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TREATMENT AND ECONOMICS

Cost-effectiveness of omalizumab in severe persistent asthma in Spain: a real-life perspectiveAlberto Nahon Levy, MD PhD¹, Antonio J. García a Ruiz, MD PhD², Nuria García-Agua Soler, MD², and María Victoria Hidalgo Sanjuan, MD PhD¹¹Servicio de Neumología, Hospital Universitario Virgen de la Victoria, Málaga, Spain and ²Departamento de Farmacología, Facultad de Medicina, Cátedra de Economía de la Salud y URM, Universidad de Málaga, Málaga, Spain**Abstract**

Objectives: To determine the cost-effectiveness of omalizumab compared with routine clinical practice in the treatment and control of severe persistent asthma. **Methods:** Cost-effectiveness analysis using pre- and post-treatment with omalizumab after 10 months of 47 patients diagnosed with uncontrolled severe persistent asthma attended by the Pneumology Service, Hospital Universitario Virgen de la Victoria, Malaga. Effectiveness was assessed by the number of emergency room (ER) visits for exacerbations and quality-adjusted life years (QALY) gained. The costs of treatment with omalizumab and ER visits were analyzed using the National Health System perspective. Results are expressed in cost per QALY gained and cost per ER visit avoided (costs €2012). **Results:** Exacerbations with ER visits decreased significantly ($p < 0.001$) after 10 months of omalizumab treatment compared with the previous 10 months [7.94 (6.52–9.37) vs 0.19 (0.03–0.35)]. Health utilities increased significantly ($p < 0.001$) during the same period [0.5967 (0.5722–0.6212) vs 0.7566 (0.7232–0.7900)], representing 0.1333 (0.1053–0.1612) QALYs gained ($p < 0.001$). The mean cost per patient was €1850.78 (1519.46–2182.10) in the 10 months before treatment and €5431.87 (4930.72–5933.02) after 10 months of omalizumab treatment. The incremental cost-effectiveness ratios (ICERs) were €462.08/exacerbation avoided (347.65–606.22) and €26 864.89/QALY gained (21 632.07–33 859.49). **Conclusions:** Our results confirm that adding omalizumab to the treatment of patients with uncontrolled severe persistent asthma reduces the number of exacerbations with ER visits and increases health-related quality of life after 10 months of treatment and produces ICERs favorable to omalizumab and acceptable from the health system perspective.

Keywords

Asthma, cost-utility, effectiveness, healthcare costs, omalizumab

History

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Introduction

The clinical manifestations of asthma can be controlled with correct treatment. Controlled asthma should not cause anything more than decompensations, and severe exacerbations should be rare. It is estimated that asthma affects 300 million people worldwide [1] and 5% of the adult population in Spain [2], although the prevalence among adolescents is increasing [3].

Severe asthma is estimated to occur in approximately 10% of the affected population, and a substantial proportion of severe cases are attributable to allergic immunoglobulin E (IgE) mechanisms [4].

The severity of asthma is classified on the basis of the intensity of treatment required to achieve good control of symptoms [1]. Mild to moderate persistent asthma can usually be controlled with low or medium doses of inhaled corticosteroids (ICS) and long-acting β_2 -adrenergic agonists, while

severe persistent asthma is often not well controlled with these treatments.

Omalizumab is a humanized monoclonal antibody that targets circulating IgE molecules. Omalizumab is administered subcutaneously in inflammatory processes due to allergic asthma that underlie the symptoms observed in patients with severe persistent allergic asthma, with frequent exacerbations and a lack of response to the drugs commonly used in this disease [5].

The therapeutic efficacy and safety of omalizumab added to ICS-based treatments have been evaluated in several clinical trials in both adults and adolescents and children with persistent allergic asthma. The rate of asthma exacerbations per patient was significantly lower (reductions between 25% and 48%) in patients treated with omalizumab compared with those receiving placebo in all studies assessing this outcome as the primary endpoint, and there was a reduction in asthma symptoms [6–10] and the need to use ICS and rescue medication [7,11,12]. These results have been corroborated in clinical practice by multiple observational studies that have shown that omalizumab is effective as an

additional treatment in patients with severe persistent allergic asthma [13–20].

