Symptom- and fraction of exhaled nitric oxide–driven strategies for asthma control: A cluster-randomized trial in primary care

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Background: Aiming at partly controlled asthma (PCa) instead of controlled asthma (Ca) might decrease asthma medication use. Biomarkers, such as the fraction of exhaled nitric oxide (FENO), allow further tailoring of treatment.
Objective: We sought to assess the cost-effectiveness and clinical effectiveness of pursuing PCa, Ca, or FENO-driven controlled asthma (FCa).
Methods: In a nonblind, pragmatic, cluster-randomized trial in primary care, adults (18-50 years of age) with a doctor's diagnosis of asthma who were prescribed inhaled corticosteroids were allocated to one of 3 treatment strategies: (1) aiming at PCa (Asthma Control Questionnaire [ACQ] score <1.50); (2) aiming at Ca (ACQ score <0.75); and (3) aiming at FCa (ACQ score <0.75 and FENO value <25 ppb). During 12 months' follow-up, treatment was adjusted every 3 months by using an online decision support tool. Outcomes were incremental cost per quality-adjusted life year gained, asthma control (ACQ score), quality of life (Asthma Quality of Life Questionnaire score), asthma medication use, and severe exacerbation rate.
Results: Six hundred eleven participants were allocated to the PCa (n = 219), Ca (n = 203), or FCa (n = 189) strategies. The FCa strategy improved asthma control compared with the PCa strategy ($P < .02$). There were no differences in quality of life ($P \geq .36$). Asthma medication use was significantly lower for the PCa and FCa strategies compared with the Ca strategy (medication costs: PCa, $452; Ca, $551; and FCa, $456; $P \leq .04$). The FCa strategy had the highest probability of cost-effectiveness at a willingness to pay of $50,000/quality-adjusted life year (86%; PCa, 2%; Ca, 12%). There were no differences in severe exacerbation rate.
Conclusion: A symptom- plus FENO-driven strategy reduces asthma medication use while sustaining asthma control and quality of life and is the preferred strategy for adult asthmatic patients in primary care. (J Allergy Clin Immunol 2015;135:682-8.)

Key words: *Quality of life, fraction of exhaled nitric oxide, asthma exacerbations, asthma control, cost-effectiveness, online decision support*

Globally, an estimated 300 million persons have asthma,[1] representing a considerable and increasing burden to patients, health care, and society at large. Asthma has a significant effect not only on an individual patient's health-related quality of life but also on society and the economy through work absence, premature retirement, and high costs for asthma treatment.[2-6] Cost-effective treatment strategies are required to face the burden of asthma.

According to guidelines, the aim of asthma treatment is to achieve and maintain control of clinical manifestations for prolonged periods of time. Patient safety, including prevention of exacerbations and side effects of medication, and keeping in check the cost of treatment are also important goals.[7-11] The severity of clinical manifestations of asthma is classified into controlled asthma (Ca), partly controlled asthma (PCa), and uncontrolled asthma categories to direct treatment decisions.[8] In practice, symptoms in up to 75% of patients are controlled suboptimally (partly controlled or uncontrolled).[12-14] In these patients a step up of asthma medication is advocated to achieve controlled asthma. Because the dose-response relationship flattens at higher levels of inhaled corticosteroids (ICSs) and the risk of side effects increases,[15,16] the benefits of stepping up treatment to achieve Ca might be limited.

Recent studies have shown that biomarkers, including fraction of exhaled nitric oxide (FENO), help to distinguish between patients who benefit more from adding a long-acting β-agonist (LABA) and those requiring a change in ICS dosage by providing additional information regarding the level of bronchial inflammation.[17-20] However, in primary care the current recommendation is to guide treatment decisions based solely on controlling the clinical features of disease because assessments of biomarkers are unavailable, likely to increase health care costs because of expensive equipment, or both.[8]

Recently, easy-to-use and cheaper handheld FENO devices have been introduced.[21] To date, it is unknown whether in primary care

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Abbreviations used
ACQ: Asthma Control Questionnaire
Ca: Controlled asthma
EQ-5D: EuroQol classification system
FCa: FENO-driven controlled asthma
FENO: Fraction of exhaled nitric oxide
GOAL: Gaining Optimal Asthma Control
GP: General practitioner
ICS: Inhaled corticosteroid
LABA: Long-acting β-agonist
MARS: Medication Adherence Report Scale
PCa: Partly controlled asthma
PN: Practice nurse
QALY: Quality-adjusted life year

the pursuit of improving asthma control through assessment of airway inflammation by using FENO measurements is helpful to achieve and benefit from controlled asthma with regard to the patient's quality of life, exacerbation rates, and cost of treatment.

To that end, we performed a 3-armed cluster-randomized trial comparing 3 strategies aiming at either PCa, Ca, or FENO-driven controlled asthma (FCa).

METHODS

This was an entirely investigator-designed and investigator-driven study. A detailed description of study procedures, sample size calculation, and measurements has been published elsewhere.[22]

Setting and participants

General practices from both rural and urban areas in The Netherlands were invited to participate. Inclusion criteria were age of 18 to 50 years, doctor-diagnosed asthma according to the Dutch national guidelines,[10] a prescription for ICSs for at least 3 months in the previous year, and asthma being managed in primary care. Exclusion criteria were significant comorbidity (at the general practitioner [GP]'s discretion), inability to understand Dutch, and a prescription for oral corticosteroids in the previous month. The trial was approved by the Medical Ethics Committee of Leiden University Medical Center. All included patients provided written informed consent. The trial was registered at www.trialregister.nl (NTR 1756).

