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Dear Colleague,

We are pleased to share with you the full manuscript for ***Leukotriene Antagonists as First-Line or Add-on Asthma-Controller Therapy***, published on 5 May 2011 in the **New England Journal of Medicine**. This study, led by the University of East Anglia (UEA) has received vast amount of interest from medical communities as well as the media in the UK and beyond.

Leukotriene Antagonists as First-Line or Add-on Asthma-Controller Therapy

David Price, F.R.C.G.P., Stanley D. Musgrave, M.D., Lee Shepstone, Ph.D., Elizabeth V. Hillyer, D.V.M., Erika J. Sims, Ph.D., Richard F.T. Gilbert, M.R.C.G.P., Elizabeth F. Juniper, M.C.S.P., M.Sc., Jon G. Ayres, M.D., Linda Kemp, B.Sc., Annie Blyth, M.A., Edward C.F. Wilson, M.Sc., Stephanie Wolfe, M.Sc., R.G.N., Daryl Freeman, M.R.C.G.P., H. Miranda Mugford, Ph.D., Jamie Murdoch, Ph.D., and Ian Harvey, F.R.C.P.

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Department of Health Disclaimer: The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Department of Health.

Yours sincerely,

David Price

Lead author, Professor David Price of the University of Aberdeen and University of East Anglia, on behalf of the study authors

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ABSTRACT

BACKGROUND

Most randomized trials of treatment for asthma study highly selected patients under idealized conditions.

METHODS

We conducted two parallel, multicenter, pragmatic trials to evaluate the real-world effectiveness of a leukotriene-receptor antagonist (LTRA) as compared with either an inhaled glucocorticoid for first-line asthma-controller therapy or a long-acting beta$_2$-agonist (LABA) as add-on therapy in patients already receiving inhaled glucocorticoid therapy. Eligible primary care patients 12 to 80 years of age had impaired asthma-related quality of life (Mini Asthma Quality of Life Questionnaire [MiniAQLQ] score ≤6) or inadequate asthma control (Asthma Control Questionnaire [ACQ] score ≥1). We randomly assigned patients to 2 years of open-label therapy, under the care of their usual physician, with LTRA (148 patients) or an inhaled glucocorticoid (158 patients) in the first-line controller therapy trial and LTRA (170 patients) or LABA (182 patients) added to an inhaled glucocorticoid in the add-on therapy trial.

RESULTS

Mean MiniAQLQ scores increased by 0.8 to 1.0 point over a period of 2 years in both trials. At 2 months, differences in the MiniAQLQ scores between the two treatment groups met our definition of equivalence (95% confidence interval [CI] for an adjusted mean difference, −0.3 to 0.3). At 2 years, mean MiniAQLQ scores approached equivalence, with an adjusted mean difference between treatment groups of −0.11 (95% CI, −0.35 to 0.13) in the first-line controller therapy trial and of −0.11 (95% CI, −0.32 to 0.11) in the add-on therapy trial. Exacerbation rates and ACQ scores did not differ significantly between the two groups.

CONCLUSIONS

Study results at 2 months suggest that LTRA was equivalent to an inhaled glucocorticoid as first-line controller therapy and to LABA as add-on therapy for diverse primary care patients. Equivalence was not proved at 2 years. The interpretation of results of pragmatic research may be limited by the crossover between treatment groups and lack of a placebo group. (Funded by the National Coordinating Centre for Health Technology Assessment U.K. and others; Controlled Clinical Trials number, ISRCTN99132811.)

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Results of double-blind, randomized, controlled trials provide, appropriately, the bedrock of evidence in determining the efficacy of therapeutic interventions. Proof of efficacy in the trial setting of optimized adherence and follow-up for selective patient populations does not, however, guarantee that a particular therapy will be effective in the diverse patient populations seen in clinical practice.[1-3] In the case of asthma, for example, the eligibility criteria in most such trials exclude an estimated 95% of patients with a current diagnosis of asthma, including smokers and those who have "insufficient" bronchodilator reversibility or impaired pulmonary function.[4,5] Moreover, the design of such trials rarely accounts for the long-term factors that clinicians must consider, such as adherence, inhaler technique, tolerability, and physician and patient preferences.[4-6]

Although the results of observational research and pragmatic trials can complement those of classic randomized, controlled trials, they must be interpreted carefully.[1,3,7] In particular, the very features of pragmatic trials that support the generalizability, or applicability, of their results to real-world practice may also reduce assay sensitivity and therefore limit the interpretation of results.[7,8] These features include heterogeneous patient populations, a lack of blinding, the absence of a placebo group, and adherence to therapy that is often less than optimal.

