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Systematic Review and Meta-Analysis of the Magnitude of the Effect on the AQLQ and ACQ in Asthma Clinical Trials

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BACKGROUND

- There is increasing interest in combining treatments to address unmet needs in moderate and severe asthma. New treatment modalities, such as tiotropium, biologicals, and bronchial thermoplasty, are being added to current treatments. Selecting appropriate endpoints for studies of add-on treatments is challenging.
- Many health authorities require evidence of benefit in patient-reported outcomes for the registration and positioning of new treatments. These include health-related quality of life (often measured using the Asthma Quality of Life Questionnaire [AQLQ]) and asthma control (often measured using the Asthma Control Questionnaire [ACQ]).
- Both the AQLQ and ACQ were developed and validated in patients with asthma, most of whom were either steroid-naïve or receiving inhaled corticosteroids (ICS) alone as controller.
- We examined the magnitude of effect observed in clinical trials of different treatments with the AQLQ and ACQ and, specifically, the appropriateness (achievability) of the accepted minimum important difference (MID) of 0.5 in studies in which additional controllers were added to ICS treatment.

METHODS

- A systematic literature search was conducted using PubMed, Embase, the National Health Service Economic Evaluation Database (NHS EED), conference websites, and the study register clinicaltrials.gov.
- Double-blinded randomized controlled trials (RCTs) of adolescent and adult patients with uncontrolled or symptomatic asthma at baseline were included if they reported overall score change from baseline values for the AQLQ and/or ACQ after receiving one or more of the following treatments: ICS, long-acting beta-agonists (LABA), leukotriene antagonists (LTRA), short-acting beta-agonists (SABA), omalizumab, theophylline.
- For each instrument, a mixed treatment comparison (MTC), combined with meta-regression, was performed using direct and indirect evidence from a network diagram of evidence in which treatments from the clinical trials that compared them were connected.
- Linear mixed models with trials as random effects were constructed using the PROC MIXED procedure in SAS (version 9.3, SAS Institute Cary, NC) and used to estimate adjusted least squares means and adjusted mean differences between any two treatments. The inverse of the standard error (SE) of mean change from baseline in the instrument was used as a weighting variable in the MTC model.
- To address heterogeneity and reduce inconsistency between treatment comparisons, a number of covariates were assessed for inclusion in the MTC model.

RESULTS

Systematic Literature Review

- Of the initial 4,533 unique records identified from searching PubMed, NHS EED, and Embase databases and the 482 records identified from conference websites, 500 studies were selected for full-text review.
- Sixty studies reporting on 64 double-blinded RCTs (42,527 patients) met the inclusion criteria and were included in MTC models.

Baseline Characteristics of Included Studies

Table 1. Summary of Baseline Characteristics of Double-Blinded RCTs

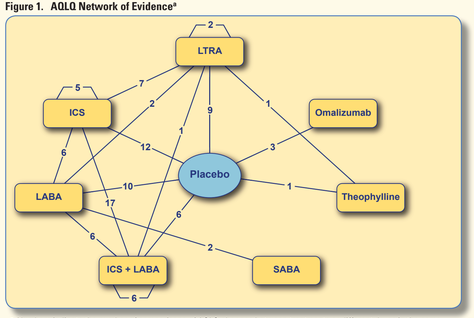
Treatments	Number of Studies	Pooled Number of Patients	Mean Age (Years)	Mean BMI	Reversibility (%)	Female (%)	White (%)	Never Smoked (%)	Baseline Mean FEV1(L)
ICS	33	8,525	40.3	26.6	23.0	59.0	77.0	80.9	2.32
LABA	17	4,811	40.2		22.0	57.8	81.6		2.31
ICS + LABA	25	14,988	41.2	27.7	23.6	60.2	54.9	81.6	2.21
LTRA	19	5,336	37.5		17.8	56.6	78.3	74.4	2.43
SABA	5	1,763	41.6		23.3	59.1			2.18
Omalizumab	6	1,407	41.5		24.6	58.5	80.4	76.2	2.58
Theophylline	1	161	41.0			75.0	60.0		
Placebo	33	5,536	39.1		25.0	57.0	78.8	79.5	2.40
All treatments	65	42,527	40.2	26.7	22.9	58.8	73.5	80.3	2.3

BMI = body mass index; FEV1 = forced expiratory volume in 1 second.