Economic evaluations are a useful rationing tool in healthcare decisions. Cost-effectiveness analysis (CEA) allows the comparative analysis of new health technologies in terms of their costs and their clinical outcomes. The results of CEA can be measured in a comparable unit in terms of health, such as quality-adjusted life years (QALY), i.e. the result of this type of analysis provides information on the cost of a QALY gained between the various treatment options compared, thus estimating their relative value [21]. These special cases of CEA, when clinical outcomes are expressed in terms of QALY, are usually called cost-utility analyses.

European studies evaluating the effectiveness of omalizumab (added to optimal standard treatment in patients with severe persistent asthma) have shown that omalizumab is a cost-effective option with a cost per QALY gained of between €23 880 and €56 091 [22–24]. Conversely, Wu et al. [25] using a mathematical model showed that omalizumab is not cost-effective for most patients with severe asthma over a 10-year time horizon. In Spain, there are as yet no data on the cost-effectiveness of omalizumab. Therefore, research about cost-effectiveness of omalizumab in the real Spanish clinical practice shall be helpful to health-policy decision makers in Spain.

The objective of this study was to determine the cost-effectiveness of omalizumab compared with routine clinical practice in the treatment and control of severe allergic asthma based on clinical data obtained from the Severe Asthma Unit, Pneumology Service, Hospital Universitario Virgen de la Victoria (HUVV), Malaga.

Materials and methods

Design and study population

This study was an *ad hoc* analysis of a cohort of 79 patients attended by the Severe Asthma Unit, HUVV, between 1 July 2008 and 1 July 2012. We carried out a CEA of omalizumab compared with routine clinical practice in the treatment and control of severe allergic asthma based on clinical data and the use of resources registered. The clinical consequences (measured in exacerbations and translated into QALYs) and economic consequences (cost per patient) were calculated for each option compared.

The registry collected the number of exacerbations resulting in emergency room (ER) visits, spirometric variables such as fractional exhaled nitric oxide (FeNO) and forced expiratory volume in 1 second (FEV₁) and the quality of life through administration of the reduced Spanish version of the Mini Asthma Quality of Life Questionnaire (MiniAQLQ) [26]. This self-administered questionnaire consists of 15 validated questions grouped into four areas: symptoms, activity limitation, emotional function and environmental stimuli. Responses were rated on a scale of 1–7 (where 1 represents the highest degree of disability and 7 the highest degree of autonomy).

Patients who fulfilled the following inclusion criteria were selected for evaluation: age >14 years, diagnosed with severe persistent asthma not controlled after >1 year of follow-up

and who had been seen at 4 and 10 months after the initiation of treatment with omalizumab. Severe persistent asthma was diagnosed and defined according to the Spanish Guidelines for Asthma Management [27]. Before treatment with omalizumab, the patients had been treated with the standard treatment for this type of diagnosis according to the Spanish Guidelines for Asthma Management [27]. Smokers, ex-smokers of less than one year, pregnant women, patients with comorbidities such as intercurrent infections or active neoplasm and patients diagnosed with chronic occlusive pulmonary disease were excluded.

At the initiation of omalizumab treatment, patients were asked about their history of exacerbations in the three months before treatment with omalizumab to verify information registered in each patient medical record, were administered the MiniAQLQ and spirometric variables were collected. In subsequent visits, 4 and 10 months after initiation of treatment with omalizumab, the number of exacerbations and spirometric variables were collected and the MiniAQLQ administered again. The number of exacerbations before the start of treatment with omalizumab (data for three months, collected from each patient medical record and verified in a personal interview with each patient) was linearly extrapolated to 10 months (by multiplying by 10/3) in order to facilitate the comparison.

Options to compare

The efficiency of two treatment alternatives was compared:

- (1) Standard therapy for severe persistent asthma, understood as the treatment indicated by clinical guidelines for the management of this condition (pre-omalizumab period).
- (2) The addition of omalizumab to previous standard treatment and treatment monitoring in a specific severe persistent asthma unit (post-omalizumab period).

Measures of effectiveness

Effectiveness data were based on the results at 10 months for patients who initiated omalizumab therapy, compared with the 10 months before initiation of omalizumab therapy.

The effectiveness indicators used to compare the options were as follows: (1) the number of exacerbations with ER visits and (2) QALYs calculated from the utilities obtained from the MiniAQLQ.

Utilities

Utilities or the preferences of the patients were used to consider the impact of treatment on the quality of life. Utility values were expressed on a numerical scale where the extreme values were 0 and 1, with 0 representing “death” and 1 representing “perfect health” [28]. Thus, when the quality of life worsens, the utilities and QALYs are reduced. QALYs are overall measures of health outcomes that weight the life expectancy of patients with an estimate of their health-related quality of life score (utilities).