Asthma treatment guidelines recommend inhaled glucocorticoids as the first-line controller medication for asthma control in patients with mild persistent asthma.[9,10] These agents have little effect on the formation or action of cysteinyl leukotrienes, inflammatory mediators in asthma.[11] Leukotriene-receptor antagonists (LTRAs) have proved to be beneficial in double-blind, randomized, placebo-controlled trials.[12-14] Results of prior comparisons of LTRA and inhaled glucocorticoids, mostly double-blind, randomized, controlled trials, have been mixed, with some suggesting that LTRAs are less efficacious than inhaled glucocorticoids for patients with mild persistent asthma,[14-17] and others reporting similar overall asthma control and proportions of patients meeting asthma-control criteria.[18-20] For patients whose symptoms are not controlled with low-dose inhaled glucocorticoids, step-up therapy consists of an increased dose or the addition of LTRA or an inhaled long-acting beta$_2$-agonist (LABA).[9,10] Results of randomized clinical trials indicate generally better improvements in lung function and symptoms and a reduction in the need for a short-acting bronchodilator with step-up therapy consisting of add-on LABA, as compared with add-on LTRA.[21,22] However, results of long-term trials (48 weeks) suggest that clinical outcomes such as exacerbations, hospitalizations, and rates of emergency treatment are similar with the two types of add-on therapy.[23]

This study, commissioned and predominantly funded by the U.K. Health Technology Assessment Programme, comprised two separate, 2-year pragmatic trials designed to evaluate the effectiveness of LTRA for primary care patients receiving asthma therapy under real-world conditions. One trial compared LTRA and inhaled glucocorticoids for patients in whom asthma-controller therapy was being initiated (first-line controller therapy trial), and the second compared LTRA and LABA as add-on therapy for patients with uncontrolled asthma while they were receiving inhaled glucocorticoids (add-on therapy trial). We hypothesized that initiating treatment with an LTRA or adding it to ongoing glucocorticoid therapy would lead to clinical improvements in asthma-related quality of life, a patient-oriented measure of effectiveness,[9,24,25] that would be equivalent to those with the alternative treatment options studied.

Methods

The study protocol and a detailed description of study methods are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. The trials were conducted in parallel, and the study procedures were similar in the two trials. Both trials were conducted in accordance with the protocol.

The primary funder and sponsor (National Coordinating Centre for Health Technology Assessment U.K.) provided input with regard to the study design through its commissioning and monitoring brief but played no role in data collection, analysis, or interpretation; the writing of the article; or the decision to submit the article for publication. The pharmaceutical-industry funders had no role in any aspect of the study. Patients were responsible for obtaining their own medications, as would occur in real life.

STUDY PATIENTS

The two trials, which were conducted at 53 primary care practices in the United Kingdom, enrolled patients 12 to 80 years of age with a physician's diagnosis of asthma. In the first-line controller therapy trial, eligible patients had asthma symptoms deemed by their physician to require initiation of asthma-controller therapy. In the add-on therapy trial, eligible patients had received an inhaled glucocorticoid for at least 12 weeks and had symptoms requiring an increase in therapy. Other eligibility criteria for both trials included, at screening, a peak expiratory flow (PEF) greater than 50% of the predicted value after an inhaled beta$_2$-agonist had been withheld for 4 hours or longer and, at the baseline visit, evidence of impaired asthma-related quality of life (a score ≤6 on the Mini Asthma Quality of Life Questionnaire[25,26] [MiniAQLQ]) or impaired asthma control (a score ≥1 on the Asthma Control Questionnaire[27] [ACQ]). The validated 15-item MiniAQLQ is scored from 1 to 7, with higher scores indicating less impairment and a minimal clinically important difference (MID) of 0.5.[25,26] We used a validated, shortened version of the ACQ (excluding percent of predicted normal forced expiratory volume in one second but including short-acting bronchodilator use), on which scores range from 0 to 6, with higher scores indicating worse asthma control and an MID of 0.5.[27] Main exclusion criteria were prior treatment within 12 weeks with an inhaled glucocorticoid or LTRA (in the first-line controller therapy trial) or LTRA or LABA (in the add-on therapy trial).

The study protocol was reviewed and approved by the Eastern Multi Centre Research ethics committee and local ethics and research governance committees. All patients (and parents or guardians of patients under 16 years of age) gave written informed consent.

STUDY PROCEDURES

Patients who met the eligibility criteria completed a validated asthma-symptom diary[28] for 2 weeks before the baseline visit for an assessment of PEF variability and to record current symptoms. After the screening visit (week –2) and baseline visit (week 0), study assessments by telephone or in the clinic were scheduled at months 2, 6, 12, 18, and 24.

An automated, computerized telephone center randomly assigned eligible patients at baseline to open-label treatment with either an LTRA (montelukast or zafirlukast) or an inhaled glucocorticoid (beclomethasone, budesonide, or fluticasone) in the first-line controller therapy trial and with either an LTRA or LABA (salmeterol or formoterol) together with an inhaled glucocorticoid in the add-on therapy trial. Randomization was stratified by practice, with a block size of 6.

Clinical and lung-function data were recorded by clinic staff who were aware of the treatment assignments. Data collection and statistical analyses were performed by study personnel who were unaware of the treatment assignments; questionnaire-based data were collected under blinded conditions, and routine practice data (including a history of exacerbations) were extracted with the use of dedicated software.

Practice staffs were asked to provide each patient with a written individualized asthma-action plan. For each of the assigned treatments, choices of individual drugs and devices were made according to normal clinical practice and British asthma guidelines.[29] The protocol discouraged substantial treatment changes between randomization and the 2-month visit. If a patient required a disallowed asthma medication, this fact was noted, and the patient remained in the study. Patients who withdrew from the study continued to receive care from their usual clinician.

OUTCOME MEASURES

The primary outcome measure was the MiniAQLQ score.[25,26] Secondary outcome measures included the ACQ score[27]; the score on the not-yet-validated Royal College of Physicians 3-item asthma questionnaire (RCP3) (range of scores, 0 to 3, with higher scores indicating worse asthma control)[30]; the score on the validated 14-item Mini Rhinoconjunctivitis Quality of Life Questionnaire (MiniRQLQ) (range of scores, 0 to 6, with higher scores indicating worse rhinitis-related impairment and with an MID of 0.7)[31]; and the frequency of asthma exacerbations, which were defined as the need for an oral course of glucocorticoids or hospitalization for asthma.

