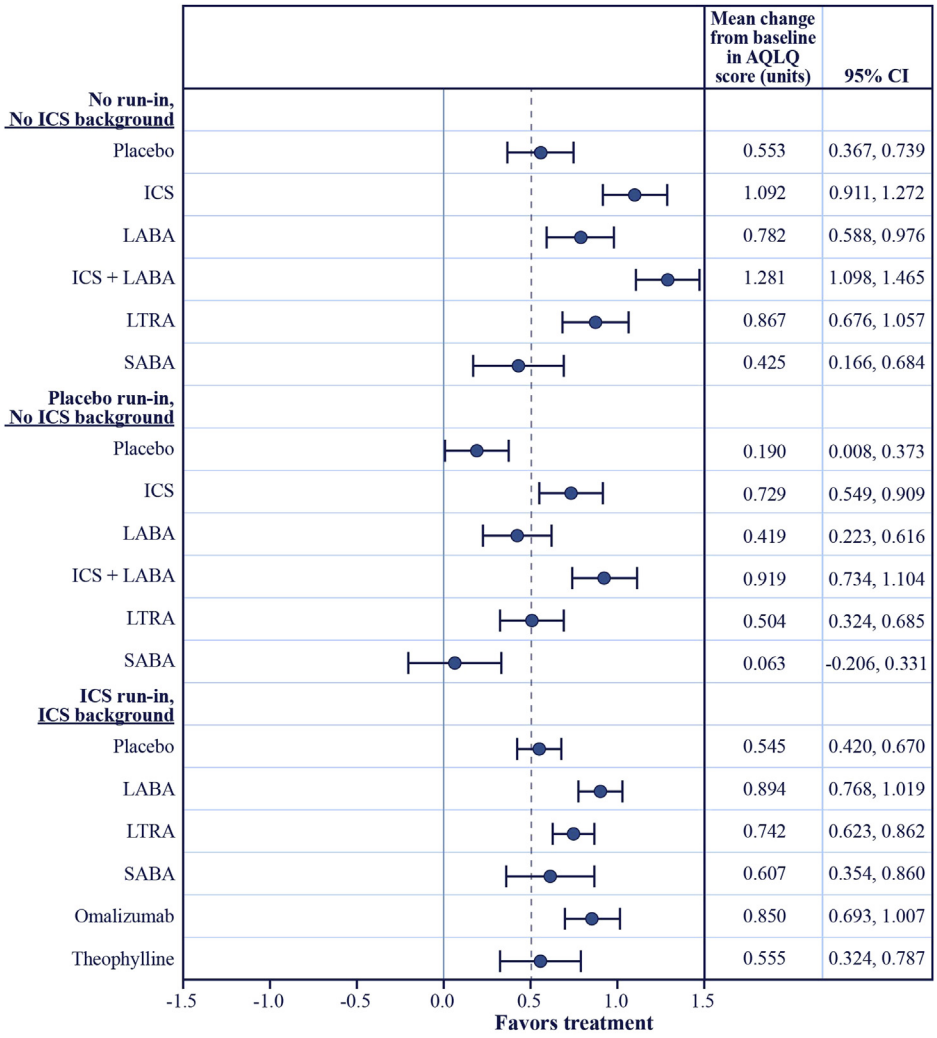

FIG 3. Adjusted mean change from baseline in overall AQLQ score using the AQLQ original version. *SABA,* Short-acting β-agonist.

Comparisons between treatments

Comparison of active versus placebo treatments in patients with and without background ICSs using the same treatment during the run-in period are presented in Fig 4. When background treatment did not include a controller ICS, only ICS plus LABA and ICS alone achieved a mean improvement of greater than 0.5 units. For ICS plus LABA treatment, the increase was large and clinically significant (0.729; 95% CI, 0.658-0.799), but for ICS treatment, the increase was of only probable clinical significance (0.539; 95% CI, 0.479-0.599). LABAs and LTRAs added to concurrent ICS treatment achieved increases of only 0.229 (95% CI, 0.135-0.323) and 0.314 (95% CI, 0.230-0.398), respectively, which were not clinically significant (Fig 4).

When the background concurrent treatment during the active treatment phase of trials was an ICS, improvements in AQLQ scores achieved with active treatments relative to placebo were considerably smaller. With the addition of a LABA (0.349; 95% CI, 0.271-0.427), LTRA (0.198; 95% CI, 0.127-0.269), or omalizumab (0.305; 95% CI, 0.202-0.408), the change was not clinically significant, and theophylline (0.011; 95% CI, −0.198 to 0.219) had no effect (Fig 4).