Utilities were calculated from MiniAQLQ scores. To our knowledge, there are no mappings from MiniAQLQ to EQ-5D index values. Then, in our approach MiniAQLQ scores were transferred to the EQ-5D metric, using linear models based

on the correlation between both scores according to Chen et al. [29].

Utilities for the pre-omalizumab period were measured at baseline (time point 0), and utilities for the post-omalizumab period were measured at 10 months after time point 0. Then, QALYs were estimated from utility measures (pre- and post-omalizumab) and refer to 10 months.

Costs

Direct healthcare costs (updated to 2012) were derived from the recorded number of ER visits for exacerbations and the additional use of omalizumab. The costs of standard treatments were not taken into account because they were considered to be the same for both periods. Similarly, medical visits were considered to be the same for both periods, since the patients were attended by the Severe Asthma Unit with the same periodicity in both periods. The cost per ER visit was €233 (internal hospital data), and the cost of treatment with omalizumab was 2.46€/mg [30].

Cost-effectiveness calculations

In terms of cost-effectiveness, the incremental cost per ER visit avoided and QALY gained was obtained using the incremental cost-effectiveness ratio (ICER). The ICER is defined as the ratio of the change in costs to the change in effects of a specific intervention compared to an alternative. The ICER indicates the additional cost of obtaining one additional unit of outcome. The ICER was calculated using the formula:

$$\frac{\text{Cost}_{\text{post}} - \text{cost}_{\text{pre}}}{\text{Effectiveness}_{\text{post}} - \text{effectiveness}_{\text{pre}}}$$

Confidence intervals (CIs) for the ICER were computed based on bootstrapping using sampling with replacement (the size of the new samples was equal to the original size). We ran 10 000 simulations, and the 2.5th and 97.5th percentiles from the simulations were used to determine a 95% CI.

Perspective and time horizon

The economic evaluation was conducted from the perspective of the Spanish National Health System (NHS). The time horizon of the analysis was the 10 months before and after initiation of treatment with omalizumab in the severe asthma unit.

Sensitivity analysis

In order to evaluate the uncertainty around the extrapolation assumption for pre-omalizumab outcomes and the unit costs, univariate sensitivity analyses were performed. First, we changed the multiplication factor of the extrapolation (base case, 10/3) assuming two different factors: multiplying by 2 or by 5. Second, we tested the effect of varying the costs of ER visit to two-fold and five-fold the costs of the base case (€233).

Statistical analysis

Effectiveness and costs in the two periods were compared using the nonparametric Mann–Whitney *U* test, due to the non-normal distributions of the variables. The level of

significance was established as 5%. All analyzes were performed using the R version 3.1.0 statistical package [31].

Results

Of the 79 patients of the initial cohort of study, 50 patients had a minimum follow-up of 10 months for comparing proposes. Of them, three patients were excluded because they had missing data for the study outcomes. The final sample for analysis included 47 patients.

Fourteen (29.8%) patients were males with a mean baseline age of 54 (SD = 12.67) years. A reduction of ICS and rescue medication was observed from initial visit and at 10 months of follow-up. While 34 (72.3%) patients needed inhaled and oral corticosteroids at the initial visit, no patient needed such treatment 10 months later. The quality of life increased significantly ($p < 0.001$) according to the MiniAQLQ scores at the initial visit and after 10 months of omalizumab treatment [2.21 (1.92–2.49) vs. 4.05 (3.65–4.44)]. This improvement was associated with a significant clinical improvement in the quantification of FeNO, with mean values of 43.67 parts per billion (ppb) (34.13–53.22) without omalizumab and 28.85 ppb (23.12–34.58) after 10 months of omalizumab ($p = 0.02$). FEV₁ values showed no significant changes [66.96 (60.46–73.45) vs. 68.79 (62.57–75.01), $p = 0.6$] (Table 1).

Omalizumab added to standard treatment provided greater effectiveness than standard treatment alone, representing 0.1333 (0.1053–0.1612) QALYs gained [0.4972 (0.4768–0.5177) vs. 0.6305 (0.6027–0.6584), $p < 0.001$] and reducing ER visits due to exacerbations in the 10 months of omalizumab by 7.75 (6.37–9.14) [7.94 (6.52–9.37) vs. 0.19 (0.03–0.35), $p < 0.001$] (Table 2).