STATISTICAL ANALYSIS

The primary effectiveness analysis was an intention-to-treat analysis of the MiniAQLQ score at 2 months (the primary time point) and at 2 years. Analysis of covariance was used, with treatment

as a fixed effect and the baseline value as a covariate. A 95% confidence interval (CI) was derived for the adjusted difference between mean scores. The study was powered for equivalence in the MiniAQLQ score, with the equivalence boundary set at a 95% CI of less than 0.3 for the MiniAQLQ score (i.e., equivalence was declared if the 95% CI was wholly included between −0.3 and 0.3). This difference reflects our use of an a priori conservative approach (0.3 is substantially lower than the MID of 0.5 for the MiniAQLQ[26]) because of uncertainty about its variability in real-world patients. Multiple imputation was used where data were missing.[32] The same analytic approach was used for the ACQ score, although the statistical analysis of the ACQ score, as for the other secondary end points, was for superiority rather than equivalence.

We determined adherence on the basis of prescriptions issued versus prescribing instructions for patients with at least 6 months without a change in therapy. We compared median adherence between treatment groups using the Mann–Whitney test, capping adherence at 100%, since adherence exceeded 100% in some cases. We also performed four predefined subgroup analyses of the MiniAQLQ and ACQ scores at 2 months, comparing results according to status with respect to smoking (current smokers vs. nonsmokers), baseline PEF (<80% vs. ≥80% of the predicted value), rhinitis versus no rhinitis, and baseline PEF reversibility (<15% vs. ≥15%).

We performed a post hoc per-protocol analysis of the MiniAQLQ and ACQ scores that included patients with data at the relevant time point (i.e., 2 months or 2 years) who had no change in the randomly assigned treatment class and no additional therapy. The predefined, stricter per-protocol analysis included patients with no change, however minor, in therapy after randomization. All analyses were carried out with the use of SAS, version 9.1, and SPSS, version 17.0, statistical software.

Sample-size calculations were based on published results for assessing the effects of treatment differences on the MiniAQLQ score, with a between-subject standard deviation of 0.78,[25,33] and were made with the use of nQuery Advisor, version 6.0 (Statistical Solutions). A sample of 178 participants was required for this equivalence study to allow for a 20% dropout rate and assuming no true difference between treatments in quality of life at a two-tailed alpha level of 0.05 and with a power of 90% to declare equivalence.

RESULTS

ENROLLMENT

Study enrollment is shown in Figures E1 and E2 in the Supplementary Appendix; additional results are detailed in Tables E1 through E28 in the Supplementary Appendix. In both trials, the reason for most exclusions after randomization was a missing MiniAQLQ or ACQ score or a baseline score that was not within the specified range for eligibility.

FIRST-LINE CONTROLLER THERAPY TRIAL

Patients

Of 326 patients randomly assigned to a study treatment, 20 were excluded after randomization; thus, 306 (94%) met all study criteria, and 300 (92%) were included in the intention-to-treat analyses (Fig. E1 in the Supplementary Appendix). There were no clinically important differences between the two treatment groups at baseline (Table 1). Scores for both the MiniAQLQ and the ACQ were available within 3 months before the end of the study for 284 of the 300 patients (95%).

Outcome Measures

Mean MiniAQLQ scores in the two treatment groups were equivalent at 2 months (Table 2 and Fig. 1). At 2 years, the 95% CI for the adjusted difference in the MiniAQLQ score was outside our equivalence limit of 0.3 (Table 2). There were no significant differences between treatment groups at 2 months or 2 years with respect to the ACQ score or any of the other secondary outcome measures (Tables 2 and 3, and Table E1 in the Supplementary Appendix), including the MiniAQLQ domain scores (Table E2 in the Supplementary Appendix). Rescue bronchodilator use, as reflected in patients' answers to question 6 of the ACQ, fell during the study and was similar in both treatment groups (Table E3 in the Supplementary Appendix).

At 2 months, 8 of the 145 patients (6%) in the LTRA group and 5 of the 155 patients (3%) in the inhaled-glucocorticoid group had some modification in the randomly assigned treatment; at 2 years, a change in drug class or the addition of therapy was recorded for 45 patients (31%) in the LTRA group and 32 (21%) in the inhaled-glucocorticoid group (Table 4). The median rate