Adjusted AQLQ relative effect estimates are presented in Table E5 in this article's Online Repository at www.jacionline.org.

Results of sensitivity analyses were generally similar to the main analysis findings, although the statistical significance of some covariates included in the models changed. The consistency tests showed a disagreement between direct and indirect evidence for the ICS-placebo-LTRA and ICS-LABA-LTRA loops, indicating that covariate adjustment was justified. However, the exact level of significance at which to reject the null hypothesis was no longer .05 because the tested loops and therefore the consistency test were not independent.[19]

MTC of ACQ results

The ACQ was an end point in 11 of the 64 blinded RCTs. Fig 5 shows the ACQ network diagram; numbered lines indicate the number of studies included in the comparison (see Table E6 in this article's Online Repository at www.jacionline.org for more detailed information on the individual studies). Lower ACQ scores indicate better control of asthma symptoms, such that decreases from baseline are considered favorable.

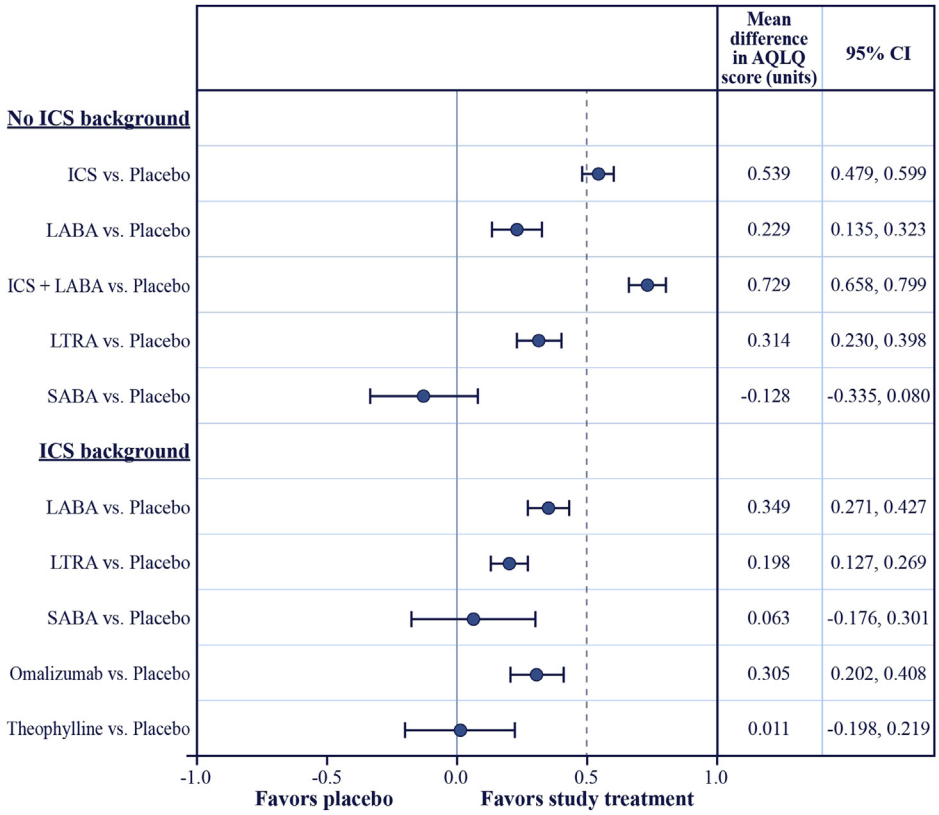

FIG 4. Differences in adjusted mean change from baseline in overall AQLQ score between treatments versus placebo. Values are presented for comparisons of active treatments with placebo in trials with the same design (ie, the same ICS background, the same run-in treatment, and the same AQLQ version). *SABA,* Short-acting β-agonist.

During the run-in period, all RCTs included ICS treatment; during the treatment phase, 7 (64%) RCTs had no background treatment, and 4 (36%) RCTs had ICS background treatment. Overall, 7 (64%) RCTs used the ACQ original version (ie, ACQ-7), and 4 (36%) RCTs used the ACQ, 5-item version. With the exception of study treatment, no statistically significant covariates were found for inclusion in the model.

