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Cost-Utility Analysis of Long-Acting Beta Agonists versus Leukotriene Receptor Antagonists in Older Adults with Persistent Asthma Receiving Concomitant Inhaled Corticosteroid Therapy

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ABSTRACT

Background: Long-acting beta agonists (LABA) and leukotriene receptor antagonists (LTRA) are the major add-on treatments in older adults with persistent asthma when inhaled corticosteroids (ICS) fail to achieve adequate asthma control. **Objectives:** To evaluate the cost-utility of ICS + LABA treatment compared with ICS + LTRA treatment in older adults with asthma. **Methods:** A Markov model was used to estimate the incremental costs and quality-adjusted life expectancy associated with ICS + LABA treatment versus ICS + LTRA treatment in older adults with asthma in the United States from the health system perspective. The HCUPnet 2010 national statistics were used to extract the costs associated with asthma and cardiovascular hospitalizations, and inpatient mortality associated with these events. Event probabilities were predicted using Medicare 2009-2010 claims for older adults with asthma. Treatment costs were estimated on the basis of average wholesale drug price listings, and utility estimates were extracted from the literature. To account for uncertainty, one-way sensitivity analysis and probabilistic sensitivity analysis were performed. **Results:** The model predicted that, compared with ICS + LTRA treatment, ICS + LABA treatment costs $5,823 more while gaining 0.03 quality-adjusted life-years (QALYs), resulting in an incremental cost-effectiveness ratio of $209,090 per QALY. Hospitalization probabilities and posthospitalization utilities were the most influential parameters in the one-way sensitivity analysis. Probabilistic uncertainty analysis using Monte-Carlo simulations showed that the probabilities that ICS + LTRA treatment is cost-effective compared with ICS + LABA treatment are 77% and 62% at $50,000 and $100,000 per QALY gained willingness-to-pay thresholds, respectively. **Conclusions:** The cost-effectiveness of ICS + LABA treatment is economically unfavorable in older adults when compared with LTRA as add-on treatment.

Keywords: asthma treatment, cost-utility analysis, hospitalization, older adults.

Introduction

Asthma is a common chronic respiratory disease that affects all ages worldwide [1]. For more than three decades, older adults have experienced the greatest burden of asthma mortality; more than 50% of asthma deaths occur among persons 65 years and older [2,3]. Older adult patients with asthma also experience high asthma-related morbidity and associated medical costs. Hospitalizations are the major driver for clinical and economic burdens associated with chronic diseases in older adults, with hospital inpatient care, medications, and outpatient care estimated to account for 54%, 35%, and 7%, respectively, of direct costs in older adult patients with asthma [4].

Treatment guidelines for asthma in older adults are primarily based on clinical trials conducted with adult populations [5], in which older people were systematically excluded as ineligible [6]. Inhaled corticosteroids (ICS), started at a low to medium dose, are the recommended initial controller therapy for patients with moderately severe to severe persistent asthma [7]. When asthma symptoms are not well controlled on low-dose ICS, it is recommended to increase the ICS dose or to add another controller agent, such as a long-acting beta agonist (LABA) or a leukotriene

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receptor antagonist (LTRA) [7]. In the present guidelines, LABA is the first-line add-on treatment among all ages [8]. In research conducted in age-pooled populations, LABA treatment was shown to be more effective than LTRA treatment as add-on treatment [9,10]. Despite its efficacy, the overall pulmonary and cardiovascular (CV) safety of LABA for asthma has been questioned in several studies [11–19]. A growing concern has been raised about asthma-related morbidity and mortality associated with LABA when given with or without ICS [11–14,16,17,19]. In a meta-analysis of randomized, placebo-controlled trials, LABA increased asthma exacerbations requiring hospitalization and life-threatening exacerbations compared with placebo [17]. CV safety of LABA agents has also emerged as a major concern [18,20]. Compared with placebo, LABA agents were shown to increase the risk for adverse CV events, including arrhythmia, ischemia, congestive heart failure, and death (relative risk 2.54; 95% confidence interval 1.59–4.05) [18].

LTRA agents have been shown to be effective in controlling asthma symptoms when compared with placebo and when added as an adjunctive treatment among all ages [21–24]. Furthermore, their safety profiles are encouraging for their use in older adult populations [25]. Their adverse events are generally milder and fewer than those associated with LABA agents [26]. Moreover, it has been suggested that the anti-inflammatory effect of LTRA treatment can be cardio-/cerebroprotective by inhibiting the development of atherosclerosis, reducing intimal hyperplasia after vascular injury, and exerting protective effects after cerebral ischemia and reperfusion [27]. Such positive effects can give LTRA treatment another advantage, especially in older adult populations in which CV and cerebrovascular diseases are very prevalent and contribute to substantial economic and clinical burdens [28,29].