Table 1. Baseline Characteristics of the Patients with Asthma.*

Characteristic	First-Line Controller Therapy Trial		Add-on Therapy Trial	
	LTRA (N=148)	Inhaled Glucocorticoid (N=158)	LTRA (N=170)	LABA (N=182)
Mean age — yr	47.6±16.5	44.1±16.4	51.0±16.0	49.7±16.1
Age group — no. of patients (%)				
<16 yr	1 (1)	4 (3)	0	0
16–25 yr	17 (12)	17 (11)	12 (7)	17 (9)
26–35 yr	22 (15)	30 (19)	24 (14)	31 (17)
36–45 yr	27 (18)	34 (22)	30 (18)	25 (14)
46–55 yr	30 (20)	33 (21)	32 (19)	39 (21)
56–65 yr	28 (19)	22 (14)	35 (21)	38 (21)
≥66 yr	23 (16)	18 (11)	37 (22)	32 (18)
Female sex — no. of patients (%)	73 (49)	83 (53)	109 (64)	111 (61)
Race — no. of patients (%)†				
White	144 (97)	153 (97)	168 (99)	178 (98)
Other or not known	4 (3)	5 (3)	2 (1)	4 (2)
Smoking status — no. of patients/total no. (%)				
Current smoker	37/147 (25)	30/155 (19)	29/168 (17)	31/180 (17)
Former smoker	54/147 (37)	54/155 (35)	63/168 (38)	75/180 (42)
Never smoked	56/147 (38)	71/155 (46)	76/168 (45)	74/180 (41)
Current smoker >45 yr of age	15/147 (10)	11/155 (7)	16/168 (10)	16/180 (9)
Peak-expiratory-flow reversibility — % (no. of patients tested)	9.2±10.7 (128)	8.7±9.2 (142)	9.0±10.1 (163)	8.3±9.6 (170)
Time since asthma diagnosis — yr				
Median	8.5	10	11	11
Interquartile range	3–19	4–16.5	5–22.5	6–21
Assigned therapy — no. of patients/total no. (%)				
Montelukast	127/143 (89)		158/166 (95)	
Zafirlukast	16/143 (11)		8/166 (5)	
Beclomethasone		146/157 (93)		
Budesonide		8/157 (5)		
Fluticasone		3/157 (2)		
Salmeterol				167/181 (92)‡
Formoterol				14/181 (8)‡
Dose of glucocorticoid — μg/day (no. of patients)§			425±351 (170)	451±390 (182)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. Patients in the add-on therapy trial were already receiving an inhaled glucocorticoid. LABA denotes long-acting beta$_2$-agonist, and LTRA leukotriene-receptor antagonist.
† Race was reported by the examiner.
‡ In 18 patients given salmeterol and in 5 patients given formoterol, these drugs were given in fixed-dose combinations with an inhaled glucocorticoid.
§ The doses of glucocorticoids were standardized to equivalence with the dose of chlorofluorocarbon–beclomethasone, with doses converted as necessary in the following ratios relative to chlorofluorocarbon–beclomethasone: budesonide, 1:1; fluticasone propionate, 2:1; beclomethasone in solution, 2:1; and mometasone, 2:1.

of adherence to therapy was higher with LTRA than with the inhaled glucocorticoid, but not significantly so (Table 3).

The post hoc per-protocol results approached but did not meet equivalence for the effect on the MiniAQLQ score at 2 months and 2 years (Table 2). ACQ scores did not differ significantly between the LTRA and inhaled-glucocorticoid

Table 2. Scores on the MiniAQLQ and ACQ at 2 Months and 2 Years in the Intention-to-Treat and Per-Protocol Populations.*

Outcome Measure	Treatment Group				Mean Difference (95% CI)	Adjusted Mean Difference (95% CI)†
	LTRA		Inhaled Glucocorticoid		LTRA vs. Inhaled Glucocorticoid	LTRA vs. Inhaled Glucocorticoid
	no. of patients tested	*mean score*	*no. of patients tested*	*mean score*		
First-line controller therapy trial						
ITT MiniAQLQ						
At baseline	148	4.75±0.92	158	4.72±0.95		
At 2 mo	122	5.25±1.03	132	5.28±1.10	0.00 (–0.25 to 0.26)	–0.02 (–0.24 to 0.20)
At 2 yr‡	145	5.52±1.07	155	5.63±1.16	–0.10 (–0.35 to 0.17)	–0.11 (–0.35 to 0.13)
PP MiniAQLQ						
At 2 mo	115	5.26±1.02	127	5.35±1.04	–0.09 (–0.35 to 0.18)	–0.08 (–0.31 to 0.15)
At 2 yr	98	5.61±1.03	120	5.65±1.16	–0.04 (–0.34 to 0.25)	–0.12 (–0.38 to 0.14)
ITT ACQ						
At baseline	148	1.99±0.70	158	2.06±0.84		
At 2 mo	123	1.54±0.93	132	1.53±1.00	–0.02 (–0.24 to 0.21)	0.01 (–0.20 to 0.22)
At 2 yr‡	145	1.23±0.95	155	1.15±0.92	0.10 (–0.11 to 0.32)	0.13 (–0.07 to 0.33)
	LTRA		LABA		LTRA vs. LABA	LTRA vs. LABA
Add-on therapy trial						
ITT MiniAQLQ						
At baseline	170	4.63±1.03	182	4.41±1.04		
At 2 mo	153	5.09±1.15	156	5.04±1.11	0.06 (–0.18 to 0.30)	–0.10 (–0.29 to 0.10)
At 2 yr‡	169	5.43±1.14	181	5.42±1.08	0.01 (–0.22 to 0.25)	–0.11 (–0.32 to 0.11)
PP MiniAQLQ						
At 2 mo	147	5.11±1.15	156	5.04±1.11	0.07 (–0.19 to 0.32)	–0.09 (–0.29 to 0.11)
At 2 yr	121	5.59±1.04	176	5.44±1.08	0.15 (–0.10 to 0.40)	0.01 (–0.21 to 0.24)
ITT ACQ						
At baseline	170	2.01±0.85	182	2.19±0.87		
At 2 mo	153	1.62±1.00	156	1.60±0.98	0.01 (–0.20 to 0.22)	0.12 (–0.06 to 0.30)
At 2 yr‡	169	1.31±0.96	181	1.34±0.92	0.04 (–0.24 to 0.16)	0.04 (–0.15 to 0.22)