The mean costs per patient were €5431.87 (4930.72–5933.02) for the 10 months of omalizumab treatment and €1850.78 (1519.46–2182.10) for the pre-omalizumab period (Table 2). Therefore, the ICER in terms of cost per life year gained between the two periods was €26 864.89/QALY (21 632.07–33 859.49). The ICER evaluating the reduction in exacerbations was €462.08/exacerbation avoided (347.65–606.22) (Table 3).

Table 4 presents the results of the sensitivity analysis when the assumptions on the extrapolation of exacerbations for the pre-omalizumab period and on unit cost for ER visits were changed. The results suggest that the ICER is sensitive to the change in the extrapolation multiplication factor and unit costs. When the multiplication factor of the extrapolation increased, the ICERs decreased, which means that the cost for each additional unit of clinical outcome was lower. Similarly, when unit cost for ER visits increased, the ICERs decreased. The results were maintained at the cost-effectiveness thresholds.

Discussion

We evaluated the efficiency of treatment with omalizumab compared with standard treatment in 47 patients with severe persistent asthma. The addition of omalizumab was more effective than previous standard treatment, providing 0.1333 (0.1053–0.1612) QALYs gained. The difference in mean costs per patient was €3581.09 (3015.24–4146.95). Therefore, the ICER of omalizumab compared to previous standard

Table 1. Baseline and follow-up characteristics of patients included in analysis^a.

	Baseline	Follow-up of 10 months
Initial age [years], mean (SD)		54 (12.67)
Male, n (%)		14 (29.8%)
FEV ₁ [%], mean (SD)	66.96 (22.12)	68.79 (21.19)
FeNO [ppb], mean (SD) ^b	43.67 (32.13)	28.85 (19.52)
Asthma medications, n (%) ^b		
without inhaled corticosteroids	0 (0.0%)	1 (2.1%)
with low-dose inhaled corticosteroids	0 (0.0%)	19 (40.4%)
with high-dose inhaled corticosteroids	12 (25.5%)	26 (55.3%)
inhaled and oral corticosteroids	34 (72.3%)	0 (0.0%)
Monthly dose of omalizumab [mg], mean (SD)	–	217.02 (66.78)
Exacerbations with ER visits, mean (SD)	2.38 (1.45) ^c	0.19 (0.54)
MiniAQLQ score, mean (SD)	2.21 (0.97)	4.07 (1.32)

^aN = 47 patients with no missing data for the variables: exacerbations with ER visits, MiniAQLQ score and cost variables.
^bSome data were missing. Percentages at baseline and at 10 months of follow-up, respectively, were: FeNO, 2.1% and 0.0%; asthma medications, 2.1% and 2.1%.
^cData collected at the initial visit on the three previous months.

Table 2. Effectiveness and costs before and after treatment with omalizumab.

	Pre-omalizumab Mean (95% CI)	Post-omalizumab Mean (95% CI)	Δ (95% CI) ^a	p ^b
Exacerbations with ER visits	7.94 (6.52–9.37)	0.19 (0.03–0.35)	7.75 (6.37–9.14)	<0.001
Utility values	0.5967 (0.5722–0.6212)	0.7566 (0.7232–0.7900)	0.1599 (0.1264–0.1934)	<0.001
QALYs	0.4972 (0.4768–0.5177)	0.6305 (0.6027–0.6584)	0.1333 (0.1053–0.1612)	<0.001
Cost per patient (€)	1850.78 (1519.46–2182.10)	5431.87 (4930.72–5933.02)	3581.09 (3015.24–4146.95)	<0.001

Data for the pre-omalizumab period are data at 10 months extrapolated from the data collected at the initial visit on the three previous months. Data for the post-omalizumab period correspond to the visit at the tenth month after the addition of omalizumab.
CI, confidence interval; ER, emergency room; QALYs, quality-adjusted life years.
^aΔ = (pre-omalizumab) – (post-omalizumab) for exacerbations with ER visits. Δ = (post-omalizumab) – (pre-omalizumab) for utility, QALYs and costs.
^bMann–Whitney *U* test.

Table 3. Incremental cost-effectiveness ratio.

ICER (95% CI)	
Cost per exacerbation avoided	€462.08/exacerbation avoided (347.65–606.22)
Cost per QALY	€26 864.89/QALY (21 632.07–33 859.49)

ICER = incremental cost-effectiveness ratio and QALY = quality-adjusted life year.

Table 4. Univariate sensitivity analyses.

