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EDITORIAL

# Economic analysis of biological therapies for severe asthma treatment

Análisis económico de las terapias biológicas en asma grave

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Severe asthma patients (SA) represent a low percentage (5-10%) within the global asthmatic population. However, they represent the most affected group of patients on their quality of life, associated morbidity[1] and resources consumption[2]. Asthma has become a worldwide public health concern, of increasing magnitude and prevalence[3].

Economic burden of SA is considerable in terms of direct and indirect costs[2,3]. Pharmacological therapies represent the main component of direct medical expenses, due -among other factors- to the introduction and availability in recent years of more expensive options, such as biological therapies with monoclonal antibodies (moAb)[4]. This fact insists on the importance of evaluating the costs and results of the different therapeutic options through economic assessments[5], which ensure the sustainability of our health system. Among the economic evaluations, asthma cost-effectiveness analyses (CEA) have been considered as essential to establish the most efficient choice of treatment, when assessing the consequences in natural units (such as the proportion of days without symptoms, improvements in control and number of exacerbations), or in terms of health measures based on quality-adjusted life years (QALY) or disability-adjusted life years (DALY) in a variant of these studies, called cost-utility analysis (CUA)[6].

In Spain, four CEA studies have been published in real life on the use of omalizumab for the treatment of patients with severe asthma[7-10]. The first two studies[7,8] were performed on small samples of patients. Both studies show -with design limitations, such as performing retrospective studies and having a small number of patients-, that omalizumab therapy presented a moderate incremental cost-effectiveness ratio (ICER) (between € 462.08 and € 5423.13), evaluated by the number of exacerbations avoided and a three-point clinically significant increase in the Asthma Control Test (ACT). One of the studies[7] also calculated the cost per QALY, which was amounted to € 26,865. In the third CEA study of the severe asthma with omalizumab therapy in clinical practice by Martínez-Moragón[9], 186 patients treated in the Valencian Community were included. The economic assessment was carried out

by means of an CEA, calculating the ICER, comparing the costs and effectiveness of the pre-omalizumab and post-omalizumab periods, in terms of avoided exacerbation due to asthma and increase in the ACT. To evaluate the treatment's health benefits, a CUA was performed, calculating the incremental cost-utility ratio (ICUR). Direct costs -use of health and pharmacological resources- and indirect costs -impact of the disease on labor productivity according to management data and economic evaluation in the health field- were included, obtaining a QALY cost of € 50,239.98. In a study by Entrenas[10], 220 patients with severe allergic asthma[3] under omalizumab therapy were analyzed, belonging to the communities of Andalusia and Extremadura. The ICER was calculated, and the results of one year prior to, and one year following omalizumab's introduction were compared.

These last studies[9,10], despite their limitations, both agree on the introduction of omalizumab for severe asthma therapy in clinical practice contributing to a decrease in direct and indirect costs. They have also shown very similar results for the ICER, both for calculating avoided exacerbation, and the three-point increase in the ACT, evaluated in euros of 2015 and 2016respectively.

The incorporation of other moAb -such as mepolizumab- into the therapeutic arsenal of severe asthma further complicates medical decision making and resource management[11], which determines the need for economic and budgetary impact evaluation (BIA) of this drug.

The first study carried out in Spain by García Mochón following this line of work[12] investigates the introduction of mepolizumab as a therapy for lgE mediated or not lgE mediated severe refractory eosinophilic asthma in unmonitored adult patients. Their high doses of inhaled corticosteroids (ICS) and adrenergic long-acting agonists (LABA) and/or systemic corticosteroids (SC) are being quantified from the National Health System's (NHS) perspective to calculate direct costs in 2018 euros for a period of 3 years (2018-2020).

The study population included patients older than 12 years with severe refractory asthma to the therapy in Spain. Through Spain's National Statistics Institute (NSI) data, the percentages of severe refractory asthma patients under abovementioned therapy who were diagnosed with eosinophilic asthma and IgE-mediated asthma population, candidate for treatment with omalizumab were calculated. The purpose of the first analysis was to perform a comparative evaluation for lgE mediated severe allergic asthma mediated with ICS + LABA and/or SC. This therapy, together with mepolizumab against the same treatment by adding omalizumab, was compared as well. The second analysis included non-lgE mediated refractory asthma population, and not considering other alternatives to mepolizumab. Thus, the ICS + LABA and/or SC plus mepolizumab combination was contrasted against ICS + LABA and/or SC, not including eosinophilic asthma patients treated with omalizumab. A sensitivity analysis was performed for the variables

(relevant clinical exacerbation, hospitalization and emergency assistance), as well as hospitalization and emergency assistance costs.

The effectiveness was evaluated by annual reduction of relevant exacerbations and by eosinophil count subgroups when using mepolizumab versus its therapeutic alternative. The estimate cost included direct costs from drugs and assistance in the Emergency Department, and costs derived from hospital medication administration were not included.

The results of this study provide data for IgE-mediated eosinophilic asthma (30% of the susceptible population), with increases of € 797/ patient/year of mepolizumab in comparison with omalizumab, which would mean an increase in public spending between 2.3 and € 4.6 million/ year, according to mepolizumab's degree of penetration in the market. If the highest reported price of omalizumab against mepolizumab were considered, a gradual introduction into the NHS or a replacement in the evaluated 3-year period could reduce the cost by € 5 million.

In the case of non -lgE mediated eosinophilic asthma (70% of the susceptible population), the costs for avoided exacerbation are € 5,085 (95% CI: 12,744.2-19,451.6), clearly showing in the subgroup analysis by level of eosinophils a greater relative efficacy and a very sensitive reduction of costs in patients with a higher level of baseline eosinophilia (with > 500 eosinophils/μL € 7,767 (95% CI: 6,999.9-8,999.8)). The BIA for 3 years would be € 568.1 million, which in the subgroup analysis also shows a noticeable reduction for the subgroup of patients with greater baseline eosinophilia (€ 173 million for > 500 eosinophils/μL).

The data set forces us to reflect on the situation of selecting the type of moAb, from the pharmacoeconomic and sustainability perspective. There is no solid evidence on a marker or set of markers that help the choice of one drug over another for a patient with asthma and eosinophilic component, outside the justified clinical situation. Nor do we have a direct comparison between omalizumab and mepolizumab. On the other hand, previous studies -which can include the subgroup analysis of the pivotal cost-effectiveness studies of mepolizumab[13]- show that patients with a greater baseline eosinophilic component obtain greater benefit, which makes mepolizumab to be used as a priority -except for justified exceptional nature- in patients with non-lgE mediated severe refractory eosinophilic asthma, in patients with greater than or equal to 500/ μL eosinophil plasma levels, as indicated in the therapeutic positioning report[13].

Bermejo[14] describes the mepolizumab evaluation process by the National Institute for Health and Care Excellence (NICE), and shows similar results to those obtained in García Mochón's work[12] in cost per QALY for a greater than or equal to 300/μL eosinophil count. Other studies that perform CUA of added mepolizumab to the standard therapy[15], and that determine the incremental cost per QALY in a lifetime horizon, conclude that in their environment (United States of America), this cost exceeds the coverage thresholds used, even in the

case of respondents to mepolizumab. Therefore, these authors[15], as in the work of García Mochón[12], suggest that health authorities should consider negotiating significant discounts on mepolizumab prices. The economic evaluation, in a limited resources context, should make the clinician reflect on the most efficient treatment in this profile of patients with severe refractory asthma to conventional treatment.

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