* Plus–minus values are means ±SD. In the first-line controller therapy trial, there were 148 patients in the LTRA group and 158 in the inhaled-glucocorticoid group at baseline; at 2 months and 2 years, these totals were 145 and 155, respectively. In the add-on therapy trial, there were 170 patients in the LTRA group and 182 in the LABA group; at 2 months and 2 years, these totals were 169 and 181, respectively. ACQ denotes Asthma Control Questionnaire, CI confidence interval, ITT intention-to-treat, LABA long-acting beta$_2$-agonist, LRTA leukotriene-receptor antagonist, MiniAQLQ Mini Asthma Quality of Life Questionnaire, and PP per protocol. Scores on the ACQ range from 0 to 6, with higher scores representing worse control; scores on the MiniAQLQ range from 1 to 7, with higher scores representing better quality of life. The post hoc per-protocol analysis includes patients for whom the randomly assigned treatment was not changed.

† Values have been adjusted for baseline MiniAQLQ or ACQ score.

‡ Multiple imputation was used to impute missing data for the intention-to-treat analyses.

groups (Table E4 in the Supplementary Appendix). In the predefined, stricter per-protocol analysis (Tables E5 through E8 in the Supplementary Appendix), MiniAQLQ scores were better in the LTRA group than in the inhaled-glucocorticoid group and outside the equivalence limit, with an adjusted mean difference of 0.14 (95% CI, –0.15 to 0.44) at 2 months and 0.05 (95% CI, –0.28 to 0.37) at 2 years (Table E6 in the Supplementary Appendix).

There were no significant differences between treatment groups in asthma-diary findings; how-

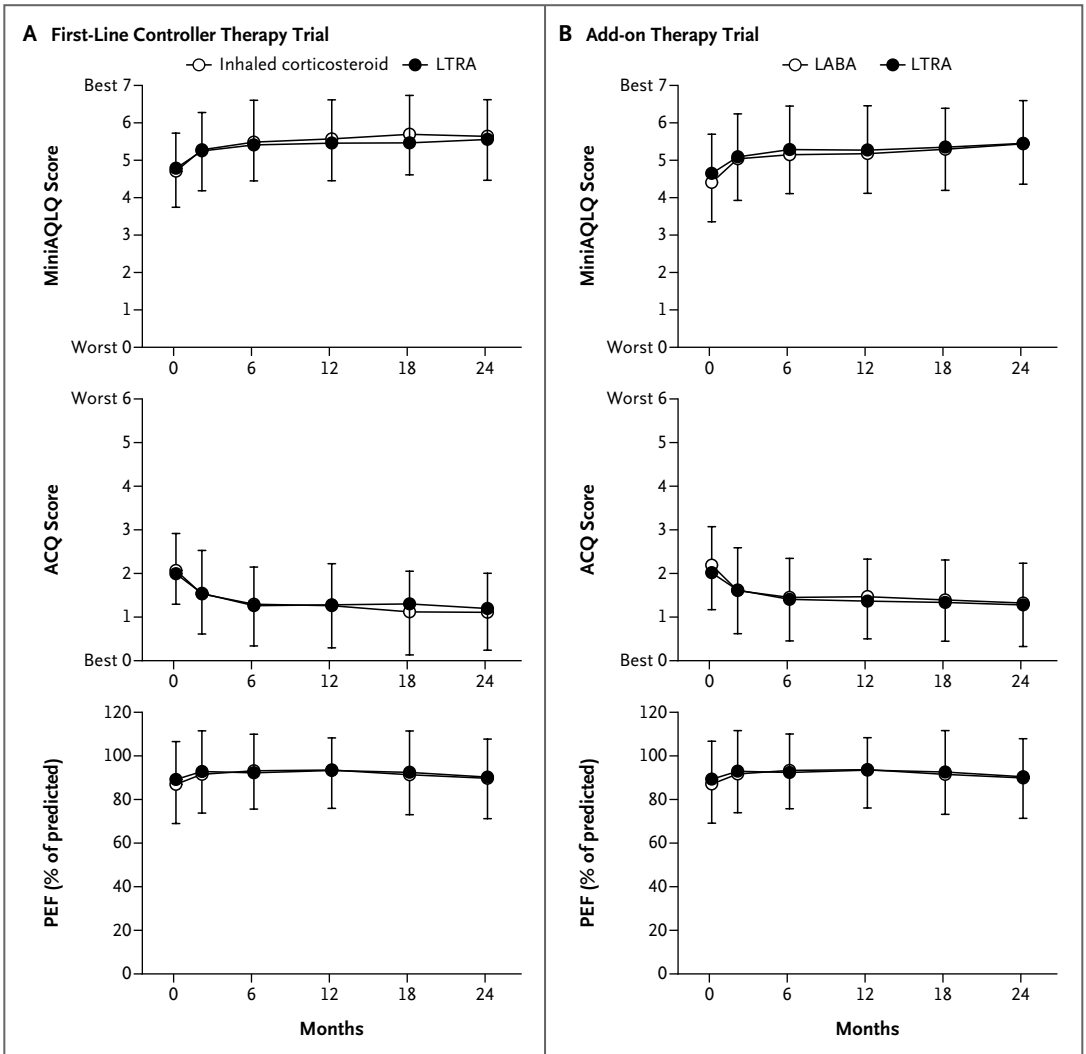

Figure 1. Time Course of Improvements in ACQ and MiniAQLQ Scores and Peak Expiratory Flow over a 2-Year Period in Patients with Asthma.

