

# A pragmatic single-blind randomised controlled trial and economic evaluation of the use of leukotriene receptor antagonists in primary care at steps 2 and 3 of the national asthma guidelines (ELEVATE study)

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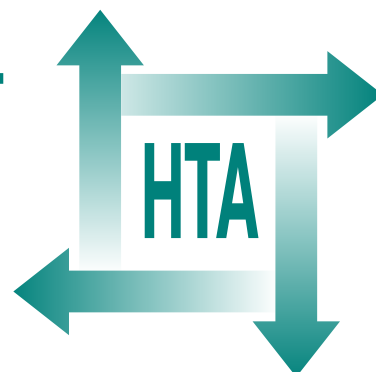


## Executive summary

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## Executive summary

### Background

The role of leukotriene receptor antagonists is not clear for primary care asthma management of patients who are uncontrolled on short-acting  $\beta_2$ -agonists alone [British Thoracic Society (BTS) Guidelines step 2] or uncontrolled on low-dose inhaled corticosteroid (ICS) alone (BTS Guidelines step 3). Most clinical trials evaluating the role of leukotriene antagonists compared with conventional treatment (ICS as initial controller therapy at step 2, and long-acting  $\beta_2$ -agonist as add-on therapy to ICS at step 3) are short term in nature, are not representative of 'real-life' asthma populations and management in primary care, and do not include a full prospective cost evaluation.

### Objective

The aim of our study was to evaluate, under real-life practice conditions in UK primary care, asthma-specific quality of life (QOL), markers of asthma control, and cost-effectiveness of commencing therapy with leukotriene antagonists compared with ICS as initial controller therapy and compared with long-acting  $\beta_2$ -agonist as add-on therapy for patients with uncontrolled asthma already receiving ICS. Comparisons were made in terms of short-term efficacy and longer-term effectiveness at 2 months and 2 years, respectively.

### Methods

This study comprised two separate randomisations, thus two pragmatic randomised controlled trials, powered for equivalence, enrolling patients aged 12–80 years with asthma uncontrolled by (1) short-acting  $\beta_2$ -agonist (step 2) or (2) ICS (step 3) and a score of  $\leq 6$  points on the Mini Asthma Quality of Life Questionnaire (MiniAQLQ) (best score = 7) and/or  $\geq 1$  point on the Asthma Control Questionnaire (ACQ) (score of  $\leq 0.75$  denotes well-controlled asthma). Study visits were scheduled to coincide with routine patient follow-up as per usual care for asthma, and the study was conducted so as to minimally interfere with normal clinical practice.

Health-care providers and patients were aware of treatment allocations, while study data collection and statistical analyses were blinded.

The primary study outcome was the MiniAQLQ, a validated disease-specific asthma QOL scale, chosen because it captures outcomes of relevance to patients and their primary care providers and reflects asthma control. An analysis of covariance was used, with treatment as a fixed effect, and baseline value as covariate, to analyse MiniAQLQ scores at 2 months (the primary time point), examining efficacy, and 2 years, as a measure of effectiveness, using an intention-to-treat approach. A 95% confidence interval (CI) for the difference between treatment mean scores was derived. While the minimum clinically important difference for the MiniAQLQ score is 0.5, we conservatively defined equivalence as a difference of 0.3; thus, 95% CI of less than  $\pm 0.3$ .

Other outcome measures were two markers of asthma control: the validated ACQ, which evaluates symptoms of asthma and reliever treatment usage, and asthma exacerbations requiring oral steroid therapy or hospitalisation. Incremental cost-effectiveness approaches were used to study health-economic outcomes utilising NHS and societal costs with markers of disease control and disease-specific and generic health-related QOL [European Quality of life-5 Dimensions questionnaire (EQ-5D)], with calculation of quality-adjusted life-years (QALYs). Additional outcome measures included per cent predicted peak expiratory flow (%PPEF), Royal College of Physicians three (RCP3) asthma questions, Mini Rhinitis Quality of Life Questionnaire (mRQLQ), respiratory tract infections, and consultations for respiratory tract infection, and, for step 3 only, change in ICS dose.

### Results

Six hundred and eighty-seven patients, recruited from 53 primary care practices, were randomised and 650 participants (95%) had evaluable data for the primary study outcome (145 leukotriene antagonist and 155 ICS for initial controller

therapy, and 169 leukotriene antagonist and 181 long-acting  $\beta_2$ -agonist as add-on therapy to ICS). Of those receiving initial controller therapy, 51% were women; the mean age was 46 years and 22% were current smokers. Of those receiving add-on therapy, 63% were women; the mean age was 50 years and 17% were current smokers.

All treatments were associated with substantial mean improvements in outcome measures with no significant between-group differences in MiniAQLQ or ACQ score or QALYs gained at 2 months and 2 years.

### Leukotriene antagonists compared with ICSs as initial controller therapy

At 2 months, the MiniAQLQ scores met our equivalence criterion, with adjusted difference (95% CI) between leukotriene antagonist and ICS of  $-0.02$  ( $-0.24$  to  $0.20$ ). At 2 years, however, the 95% CIs excluded the threshold for equivalence of 0.3, favouring ICS [ $-0.11$  ( $-0.35$  to  $0.13$ )]. No significant between-group differences were found in ACQ score at either 2 months [adjusted difference  $0.01$  ( $-0.20$  to  $0.22$ )] or 2 years [ $0.13$  ( $-0.07$  to  $0.33$ )]. The 95% CIs were well within the minimum clinically important difference of 0.5 for the ACQ. No significant differences between leukotriene antagonist and ICS were found for any other secondary end point at 2 months or 2 years, including the number of asthma exacerbations, %PPEF, RCP3 questions, mRQLQ, respiratory tract infections or respiratory tract infection consultations.