Changes in ACQ scores from baseline (within-treatment comparisons)

Fig 6 presents the unadjusted least-squares means by treatment for the ACQ overall score change from baseline. No studies showed clinically significant changes in ACQ scores. The effects on ACQ least-squares mean changes from baseline were "probably clinically significant" (see the Results section in this article's Online Repository for details)[18] only for the ICS plus LABA pooled treatment group (−0.625; 95% CI, −0.767 to −0.482).

Comparisons between treatments

Fig 7 and Table E7 in this article's Online Repository at www.jacionline.org present the unadjusted relative treatment effects of ACQ overall score change from baseline versus placebo. None of the pooled treatment groups had effects on ACQ score mean change that exceeded the MID in comparison with placebo change from baseline. Mean reductions in ACQ scores ranged from −0.102 (95% CI, −0.306 to 0.101) for the addition of theophylline to −0.364 (95% CI, −0.471 to −0.257) for the comparison of LABA plus ICS with ICS alone (Fig 7). Thus all estimates revealed either no effect or no clinically significant effect. Results of the sensitivity analyses were similar to those of the main analysis. The results of these analyses should be interpreted with caution because of the small sample size and because no covariate adjustments could be made.

DISCUSSION

Our study provides several important insights into the performance of the AQLQ and ACQ in clinical trials in patients with asthma. First, it confirms that most established asthma therapies achieve a clinically significant improvement in the mean AQLQ score change when compared with baseline values. Second, it confirms that for all active asthma treatments, the placebo effect is greatest when there is no run-in period and when no controller is permitted as concurrent medication during the study period. Third, improvements in AQLQ score in placebo arms are also high in studies when ICSs are used during the run-in period. Thus not surprisingly, compared with placebo treatment arms, only groups receiving ICS plus LABA achieve a clinically significant change, and in our analysis the improvement with ICS achieved only a probably clinically significant level. Finally, when a second controller is added to ICS treatment (ie, in comparisons of placebo vs controller added to patients receiving

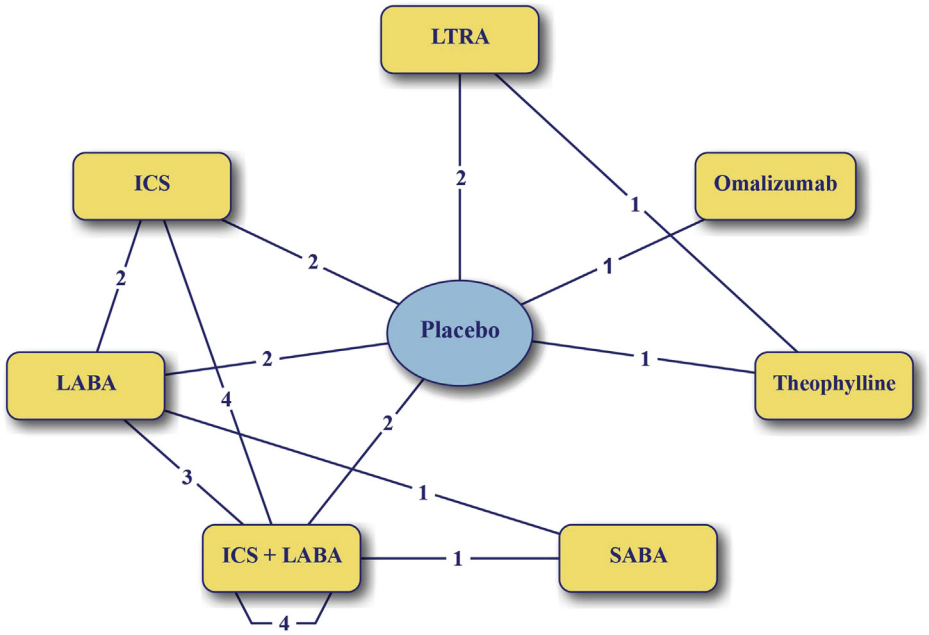

FIG 5. ACQ network of evidence. Numbers indicate the number of studies with comparisons of ACQ score changes between treatments (which could include different drugs in the same class) or different drugs in the same class in RCTs of patients with asthma. See Table E6 in this article's Online Repository for a list of studies included in this network. *SABA*, Short-acting β-agonist.

