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Optimizing the Position and Use of Omalizumab for Severe Persistent Allergic Asthma Using Cost-Effectiveness Analysis

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ABSTRACT

Background: There has been some controversy on whether the costs of omalizumab outweigh its benefits for severe persistent allergic asthma. **Objectives:** This study aimed to resolve the uncertainties and limitations of previous analyses and establish the cost-effectiveness of omalizumab under the list price and Patient Access Scheme (PAS) discounted price for the UK National Health Service. **Methods:** A decision-analytic model was developed to evaluate the long-term cost-effectiveness of omalizumab under the perspective of the National Health Service. Outcomes were expressed as quality-adjusted life-years (QALYs). Patient subgroups were defined post hoc on the basis of data collected in clinical trials: previous hospitalization, on maintenance oral corticosteroids, and three or more previous exacerbations. **Results:** The incremental cost-effectiveness ratio varied from £30,109 to £57,557 per QALY gained depending on the population considered using the PAS price; incremental cost-effectiveness ratios were over a third higher using the list price. Omalizumab is likely to be cost-effective at the threshold of £30,000 per QALY gained in the severe subgroups if the improvement in health-related quality of life from omalizumab is mapped from an asthma-specific measure to the EuroQol five-dimensional questionnaire (vs. the EuroQol five-dimensional questionnaire directly collected from patients) or asthma mortality refers to death after hospitalization from asthma (vs. asthma-mortality risk in the community). **Conclusions:** Although the cost-effectiveness of omalizumab is more favorable under the PAS price, it represents good value for money only in severe subgroups and under optimistic assumptions regarding asthma mortality and improvement in health-related quality of life. For these reasons, omalizumab should be carefully targeted to ensure value for money.

Keywords: asthma, decision-analytic model, economic evaluation, omalizumab.

Introduction

Asthma affects more than 300 million people worldwide [1]. Approximately 20% have severe asthma, of which 20% is poorly controlled [2]. Patients with poorly controlled asthma endure poor quality of life and experience increased risk of asthma exacerbations [1]. An *exacerbation* is a severe onset of symptoms (difficulty breathing, wheezing, cough, tight chest) that may require hospital treatment and may be life threatening. In 2011, in England there were more than 82,000 hospitalizations for asthma, of which 68% were accident and emergency admissions [3]. Asthma treatment follows a stepwise approach to achieve and maintain control of symptoms while minimizing adverse effects [1,4]. Treatment is stepped up until control is achieved and stepped down if more intense therapy is no longer required. Patients with severe asthma require treatment at step 4—daily use of high doses of inhaled steroids—or step 5—continuous or frequent use of oral corticosteroids (OCS). Adverse effects from long-term use of OCS include adrenal suppression, osteoporosis, cataracts, and diabetes [1,5]. Omalizumab has been shown to have a positive benefit-risk profile in that it reduces the risk of exacerbations and improves health-related quality of life (HRQOL) [6–8]. Serious adverse events are rare (frequency <1/10,000); the most frequent adverse events are headache, upper abdominal pain, fever, and infection site reactions [6]. Hence, omalizumab offers an alternative to moving up to maintenance OCS (step 5) for patients uncontrolled at step 4 and may allow a reduction in the dose of OCS in patients controlled at step 5 (who would otherwise be uncontrolled at step 4).

There has been some controversy on whether the benefits of omalizumab are outweighed by its costs [7–13]. In the United Kingdom, omalizumab was assessed by the Scottish Medicines Consortium (SMC) for the National Health Service (NHS) in Scotland [14] and by the National Institute for Health and Care Excellence (NICE) for the NHS in England and Wales [7,8]. The SMC recommended omalizumab for patients 12 years and older on maintenance OCS and in whom all other treatments have failed [15]; this recommendation was extended to children aged 6 to 11 years after the inclusion of this age group in the product license [16]. NICE assessed omalizumab for patients aged 12 years and older and for patients aged 6 to 11 years in two separate technology appraisals (TAs). In TA133, in 2007, NICE recommended omalizumab for patients aged 12 years and older with severe unstable disease who are at an elevated risk of asthma mortality [7]. TA201, which assessed omalizumab in patients aged 6 to 11 years in 2010, did not recommend omalizumab because the incremental cost-effectiveness ratios (ICERs) were well above conventional

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thresholds of cost-effectiveness used in the United Kingdom [8]. Even for more severe patients, defined as those experiencing at least three exacerbations in the previous year, the ICER was £82,600 per quality-adjusted life-year (QALY) gained. In 2012, NICE decided to review these recommendations by commissioning a new appraisal on the clinical effectiveness and cost-effectiveness of omalizumab for severe persistent allergic asthma in both adults and children.

This study reports the independent cost-effectiveness assessment of omalizumab for severe persistent allergic asthma for the entire licensed population and subgroups using both the list price and the discounted Patient Access Scheme (PAS) price, details of which are confidential. Therefore, it provides important information to assist clinicians and other reimbursement agencies in optimizing the position of omalizumab on the basis of clinical effectiveness and cost-effectiveness considerations and the role that formal or informal price negotiation with the manufacturer might play. In addition, it builds on the previous assessments by addressing the key areas of uncertainty identified from previous TAs and published cost-effectiveness analyses, by exploring the sensitivity of the results to the major drivers of cost-effectiveness and by examining whether there are more severe patient subgroups for which omalizumab represents good value for money. Full details on the NICE technology appraisal can be found at http://www.nice.org.uk/guidance/ta278.