### Leukotriene antagonist compared with long-acting $\beta_2$ -agonist as add-on therapy to ICS

At 2 months, the MiniAQLQ scores met our equivalence criterion, with adjusted difference (95% CI) between leukotriene antagonist and long-acting  $\beta_2$ -agonist of  $-0.10$  ( $-0.29$  to  $0.10$ ). At 2 years, the 95% CIs for MiniAQLQ score were marginally over the equivalence threshold, favouring long-acting  $\beta_2$ -agonist as add-on therapy [adjusted difference at 2 years  $-0.11$  ( $-0.32$  to  $0.11$ )]. However, there were no significant between-group differences in ACQ score at either 2 months [ $0.12$  ( $-0.06$  to  $0.30$ )] or 2 years [ $0.04$  ( $-0.15$  to  $0.22$ )]. Daily ICS dose did not differ between the two treatment groups. No significant differences were found in exacerbations, %PPEF, RCP3

questions, or mRQLQ, respiratory tract infections or respiratory tract infection consultations.

### Cost-effectiveness results

Compared with those receiving ICS as initial controller therapy, participants receiving leukotriene antagonist had significantly higher NHS and societal costs at both time points. ICS numerically dominated leukotriene antagonist in terms of cost-effectiveness, although outcomes were not statistically significantly different.

For patients receiving add-on therapy to ICS, no significant differences between leukotriene antagonist and long-acting  $\beta_2$ -agonist in NHS or societal cost were found at 2 months, but, after 2 years, participants receiving leukotriene antagonist had higher societal costs of borderline statistical significance. The extra cost per extra QALY gained was £22,589 (2-year time horizon, societal perspective). Given a willingness to pay of £30,000 per QALY gained, there is a probability of between 51.6% and 54.6% that leukotriene antagonist is a cost-effective alternative to long-acting  $\beta_2$ -agonist as add-on therapy to ICS, depending on time horizon and perspective.

The broad inclusion criteria for this study meant that active smokers, those with smaller impairments of lung function and patients with other comorbidities, who are typically excluded from clinical trials, were included in our study population. The conduct of this study in patients' own primary care practices by their normal health-care providers retained the 'real-life' setting, thereby enabling the generalisability of our results to primary care. This also resulted in extremely low dropouts from the study, which contrasts strongly with most published randomised trials in respiratory disease. A limitation of this study is that by 2 years many patients were switched from initial randomised therapy to alternate therapy due to a range of factors, including practice protocols for inhalers and chlorofluorocarbon transition. We speculate that another factor may be the shorter durations of drug supplies in those randomised to leukotriene antagonist and resulting greater review, providing greater opportunities to change therapy.

### Conclusions

Results of this pragmatic trial in UK primary care were equivalent with regard to asthma-specific

QoL (MiniAQLQ) at 2 months after commencing controller therapy with leukotriene antagonist or ICS (step 2 of the BTS guidelines). Our equivalence criterion for MiniAQLQ was not met at 2 years; however, there were no statistically significant differences between treatment groups at this time. There were no differences in asthma control measures (ACQ score and exacerbations) at 2 months or 2 years; thus, any possible advantage of one over the other appears to be clinically unimportant. All treatments were associated with substantial mean improvements, which may, at least in part, have been due to regression to the mean or treatment effects. At 2005 UK prices of leukotriene antagonist and ICS, leukotriene antagonist was not a cost-effective alternative to inhaled corticosteroid at step 2.

Results of add-on therapy with leukotriene antagonist or long-acting  $\beta_2$ -agonist for patients with uncontrolled asthma already receiving ICS (step 3) were equivalent at 2 months (step 3 of the BTS guidelines), and at 2 years almost met our equivalence criterion. There were no significant differences between treatment groups in ACQ score or exacerbations. Leukotriene antagonist was of borderline cost-effectiveness compared with long-acting  $\beta_2$ -agonist.

## Implications for health care

The evidence suggests that, while any advantage of one treatment over the other appears to be clinically unimportant, leukotriene antagonists are unlikely to be a cost-effective alternative to ICSs, at 2005 prices, as initial asthma controller therapy at step 2. In addition, the evidence suggests that leukotriene antagonists may be clinically equivalent to long-acting  $\beta_2$ -agonists as add-on to ICSs in terms of QoL as well as secondary measures, and, furthermore, suggests that leukotriene antagonists could be repositioned as an equal alternative to long-acting  $\beta_2$ -agonists at step 3 of the BTS guidelines.

When generic leukotriene antagonist formulations become available in the next few years their cost-

effectiveness as an alternative to ICS may justify further evaluation, particularly in the subgroup of patients with limited impairment of lung function, those newly diagnosed with asthma to minimise inhaler education and those with fears about inhalers or inhaled steroids.

## Recommendations for research

- Establish, in primary care, whether leukotriene antagonists will be more or less beneficial than ICSs alone or as an add-on to ICSs in treating patients with asthma who are also active smokers.
- Determine why the ACQ correlates more poorly with economic outcomes of asthma than the MiniAQLQ and EQ-5D.
- Understand further the reasons why patients were switched from study medication when there was no real clinical indication to do so and examine ways to minimise this happening in future pragmatic primary care-based clinical trials.

## Trial registration

This trial is registered as ISRCTN99132811.

## Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

## Publication

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