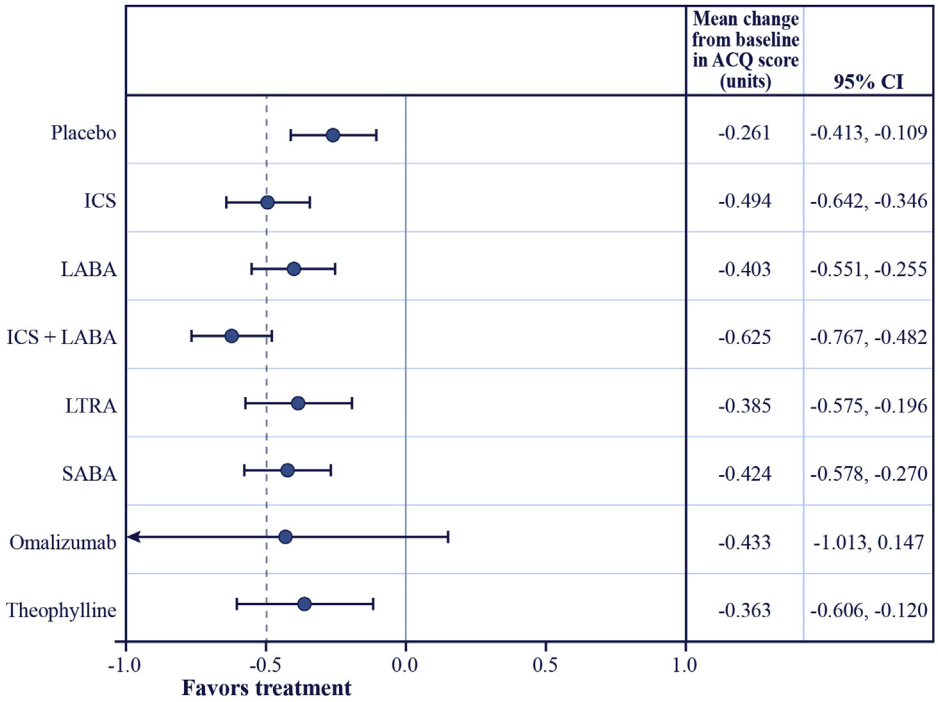

FIG 6. Adjusted mean change from baseline in overall ACQ score. *SABA*, Short-acting β-agonist.

ICSs during the active treatment phase), none of the comparators achieve a clinically significant or even a probably clinically significant result.

The results of our analysis of the ACQ are in line with those for the AQLQ, with none of the differences from placebo exceeding the MID and ICS-based treatments showing the greatest effect. However, this conclusion should be interpreted with caution because of the smaller number of studies suitable for analysis.

This study has several limitations. Reports of trials do not present score values in a consistent manner, and baseline score values were available for only three quarters of the trials. SEs had

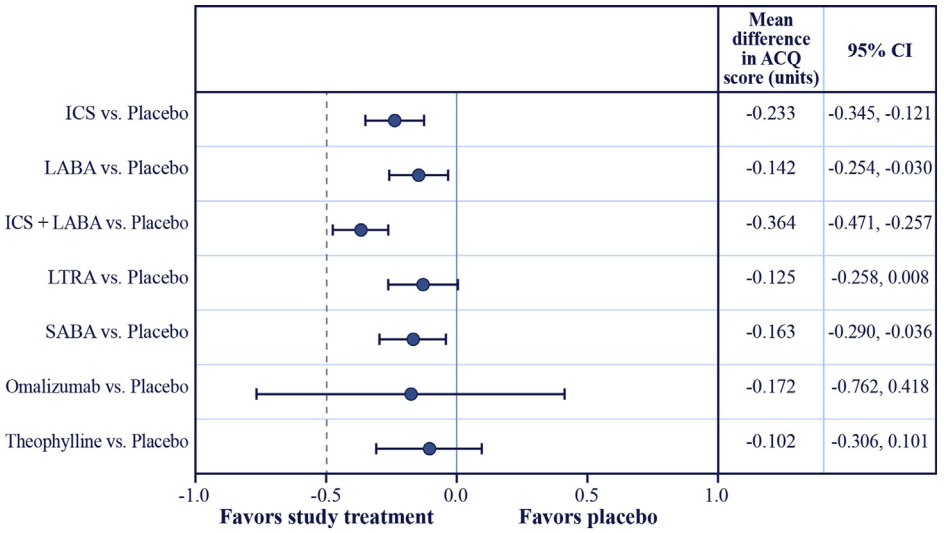

FIG 7. Differences in adjusted mean change from baseline in overall ACQ score between treatments versus placebo. *SABA,* Short-acting β-agonist.

to be derived for more than one half of the trials. Several variables (eg, FEV_1 and baseline AQLQ score) could not be used as covariates in the MTC model because of missing values.