To date, the safety and efficacy of ICS + LABA and ICS + LTRA treatments, which are the two major treatment strategies in persistent asthma, have not been directly compared in a representative older adult population. In making health care decisions in older adults, looking for only asthma treatment effectiveness is not enough. The safety of pharmacological treatments must also be considered, especially because older adult patients tend to die more frequently from other chronic diseases and especially from cardiovascular disease than from asthma [30].

The objective of this study was to compare the cost and quality-adjusted survival associated with severe CV and asthma exacerbations between ICS + LABA and ICS + LTRA treatments in an older adult population with asthma. This study is innovative in combining effectiveness and CV safety outcomes in a single analysis for older adults in whom both outcomes have not yet been well studied.

Methods

Analytical Model

A Markov model was developed to estimate the incremental costs and quality-adjusted life expectancy associated with the most commonly used asthma treatment strategies in older adults with persistent asthma in the United States. We simulated a cohort of older adults, 66 years of age or older, who were treated for their persistent asthma by ICS + LABA treatment, ICS + LTRA treatment, or ICS (as a reference group). Our simulated cohort patients transitioned, in 1-month cycles, through five clinical health states: healthy without any exacerbation, postasthma exacerbation, post-CV exacerbation, postasthma/CV exacerbation, and dead. CV and asthma exacerbations are defined as severe exacerbations requiring hospitalization. The cohort was followed over 20 years in 240 monthly cycles to evaluate long-term effects of these treatment strategies. In each cycle, patients could survive or die from experiencing asthma exacerbation or CV exacerbation. In addition, patients could be considered dead on the basis of age-based mortality from US life tables. We applied half-cycle corrections to account for the possibility that state transitions could occur at any time within each cycle [31] (Fig. 1).

Our base-case analysis evaluated strategy costs and effectiveness using parameter mean values as listed in Table 1. Next, we conducted a one-way sensitivity analysis in which all the base-case parameters were varied individually using the ranges presented in Table 1. Furthermore, because of the uncertainty in estimating clinical parameters, a probabilistic sensitivity analysis was performed using Monte-Carlo simulation, varying all parameters simultaneously over distributions, with parameter distributions chosen on the basis of data types and characteristics (see Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2016.02.004). An additional sensitivity analysis scenario was investigated in which we tested the robustness of the results toward using higher strength of ICS treatment (fluticasone 220 μg)

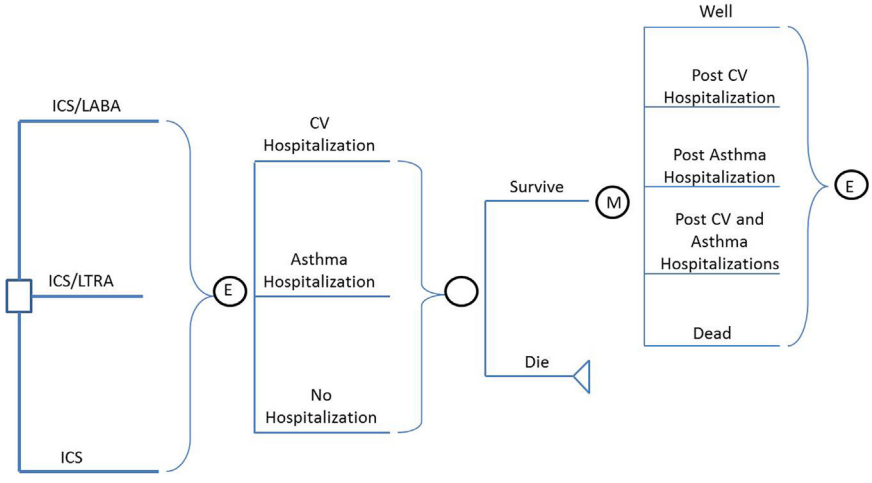

Fig. 1 – Markov model structure. Patients transitioned through five clinical health states: healthy without any exacerbation (*well*), postasthma exacerbation, post-CV exacerbation, post-asthma/CV exacerbation, and dead. In each cycle, patients could survive or die from experiencing asthma or CV events (E). CV, cardiovascular; ICS, inhaled corticosteroids; LABA, long-acting beta agonists; LTRA, leukotriene receptor antagonists; M, Markov node.