Panel A shows outcomes over a 2-year period for patients receiving a leukotriene-receptor antagonist (LTRA) or an inhaled glucocorticoid as first-line asthma-controller therapy. Panel B shows outcomes over a 2-year period for patients receiving an LTRA or a long-acting beta$_2$-agonist (LABA) as an add-on to an inhaled glucocorticoid. ACQ denotes Asthma Control Questionnaire (on which scores [shown as means ±SD] range from 0 to 6, with higher scores representing worse control and a minimal clinically important difference [MID] of 0.5), MiniAQLQ Mini Asthma Quality of Life Questionnaire (on which scores [shown as means ±SD] range from 1 to 7, with higher scores representing better quality of life and an MID of 0.5), and PEF peak expiratory flow (shown as medians with I bars representing the interquartile ranges).

ever, completion rates were low (Tables E9, E10, and E11 in the Supplementary Appendix). There was no evidence of differential treatment effects on subgroup analyses (Tables E12, E13, and E14 in the Supplementary Appendix).

One serious reaction occurred during the study (an increase in epileptic-seizure frequency) and was ascribed by the health care provider to montelukast. The patient discontinued treatment and recovered.

ADD-ON THERAPY TRIAL

Patients

Of 361 patients randomly assigned to treatment in the add-on therapy trial, 9 were excluded after randomization; thus, 352 (98%) met all study cri-

Table 3. Secondary Outcome Measures.*

Outcome Measure	Treatment Group		Rate Ratio (95% CI)†	P Value
	LTRA (N=148)	Inhaled Glucocorticoid (N=158)	LTRA vs. Inhaled Glucocorticoid	
First-line controller therapy trial				
Asthma exacerbations				
Any — no. of exacerbations	0.44±0.94	0.35±0.95	1.27 (0.83–1.92)	0.23
1 — no. of patients/total no. (%)	19/148 (13)	13/158 (8)		
>1 — no. of patients/total no. (%)	17/148 (11)	14/158 (9)		
Adherence				
No. of patients	108	101		
Rate — %				0.11
Median	65	41		
Interquartile range	15–92	21–62		
	LTRA (N=170)	LABA (N=182)	LTRA vs. LABA	
Add-on therapy trial				
Asthma exacerbations				
Any — no. of exacerbations	0.62±1.13	0.61±1.03	1.02 (0.74–1.41)	0.90
1 — no. of patients/total no. (%)	32/170 (19)	41/182 (23)		
>1 — no. of patients/total no. (%)	26/170 (15)	25/182 (14)		
Adherence				
No. of patients	136	142		
Rate — %				0.007
Median	74	46		
Interquartile range	14–100	16–73		
Adherence to inhaled glucocorticoid				
No. of patients	103	128		
Rate — %				0.26
Median	76	64		
Interquartile range	27–100	34–91		

* Plus–minus values are means ±SD. P values are for the comparison between treatment groups (with the use of the Wald chi-square test from the Poisson model for exacerbations and the Mann-Whitney test for adherence). LABA denotes long-acting beta$_2$-agonist, and LTRA leukotriene-receptor antagonist.
† Rate ratios were obtained with the use of the Poisson model, with treatment group as the sole explanatory variable.

teria, and 350 (97%) patients were included in the intention-to-treat analyses (Fig. E2 in the Supplementary Appendix). There were no clinically important differences between treatment groups at baseline (Table 1). Both the MiniAQLQ and ACQ scores were available within 3 months before the study end for 337 of 350 (96%) patients.

Outcome Measures

Mean MiniAQLQ scores in the two treatment groups were equivalent at 2 months, whereas at 2 years, the adjusted 95% CI for the difference in the MiniAQLQ scores was just outside the equivalence limit of 0.3 (Table 2 and Fig. 1). The MiniAQLQ domain scores are summarized in Table E15 in the Supplementary Appendix.

The mean ACQ score did not differ significantly between the treatment groups (Table 2 and Fig. 1). Of the 337 patients for whom long-term data on ACQ scores were available, 80 of 162 (49%) in the LTRA group and 77 of 175 (44%) in the LABA group had controlled asthma as de-

fined by a final ACQ score of 1.0 or lower.[34] Results for the other secondary outcome measures were similar in the two groups (Table 3, and Table E16 in the Supplementary Appendix), with the exception of the MiniRQLQ score, which was significantly better at 2 months but not at 2 years for patients receiving LTRA (Table E16 in the Supplementary Appendix). Rescue bronchodilator use, recorded on the basis of the response to question 6 of the ACQ, fell during the study and was similar in the two treatment groups (Table E3 in the Supplementary Appendix).

One fourth of the patients in the LTRA group were switched to LABA or received add-on LABA, whereas there were no changes in the prescribed drug class for the LABA group over the 2 years of the trial (Table 4). Median adherence to therapy was significantly better with LTRA than with LABA (Table 3).