Surprisingly, few studies with the ACQ instrument were found in the literature. In fact, only 1 double-blind RCT of omalizumab using the ACQ instrument met our inclusion criteria.[22] This might be explained by a reporting bias (ie, underreporting of negative trial results).

A strength of our study was our attempt to include all reports containing usable data. Moreover, the inclusion of data for most accepted controller treatments for asthma provided the opportunity to compare the results of PROs with the accepted general efficacy of different classes of treatment. In general, the relative effects of treatments on AQLQ and ACQ responses were consistent with their place in treatment guidelines.

The results raise several questions regarding use of these widely accepted instruments in clinical studies of asthma. Both have been developed and validated by using standard methodologies and fulfill the characteristics of an evaluative instrument.[2,5,6,10] The size (0.5 units) of the MID might be questioned. However, the finding that a 0.5-point change on a 7-point scale is the smallest change that patients can reliably report has been observed with other PROs, such as the Chronic Respiratory Disease Questionnaire.[5,18,23] Thus it is rather a limitation and threshold of subjective perception of change than a weakness of the test and appears to be appropriate for within-subject changes. What is in question is the use of the MID for comparisons between patients or groups of patients. Although group mean improvements greater than 0.5 might be highly desirable, our analysis confirms that this is achieved only with a favorable trial design that minimizes the placebo effect and compares ICS or ICS plus LABA with placebo. The prospect of demonstrating a mean incremental benefit of greater than 0.5 through addition of a second or third controller in addition to an ICS, other controllers, or both appears remote. In these trials the Hawthorne effect[24] might be particularly pronounced because improved adherence with background treatment can result in improvements in all outcomes from baseline and a reduced opportunity to demonstrate benefit of the new treatment.

Faced with this limitation, how is the benefit of new treatments, particularly treatments that are added to a first- or second-line controller, to be quantified? Guyatt et al[7] advised that even small mean differences between treatment and control might have an important effect on patients and that the method for establishing this proportion is a continuous variable suitable for analysis. The value of the change to the patients who benefit and to society or the payer is a different consideration.

The results of our study lend support to the view that these PROs should be presented in a different way, first as a comparison of responder rates or as a net treatment benefit analysis (number of responders less those who deteriorated on the treatment) from which numbers needed to treat can be calculated. Treatment comparisons can be further expressed as a "minimum worthwhile incremental advantage," which was defined by Jones et al[23] as the percentage of patients in a treated population who experience improvement at or greater than the MID, which is considered a worthwhile benefit for the intervention.

Several factors need to be considered in arriving at a minimum worthwhile incremental advantage. A first consideration is patient need. The minimum worthwhile incremental advantage might be small in patients with severe disease (eg, asthma with frequent exacerbations, some of which might be life-threatening) in whom any benefit can be considered worthwhile. Consensus among doctors and discussion with patients can be used to test the value proposition. Considerations of adverse effects and cost to patients and society might also be relevant. For subjective outcomes, discrete-choice modeling techniques might assist in this decision.[25,26]

Our study highlights the importance of clinical study design if the difference between treatments is under study. It is essential to use methods that reduce the placebo effect seen in patients receiving an ICS as background treatment during clinical trials. These include ensuring clinical stability of asthma control during baseline, longer run-in periods (≥4 weeks), avoidance of changes in medications for extended periods before and during the run-in period, and rigorous assessment of treatment adherence before and after randomization. The use of an electronic dose-monitoring device might be of value in assessing

patient behavior and adherence during run-in and treatment phases.[27] This is of increasing importance in assessing the utility of more expensive treatments in development for severe asthma.

Initiatives such as the Critical Path Institute, which aims to develop new PRO tools for use in asthma research, may lead to instruments that are more responsive to complex interventions,[28] but the threshold for the subjective perception of change might remain a limiting factor.

In conclusion, this network analysis of the magnitude of AQLQ and ACQ responses achieved with commonly used controllers for the treatment of persistent asthma confirms that for most treatments, particularly when controllers are combined, the mean difference between treatment groups exceeding the MID is probably not achievable. Future research should focus on responder analyses and consider an individualized approach based on the value of the invention for those who respond and secondarily for society.