Methods

Overview

The cost-effectiveness of omalizumab was evaluated by comparing the additional costs of omalizumab add-on therapy to its additional benefits in terms of improvement in HRQOL and reduction in exacerbations compared with standard care alone over a lifetime horizon. Standard care included optimized therapy at step 4 or 5. Health outcomes were expressed in QALYs. Costs were expressed in UK pound sterling at a 2010 price base from the perspective of the NHS. Both costs and QALYs were discounted at 3.5% per annum as per NICE recommendations [17]. Systematic reviews evaluated the evidence on the effectiveness and safety of omalizumab; these are reported in detail elsewhere [18]. All stages of the work were informed by discussions with clinical advisors.

Population and Subgroups

The population reflects the European Union/UK product license and corresponds to the patient populations enrolled in the randomized controlled trials (RCTs) assessing the clinical effectiveness of omalizumab: patients uncontrolled at step 4 and in the process of moving up to step 5 and patients controlled at step 5 whose asthma would be uncontrolled if they were on step 4 therapy, presented separately by age (adults and adolescents aged ≥12 years and children aged 6–11 years) [6,19–21]. Patient subgroups were defined according to different indicators of severity, which were informed by both clinical and economic considerations on the basis of subgroups evaluated in the previous NICE and SMC appraisals: 1) number of hospitalizations in the past year due to an exacerbation (hospitalization subgroup as per TA133), 2) maintenance OCS use (maintenance OCS subgroup as per SMC recommendations), and 3) three or more exacerbations in the year before trial enrolment (≥3 exacerbations as per TA201).

The Technology

Omalizumab 75-mg (or 150-mg) solution for subcutaneous injection is licensed in patients aged 12 years and older with severe persistent allergic asthma who have a positive skin test result or in vitro reactivity to a perennial aeroallergen, who have reduced lung function as well as frequent daytime symptoms or night-time awakenings, and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist [6]. It is licensed in children aged 6 to 11 years with severe persistent allergic asthma who have a positive skin test result or in vitro reactivity to a perennial aeroallergen and frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist. The dose depends on the patient's weight and serum concentration of immunoglobin E at treatment initiation. Patients should be assessed at 16 weeks for response to treatment before further injections are administered.

Modeling Approach

The model is a cohort Markov model developed in MS Excel 2010 with three health states (day-to-day asthma symptoms with and without omalizumab, asthma death, and other-cause death) and two events (clinically significant severe [CSS] and clinically significant nonsevere [CSNS] exacerbations). This model was built to inform the NICE guidance on omalizumab and adapted and reanalyzed for the purposes of this study. Patients start in the day-to-day asthma symptoms state on either omalizumab add-on therapy or standard therapy alone. At 16 weeks, patients on omalizumab are assessed for response to treatment, at which point omalizumab responders are separated from nonresponders, as per product license [6]. Responders remain on omalizumab for the period of treatment duration while nonresponders are assumed to revert to standard care alone. The cycle length is 16 weeks for the first cycle and 3 months subsequently. During each cycle, patients in the day-to-day symptom state have an elevated risk of asthma mortality and a risk from death from other causes as in the general UK population. Table 1 in Appendix 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2014.07.009 summarizes and justifies the key model assumptions, and Supplemental Figure 1 presents the model structure.

Model Inputs

Table 1 presents model inputs for the base-case population (equivalent tables for each subgroup population are provided in Tables S2–S4 in Appendix 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2014.07.009). Model inputs were mostly based on evidence from the three RCTs conducted in the European Union/UK licensed population that include assessment of response to treatment—The INvestigatioN of Omalizumab in seVere Asthma TrEatment (INNOVATE) [20], Evaluate Xolair for Asthma as Leading Treatment (EXALT) [19], and IA-05 European Union Population (IA-05 EUP) [21]—which are summarized in Table 2. Systematic reviews were conducted to identify relevant studies for asthma mortality, HRQOL improvement with omalizumab, and HRQOL decrement from an exacerbation; these are reported in detail elsewhere [18].

Effectiveness and safety

Omalizumab is modeled to reduce the risk of both CSS and CSNS exacerbations, which, in turn, reduces the risk of asthma death, and to improve HRQOL. The risk ratio for CSS and CSNS exacerbations in patients aged 6 to 11 years observed in IA-05 EUP between responders and patients allocated to placebo was 0.2494 (95%CI 0.1425–0.4362) and 0.5089 (0.3291–0.7869), respectively. INNOVATE was used for the base case because its double-blind placebo-controlled design confers it a lower risk of bias than EXALT (open-label non–placebo-controlled). The proportion of responders corresponds to the proportion of responders observed in the RCTs (IA-05 EUP for patients aged 6–11 years at 74.2% and INNOVATE for patients aged 12 years and older at 56.5%). Responders are assumed to experience the exacerbation rates and