AQLQ Model

- Data from 54 double-blinded RCTs and 8 treatments were included in the MTC model for the AQLQ (Figure 1). During the run-in period, 9 (17%) RCTs had no medication (or no run-in), 9 (17%) had placebo, and 35 (66%) had ICS; during the treatment period, 38 (72%) RCTs had no background treatment and 15 (28%) had ICS background treatment.

Figure 1. AQLQ Network of Evidence[a]



[a] Numbers indicate the number of comparisons of AQLQ changes between treatments or different drugs in the same class in RCTs of patients with asthma.

- Statistically significant ($P \leq 0.05$) covariates included in the MTC model for AQLQ (1) were: study treatment; whether ICS, placebo, or no medication was administered during the run-in period; whether study treatment was administered on top of an ICS background; AQLQ instrument type (original versus standardized versions); and interaction between study treatment and background:

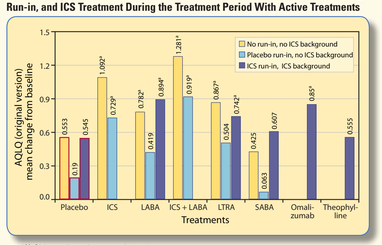
AQLQ change = study treatment + run-in + background + AQLQ type + study treatment*background (1)

- Figure 2 presents the estimated mean AQLQ changes from baseline until the time of the primary endpoint (positive mean change = improvement) assuming use of the original AQLQ for various combinations of run-in and background treatment.

AQLQ Model Findings

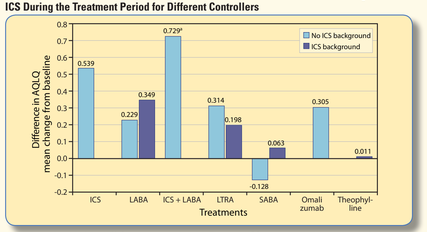
- The following trends were observed (numerical differences).
  - Improvements in AQLQ tended to be greatest and exceeded the MID in studies in which there was **no run-in period** (Figure 2).
  - A significant **placebo effect during treatment** (mean > 0.5) was observed when ICS were used during the run-in and treatment periods (Figure 2).
  - **After a placebo run-in**, the MID in the AQLQ was achieved by ICS, ICS + LABA, and LTRA. For LTRA, the lower bound of the 95% CI was less than 0.5. LABA alone and SABA alone did not achieve the MID (Figure 2).
  - **After a run-in with ICS and with ICS as background treatment**, the MID was achieved with all active treatments added (Figure 2).
  - The **comparison of active versus placebo treatments** in patients with and without background ICS, regardless of ICS treatment during run-in, and using the same AQLQ instrument (Figure 3) confirmed that **only the addition of ICS (alone or in combination with LABA) achieved the MID**. However, only for ICS + LABA treatment, the lower 95% CI was greater than 0.5.

Figure 2. Estimated Mean AQLQ Changes From Baseline to the Time of the Primary Endpoint According to the Presence of a Run-in Period, ICS Use During Run-in, and ICS Treatment During the Treatment Period With Active Treatments



[a] 95% CI lower bound greater than 0.5.
Note: Placebo is marked with a red border.

Figure 3. Estimated Mean AQLQ Changes Versus Placebo With or Without Background ICS During the Treatment Period for Different Controllers



[a] The lower bound of the 95% CI was greater than 0.5. The same ICS treatment during run-in and the same AQLQ instrument were used in both the active and placebo arms.