Post hoc per-protocol results for the MiniAQLQ score were equivalent in the two treatment groups at 2 months and 2 years (Table 2). The ACQ scores did not differ significantly between the LTRA and LABA groups (Table E17 in the Supplementary Appendix). In the predefined, stricter per-protocol analysis (Tables E18 through E21 in the Supplementary Appendix), the difference in the MiniAQLQ scores was outside the equivalence limit, with an adjusted mean difference of −0.02 (95% CI, −0.36 to 0.31) at 2 months and −0.05 (95% CI, −0.36 to 0.26) at 2 years (Table E19 in the Supplementary Appendix).

On asthma-diary cards, daytime and nighttime use of short-acting bronchodilators was significantly greater in the LTRA group than in the LABA group at 2 months but not at 2 years; card-completion rates were about 65% at 2 months and 50% at 2 years (Tables E22, E23, and E24 in the Supplementary Appendix). There was no evidence of differential treatment effects in subgroup analyses (Tables E25, E26, and E27 in the Supplementary Appendix).

DISCUSSION

Mean improvements over a period of 2 years in both the first-line controller and the add-on therapy trials were substantially greater than the MID for questionnaire scores measuring asthma-related quality of life and asthma control. For patients receiving an LTRA or an inhaled glucocorticoid as first-line controller therapy, MiniAQLQ scores were

Table 4. Changes in Treatment According to the Assigned Treatment.*

Treatment Change	No. of patients (%)
LTRA, first-line controller therapy trial	
Total in group	145
Changes at 2 mo	
Crossed over to inhaled glucocorticoid	6
Crossed over to inhaled glucocorticoid plus LABA	1
Had multiple changes	1
Total	8 (5.5)
Changes at 2 yr	
Added inhaled glucocorticoid	4
Added inhaled glucocorticoid and LABA	2
Crossed over to inhaled glucocorticoid	27
Crossed over to inhaled glucocorticoid and LABA	8
Crossed over to inhaled glucocorticoid, then added LABA	3
Had multiple changes	1
Total	45 (31.0)
Inhaled glucocorticoid, first-line controller therapy trial	
Total in group	155
Changes at 2 mo	
Added LABA	3
Crossed over to LTRA	2
Total	5 (3.2)
Changes at 2 yr	
Added LABA	28
Crossed over to LTRA	4
Total	32 (20.6)
LTRA, add-on therapy trial	
Total in group	169
Changes at 2 mo	
Crossed over to LABA	6
Added LABA	1
Total	7 (4.1)
Changes at 2 yr	
Crossed over to LABA	25
Added LABA	18
Total	43 (25.4)
LABA, add-on therapy trial	
Total in group	181
Changes at 2 mo	None
Changes at 2 yr	None

* LABA denotes long-acting beta$_2$-agonist, and LTRA leukotriene-receptor antagonist.

equivalent at 2 months, but at 2 years, these scores did not meet our prespecified criterion for equivalence, since the lower boundary of the 95% CI was −0.35. Similarly, for patients receiving add-on therapy with an LTRA or LABA, MiniAQLQ scores were equivalent at 2 months but not at 2 years (lower boundary of 95% CI, −0.32). Our equivalence boundary of 0.30 was chosen to be conservative, within the 0.5 MID for the MiniAQLQ score.[26] In both trials, secondary outcome measures were similar in the two treatment groups, including asthma control as measured by the ACQ score and the frequency of asthma exacerbations, RCP3 score, and clinic-measured PEF.

Although our findings suggest that there is little difference in real-world effectiveness between an LTRA and an inhaled glucocorticoid as first-line controller therapy and between an LTRA and a LABA as an add-on to an inhaled glucocorticoid, caution is needed in interpreting the results of these pragmatic trials. As noted by Temple and Ellenberg,[8] active-control trials may have limited assay sensitivity. Moreover, study characteristics that tend to reduce observable differences between treatments, including nonadherence, use of concomitant therapy that could affect outcomes, and enrollment of patients who do not have the disease or who have spontaneous improvement, could all be operative in the present study. Specifically, the lack of a placebo-control group limits the ascertainment of effectiveness, and open-label treatment assignments, differential adherence, crossover between treatment groups, and the (intentional) enrollment of a heterogeneous real-world patient population could bias the results toward equivalence.

We considered but rejected the addition of a placebo group when designing the study, since we believe it would have been unethical to assign patients to placebo for 2 years. All enrolled patients had evidence of asthma-related impairment on the ACQ, the MiniAQLQ, or both and were considered by their physicians to need regular therapy for their asthma after a 2-week run-in period. In contrast, other long-term studies of asthma therapy that included a placebo group either enrolled patients with mild asthma[35] or excluded patients if a delay in inhaled glucocorticoid therapy was judged by physicians to be inappropriate.[36]

Double-blind treatment, although ideal for internal validity, would have severely affected the external validity (applicability) of this study. First, not revealing treatment assignments to the patients and health care providers would have hampered our goal of assessing the effect of differential adherence to oral versus inhaled therapy under conditions of usual patient and physician behaviors and preferences. Second, it would not have been possible to charge typical prescribing costs, which might have affected adherence. Bias due to the lack of blinding would probably have favored prescription of an inhaled glucocorticoid and an add-on LABA because of clear positioning in U.K. guidelines regarding the use of these medications.