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Clinical implications: When compared with placebo, only an ICS, with or without a LABA, achieved the MID. A responder analysis might be more appropriate for expressing the clinical benefit of add-on treatments in patients with asthma.

REFERENCES

1. Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. Revised 2014. Available at: http://www.ginasthma.org/local/uploads/files/GINA_Report_2014_Aug12.pdf. Accessed September 16, 2014.
2. 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;14:902-7.
3. Barnes PJ, Casale TB, Dahl R, Pavord ID, Wechsler ME. The Asthma Control Questionnaire as a clinical trial endpoint: past experience and recommendations for future use. Allergy 2014;69:1119-40.
4. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax 1992;47:76-83.
5. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life instrument. J Clin Epidemiol 1994;47:81-7.
6. Juniper EF, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med 2005;99:553-8.
7. Guyatt GH, Juniper EF, Walter SD, Griffith LE, Goldstein RS. Interpreting treatment effects in randomised trials. BMJ 1998;316:690-3.
8. Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. Ann Intern Med 2011;154:573-82.
9. Kerstjens HA, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, et al. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med 2012;367:1198-207.
10. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. Chest 1999;115:1265-70.
11. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. Eur Respir J 1999;14:32-8.
12. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. J Clin Epidemiol 2008;61:102-9.
13. King MT. A point of minimal important difference (MID): a critique of terminology and methods. Expert Rev Pharmacoecon Outcomes Res 2011;11:171-84.
14. National Institute for Health and Care Excellence. Single technology appraisal. Specification for manufacturer/sponsor submission of evidence; June 2012. Available at: http://www.nice.org.uk/aboutnice/howwework/devnicetech/SpecificationForManufacturerSponsorSubmissionOfEvidence.jsp?domedia=1&mid=97E2DC4419B9-E0B5-D4F73F1DB153AA86. Accessed August 12, 2012.
15. Centre for Reviews and Dissemination. Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination; 2008. Available at:http://www.york.ac.uk/inst/crd/pdf/Systematic_Reviews.pdf. Accessed September 4, 2012.
16. Nixon RM, Bansback N, Brennan A. Using mixed treatment comparisons and meta-regression to perform indirect comparisons to estimate efficacy of biologic treatments in rheumatoid arthritis. Stat Med 2007;26:1237-54.
17. Lu G, Ades AE. Assessing evidence inconsistency in mixed treatment comparisons. J Am Stat Assoc 2006;101:447-59.
18. Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. Eur Respir J 2002;19:398-404.
19. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. Evidence synthesis for decision making 4: inconsistency in networks of evidence based on randomized controlled trials. Med Decis Making 2013;33:641.
20. Salanti G, Marinho V, Higgins JP. A case study of multiple-treatments meta-analysis demonstrates that covariates should be considered. J Clin Epidemiol 2009;62:857-64.
21. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997;50:683-91.
22. Garcia G, Magnan A, Chiron R, Contin-Bordes C, Berger P, Taillé C, et al. A proof of concept randomized-controlled trial of omalizumab in patients with severe difficult to control nonatopic asthma. Chest 2013;144:411-9.
23. Jones PW, Beeh KM, Chapman KR, Decramer M, Mahler DA, Wedzicha JA. Minimal clinically important differences in pharmacological trials. Am J Respir Crit Care Med 2014;189:250-5.
24. Braunholtz DA, Edwards SJL, Lilford RJ. Are randomized clinical trials good for us (in the short term)? Evidence for a "trial effect". J Clin Epidemiol 2001;54:217-24.
25. McKenzie L, Cairns J, Osman L. Symptom-based outcome measures for asthma: the use of discrete choice methods to assess patient preferences. Health Policy 2001;57:193-204.
26. King MT, Hall J, Lancsar E, Fiebig D, Hossain I, Louviere J, et al. Patient preferences for managing asthma: results from a discrete choice experiment. Health Econ 2007;16:703-17.
27. Patel M, Pilcher J, Travers J, Perrin K, Shaw D, Black P, et al. Use of metered-dose inhaler electronic monitoring in a real-world asthma randomized controlled trial. J Allergy Clin Immunol Pract 2013;1:83-91.
28. Coons SJ, Kothari S, Monz BU, Burke LB. The patient-reported outcome (PRO) consortium: filling measurement gaps for PRO end points to support labeling claims. Clin Pharmacol Ther 2011;90:743-8.