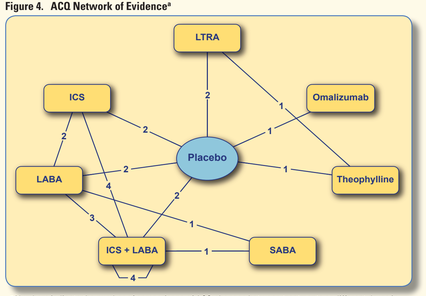
Other Findings

- The time point (period of assessment of change within the tested ranges) produced no significant and robust effect.
- The original AQLQ (which includes open questions) was associated with lower baseline values (corresponding to more impact) and a larger change from baseline than the standardized versions (AQLQ[S] and MiniAQLQ); however, overall treatment differences between groups based on the MTC model were similar.

ACQ Model

- Data from 11 double-blinded RCTs and eight treatments were included in the MTC model for ACQ (Figure 4). During the run-in period, all RCTs included ICS treatment, whereas, during the treatment period, seven (64%) RCTs had no background treatment, and four (36%) had ICS background treatment.

Figure 4. ACQ Network of Evidence[a]



[a] Numbers indicate the number of comparisons of ACQ changes between treatments or different drugs in the same class in RCTs of asthma patients.

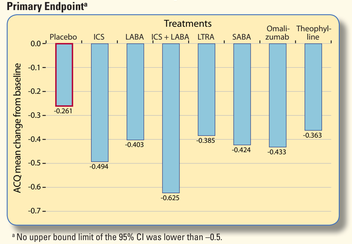
ACQ Model Findings

- With the exception of study treatment, no statistically significant ($P \leq 0.05$) covariates were found for inclusion in the model; therefore,

ACQ change = study treatment (2)

- Figure 5 presents estimated mean ACQ changes from baseline to the time of the primary endpoint (negative value = improved control) for patients on various study treatments. The mean ACQ changes from baseline were close to or above the MID for all treatments. However, no upper bound limit of the 95% CI was lower than –0.5.

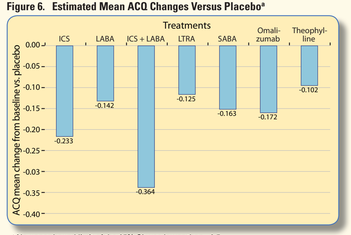
Figure 5. Estimated Mean ACQ Changes From Baseline to the Time of the Primary Endpoint[a]



[a] No upper bound limit of the 95% CI was lower than –0.5.
Note: Placebo is marked with a red border.

- Figure 6 presents estimated treatment effects versus placebo for patients on various study treatments. Compared with placebo, the treatment effect on ACQ was below the MID in all the treatments.

Figure 6. Estimated Mean ACQ Changes Versus Placebo[a]



[a] No upper bound limit of the 95% CI was lower than –0.5.

CONCLUSIONS

- In clinical studies of most established asthma therapies, the mean AQLQ expressed as change from baseline achieves the MID.
- However, when compared with placebo treatment, only groups receiving ICS with or without LABA achieve the MID (although the lower limit of the 95% CI was above 0.5 only in the ICS + LABA group).
- The magnitude of AQLQ score changes was sensitive to trial design factors, such as the presence of a run-in, treatment during the run-in, background (concurrent) treatment, and type of instrument used (original vs. shortened forms of the AQLQ).
- Use of ICS during run-in and as background is associated with a marked placebo effect, and may reduce the likelihood of demonstrating benefit of add-on treatments. This may reflect lack of adherence prior to randomization.
- The ACQ results were largely in line with those for the AQLQ, but should be interpreted with caution due to the small number of studies suitable for analysis.
- Implications for use of the AQLQ and ACQ in clinical trials of combination treatments include the following:
  - Re-evaluate the MID for the AQLQ and ACQ, when used in trials of more than one controller.
  - Consider other more responsive outcomes relevant to patients with severe asthma who require combinations of controller treatment (e.g., for asthma exacerbations) as primary outcomes for studies of new add-on treatments.
  - Improve methods for reducing the placebo effect observed in patients receiving ICS during clinical trials.

DISCLOSURE

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