Adherence to an LTRA was better than it was to the other drugs in both trials, with adherence rates that were numerically higher in the first-line controller therapy trial (65%, vs. 41% for an inhaled glucocorticoid) and significantly higher in the add-on therapy trial (74%, vs. 46% for a LABA). Although such poor and differential adherence potentially reduces assay sensitivity (particularly when coupled with treatment crossover), thus biasing results toward equivalence, both poor and differential adherence rates are realities of real-world prescribing[6] and thus part of the treatment effect. It is reassuring that the results at 2 months were similar to those at 2 years, since the 2-month time point represents a standard efficacy period with high adherence and minimal contamination associated with treatment changes. The 2-year time point better reflects the real-world effectiveness of the therapy chosen initially.

The crossover between treatment groups was regrettable but unavoidable, since this was a pragmatic trial and we allowed usual practice to occur. Treatment changes were made for more patients in the LTRA groups in both trials. This meant that, although the per-protocol results generally supported the findings in the intention-to-treat analysis, proportionately fewer LTRA-treated patients were included in the per-protocol populations.

We cannot rule out treatment failure as a reason for disparities in crossover. However, because LTRAs are not commonly prescribed in the United Kingdom as first-line or add-on anti-inflammatory therapy, or not recommended as such by U.K. guidelines, it is possible that patients in the LTRA groups, on being reviewed by a

clinician unfamiliar with the study, were switched to an inhaled glucocorticoid or add-on LABA according to normal practice protocol.[10,29] Since 7 to 10 physicians work in the typical U.K. general practice, it was difficult for us to keep all physicians apprised of the study goals and the need to maintain the study therapies. Finally, in the case of treatment failure, there was no room for change within the treatment class for the LTRA groups, whereas the inhaled glucocorticoid could be changed or the dose could be increased.

Impairment of lung function among our enrolled patients was milder than that of patients in many randomized clinical trials because a forced expiratory volume in 1 second of less than 80% of the predicted value or 15% reversibility was not required for eligibility. Since there was less room for improvement in PEF values, this measurement had poor sensitivity. However, there was considerable room for improvement in other measurements, and in all treatment groups, substantial improvements were recorded in asthma-related quality of life (an unadjusted mean increase from baseline of 0.8 to 1.0 in the MiniAQLQ score) and asthma control (a mean decrease of 0.7 to 0.9 in the ACQ score).

The limitations of these active-control equivalence trials are difficult to quantitate.[8] Comparisons with other studies are problematic because of differences in study design and patient populations; however, the baseline values and outcomes in our studies are crudely similar to those in the Gaining Optimal Asthma Control (GOAL) study[37] and the Formoterol and Corticosteroids Establishing Therapy (FACET) study,[38] and the outcomes in our study are better than those in the placebo group of the Optimal Management of Asthma (OPTIMA) study[35] (see Table E28 in the Supplementary Appendix). Nonetheless, we cannot rule out regression to the mean, and study results could simply be a reflection of the inherent variability of asthma, since patients may have been recruited at a time when their asthma was unstable.

The ACQ score and exacerbation frequency are two key markers of asthma control recognized by international consensus.[24] There were no significant differences between treatment groups in these measures for intention-to-treat or per-protocol population in either trial, although exacerbations were infrequent overall. Data for asthma-related quality of life and asthma control were available over a period of 21 months for 95% and 96% of the patients in the first-line controller and add-on therapy trials, respectively, which are completion rates higher than those in most long-term asthma-therapy trials.[35,37,39]

We designed these two pragmatic trials[7] to maximize external validity (applicability or generalizability), with the goal of studying a heterogeneous real-world population. Although this approach limits the efficacy assessment, we believe it has the advantage of exploring a question that cannot be answered in more tightly controlled, randomized, controlled trials — namely, what is the real-world effectiveness of these proven therapies for the heterogeneous population of patients seen in practice, including those who smoke and those with coexisting conditions, poor adherence, or poor inhaler technique? Active smokers are typically excluded from clinical trials, but such patients accounted for almost one fourth of our study population, with smokers over 45 years of age representing about 9% of patients in both trials. Because we did not require evidence of bronchodilator reversibility, enrolled patients may have had a combination of chronic obstructive pulmonary disease (COPD) and asthma. We estimate that 3% of the study population had some degree of COPD, since reportedly, 25% of smokers over 40 years of age who are treated for asthma in clinical practice have COPD.[40] Nonetheless, verification of the asthma diagnosis with spirometry would have been ideal, and there is clearly a need for better diagnostic standards in primary care.

Although our eligibility criteria allowed for patients as young as 12 years old to be included, few patients were younger than 25 years of age; thus, our findings apply only to adults. The standard deviation used in the power calculation is smaller than the observed standard deviation in our data, and we attribute this difference to the greater heterogeneity of our study population as compared with populations in previously reported studies[33] — a factor that should be considered in future pragmatic trials.

The results of these two pragmatic trials suggest that an LTRA is equivalent to both comparison drugs with regard to the effect on asthma-related quality of life at 2 months in a diverse

patient population with asthma. Equivalence was not proved at 2 years. Although the quality-of-life results, taken together with asthma control and other outcome measures, show little difference in clinical effectiveness between an LTRA and an inhaled glucocorticoid as first-line controller therapy and between an LTRA and a LABA as an add-on to an inhaled glucocorticoid, it is important to recognize that features of these pragmatic trials could produce a bias toward equivalence. Nonetheless, our findings suggest that caution should be applied in extrapolating results from randomized clinical trials to the broad population of patients with asthma who are treated in community settings. Clinical decision making can best be guided by viewing the results of conventional randomized, controlled trials in conjunction with the results of pragmatic trials.

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