Design overview

This was a nonblind, 3-arm, pragmatic, cluster-randomized trial with 12 months' follow-up of adult asthmatic patients in primary care. Cluster randomization was performed at the general practice level instead of the patient level to prevent intervention contamination within practices. No specific eligibility criteria applied to clusters. At local information meetings, study procedures were explained to participants, and afterward, informed consent was obtained. When the list of participants for each practice had been completed, the general practices were randomly allocated to one of 3 treatment strategies by an independent researcher using a computer-generated permuted block scheme for groups of 3 general practices stratified according to region (Amsterdam, Leiden, and Nijmegen), urbanization grade (rural vs urban), and the practice nurse (PN)'s level of experience with asthma management (>1 year vs <1 year). Allocation concealment applied to both the cluster and participant levels (Fig 1).

Interventions

The 3 treatment strategies targeting different levels of asthma control were defined as follows: (1) aiming at partly controlled asthma (PCa strategy), (2) aiming at controlled asthma (Ca strategy), and (3) aiming at FENO-driven controlled asthma (FCa strategy). In all 3 strategies patients visited the PN of their general practice every 3 months over the course of 1 year. During these visits, the PN assessed current medication use and asthma control status by using the 7-item Asthma Control Questionnaire (ACQ) that includes lung function.[23] In addition, a FENO measurement was performed in the FCa strategy. FENO values were expressed as the concentration in parts per billion and automatically adjusted for smoking, when applicable.[24] At each visit, a patient's asthma control status was classified based on the ACQ score as controlled (ACQ score ≤ 0.75), partly controlled ($0.75 <$ ACQ score ≤ 1.5), or uncontrolled (ACQ score > 1.5) and additionally in the FCa strategy as 3 subcategories of FENO: low/absence of airway inflammation for values at 25 ppb or less, intermediate at 26 to 50 ppb, and high/presence of airway inflammation at greater than 50 ppb.[19] Treatment decisions were based on a dedicated algorithm for each strategy (Table I). To increase the feasibility of implementing our strategies, we designed an online decision support tool. Current medication use and all measurements were entered into this decision support tool, which subsequently automatically generated treatment advice based on the appropriate algorithm for each of the 3 treatment strategies (Table I). Patients' current medication use was classified as an asthma treatment step ranging from 0 (only short-acting β-agonists) to 5 (oral prednisone) based on the US National Asthma Education and Prevention Program guideline.[7] When treatment was to be adjusted, in the PCa and Ca strategies professionals and patients could choose any (combination of) type or types of asthma medication they preferred within a certain treatment step (for all possibilities, see Table E1 in this article's Online Repository at www.jacionline.org), whereas the FCa strategy offered more guidance toward adding/removing LABAs or ICSs (Table I).

All unplanned doctor's office visits for increased symptoms of asthma were treated at the GP's discretion, irrespective of the participant's experimental assignment. When symptoms had normalized, patients additionally visited the PN's office, where asthma control was reassessed and therapy was adjusted by using the assigned treatment strategy.

Outcomes and follow-up

The primary outcome was the societal costs per quality-adjusted life year (QALY) gained. Patients filled out online questionnaires at home every 3 months to assess QALYs and costs from a societal perspective. QALYs were obtained by calculating the area under the health state utility curve based on the Dutch tariff of the EuroQol classification system (EQ-5D).[25] Total costs were obtained by adding the costs of 3 relevant categories: all health care costs, productivity loss, and intervention costs, including additional costs for the measurement of FENO.[26] Costs in Euros were converted to dollars by using the purchasing parity index.[27]

Secondary outcomes were asthma control, asthma-related quality of life (Asthma Quality of Life Questionnaire[28]), number of days with (asthma-related) limitations of activity, medication adherence (Medication Adherence Report Scale [MARS][29]), severe exacerbation rate, lung function, FENO value, and total medication use.

Severe exacerbations were defined as hospitalizations or emergency care visits because of asthma or systemic use of oral corticosteroids for 3 or more consecutive days.[11] Unplanned doctor's office visits for increased asthma symptoms were recorded, as were experienced symptoms and received treatment, allowing severe exacerbations to be distinguished from moderate exacerbations and periods of loss of control.

Total medication use was assessed by obtaining all medication prescriptions from local pharmacy records and from the Dutch Foundation for Pharmaceutical Statistics.[30] All ICS prescriptions were expressed as beclomethasone equivalent values based on recommendations by the Dutch pharmaceutical guidelines[31] and a panel of respiratory experts to allow comparisons between strategies.

Statistical analysis

Patients were analyzed according to the intention-to-treat methodology. Statistical uncertainty of the cost-effectiveness ratio was analyzed by using the net benefit approach.[32] The net benefit is defined as follows:

$$\lambda \times \Delta \mathrm{QALY} - \Delta \,\mathrm{costs},$$

where λ is the willingness to pay for a gain of 1 QALY. This way, the observed QALY difference is reformulated into a monetary difference. The probability