	Cost per exacerbation avoided	Cost per QALY
Extrapolation of pre-omalizumab exacerbations		
×2	943.54 (748.68–1190.11)	32 418.60 (26 609.71–40 442.73)
×5	226.60 (151.56–321.61)	19 922.73 (14 907.45–26 057.68)
Unit cost for ER visits		
×0.5	578.60 (464.15–722.72)	33 639.76 (27 688.46–41 866.46)
×2	229.02 (114.65–373.22)	13 315.30 (7811.98–19 309.08)

treatment was €26 864.89 per QALY gained (21 632.07–33 859.49), i.e. below the commonly accepted willingness-to-pay threshold in Spain of €30 000 per QALY gained [32].

The clinical results are consistent with those published in previous clinical trials [6–10] and observational studies [13–20]. Compared with the pre-omalizumab period, there was a reduction in FeNO levels and the frequency of exacerbations after treatment with omalizumab. Moreover, the quality of life improved systematically, as shown by the MiniAQLQ scores.

The results of the CEA were also consistent with those of other studies. A recent review by the National Institute for Health and Clinical Excellence of the results of six published studies evaluating the cost-effectiveness of omalizumab for asthma concluded that the most plausible ICER was £23 200/QALY (approximately €27 100/QALY) [23]. An observational Dutch study (eXpeRience) including 154 patients with a methodology similar to ours found an ICER of €38 371/QALY (sensitivity analysis: 14 504–80 332) after one year of omalizumab treatment compared to the year before [33]. Likewise, an observational study of 23 patients from northeastern Italy comparing one year of omalizumab treatment with the previous year found an ICER of €25 983/QALY [34], very close to our result, and an extension of this study to three years with 16 patients from the same cohort found an ICER of €23 880/QALY [22].

On the other hand, Wu et al. [25] showed that omalizumab is not cost-effective for patients with severe asthma over 10-year time horizon. The main differences between this study and ours is that the study by Wu et al. was based on a mathematical model with input data from published studies and extrapolated over 10 years; and our study is based on a cohort of patients in real clinical practice. Second, the unit cost for omalizumab in Spain is lower than in the United States. While the cost of omalizumab in the study of Wu et al. ranges from \$15 000 to \$44 000 (approximately, from €10 800 to €31 800) per patient-year, in this study, the mean cost of omalizumab was €6411, ranging from €4431 to €8862, per patient-year.

To the date, there are no reported studies specifically designed to evaluate the pharmacoeconomic impact of omalizumab for severe asthma in clinical conditions in terms of cost-effectiveness in Spanish patients. Therefore, the results of this study may represent the first available contribution on this subject in the Spanish context.

As in all observational studies, the study had limitations inherent in the data used. The analysis was performed with the entire data set as all patients with missing data on exacerbations were excluded. However, despite having to exclude many patients, the sample size analyzed was greater than that of other studies of the same characteristics carried out in other countries. However, the results of this study cannot be extrapolated to all patients with asthma. The study cohort consisted of patients with severe persistent asthma, so the results should only be considered in similar populations. Similarly, the high frequency of women in the study population limits the extrapolation of our results to other populations with different gender distribution.

Another limitation of this study is the selected sample for analysis. The main reason for excluding patients was lack of follow-up in post-omalizumab period due to administrative dates of study. Only three patients were excluded because data of exacerbations in pre-omalizumab period were missing. Therefore, the selection bias was minimized.

A limitation of the study is that only the cost of omalizumab was considered in the calculation of drug costs, excluding the costs of other standard treatments. These costs were not taken into account because they were considered to be the same for both periods. However, if these costs had been calculated, there would probably have been a saving in the costs incurred during the period of omalizumab treatment because a reduction in the doses of ICS and rescue medication have been observed in patients with severe persistent asthma when omalizumab is added [7,11,12]. Therefore, the ICER would have been lower than that finally obtained. Similarly, medical visits were considered to be the same for both periods, since the patients were attended by the Severe Asthma Unit with the same periodicity in both periods.

Another limitation arises from the number of exacerbations for the pre-omalizumab period. Patients were asked about their history of exacerbations in the three months before treatment with omalizumab to verify information registered in each patient medical record. This information may be biased. On the one hand, patients could have sought medical help outside the HUVV (leading to underestimation), but it is very unlikely not to report back at the initial visit. Furthermore, if some patients did not report ER visits outside the HUVV, their history of exacerbations would be underestimated and, therefore, the effectiveness results of our study would also be underestimated. On the other hand, the history of exacerbations may be affected by recall bias, but the answers of patients were verified in medical record, minimizing this potential bias.

An important limitation of the study is consequence of the extrapolation of the number of previous exacerbations to 10 months (by multiplying by 10/3). This extrapolation has not taken into account seasonality. However, patient enrolments happened all along the year. Therefore, possible

overestimation errors for some patients were offset by underestimation errors for remaining patients. In order to overcome this limitation, we performed a sensitivity analysis considering alternative multiplication factors: two assuming that data collection was performed in seasons with high risk of exacerbation and five in seasons with low risk of exacerbation. In both cases, the results of sensitivity analysis showed that costs per QALY hold at an acceptable cost-effectiveness ratios.

Another limitation of this study is the way how EQ-5D scores were obtained. Patients were administered the reduced Spanish version of the MiniAQLQ, but not the EQ-5D questionnaire, at each follow-up visits. To our knowledge, there are no mappings from MiniAQLQ to EQ-5D index values. Therefore, we used a linear model based on correlation between both scores, according to Chen et al. [29], as a way to overcome the lack of mapping studies.

Another potential limitation was that we did not study asthma-related mortality. There is evidence that patients with uncontrolled asthma have an increased risk of mortality [35,36]. However, mortality indicators should not have had much impact on this study as the time horizon of 10 months pre-and post-omalizumab, and the long-term clinical outcomes of the reduction in exacerbations would be greater in assessments carried out over the lifetime of the patients. It might be expected that if mortality had been considered, the results would have been more favorable to omalizumab treatment since the mortality risk is associated with exacerbations and there was a significant decrease in these the period with omalizumab treatment.

In conclusion, the results of this study confirm that the addition of omalizumab in patients with severe persistent allergic asthma uncontrolled by standard treatments leads to a substantial and systematic improvement in clinical outcomes and health-related quality of life. The total cost per exacerbation avoided by the use of omalizumab was €462.08, for the 10-month time horizon. In addition, an ICER of €26 864.89/QALY was obtained, which is acceptable from the Spanish NHS perspective.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

This study was carried out with the financial collaboration of Novartis.

Authors' contributions

All authors read and approved the final manuscript. A. L. N. and A. J. G. R. conceived and designed the study. A. L. N., A. J. G. R., N. G-A. S. and M. V. H. S. performed the data analysis, obtained the results and drafted the manuscript and the discussion of the selected results for publication.

References

1. Global Initiative for Asthma. Global strategy for asthma management and prevention [Online]. 2012 Dec (update). Available from: http://www.ginasthma.org/local/uploads/files/GINA_Report_March13.pdf [last accessed Sep 2013].
2. Martínez-Moratalla J, Almar E, Sunyer J, Ramos J, Pereira A, Payo F. European asthma study. Identifying and treating young

- adults with epidemiological criteria for asthma in five areas of Spain. Spanish Group of the European Asthma Study. *Arch Bronconeumol* 1999;35:223–228.
3. García-Marcos L, Quirós AB, Hernández GG, Guillén-Grima F, Díaz CG, Ureña IC, et al. Stabilization of asthma prevalence among adolescents and increase among schoolchildren (ISAAC phases I and III) in Spain. *Allergy* 2004;59:1301–1307.
 4. The ENFUMOSA Study Group. The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. *Eur Resp J* 2003;22:470–477.
 5. Xolair®. Ficha Técnica del medicamento. The European Agency for the Evaluation of Medicinal Products (EMA). Committee for Proprietary Medicinal Products (CPMP). European Public Assessment Report (EPAR): Xolair®. Available from: <http://www.ema.europa.eu>. Last Accessed January 2014.
 6. Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J, Rosen KE, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med* 2011;154:573–582.
 7. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, van As A, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001;108:184–190.
 8. Bardelas J, Figliomeni M, Kianifard F, Meng X. A 26-week, randomized, double-blind, placebo-controlled, multicenter study to evaluate the effect of omalizumab on asthma control in patients with persistent allergic asthma. *J Asthma* 2012;49:144–152.
 9. Humbert M, Beasley R, Ayres J, Slavin R, Hébert J, Bousquet J, Beeh KM, et al. Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 2005;60:309–316.
 10. Bousquet J, Cabrera P, Berkman N, Buhl R, Holgate S, Wenzel S, Fox H, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy* 2005;60:302–308.
 11. Holgate ST, Chuchalin AG, Hébert J, Lötval J, Persson GB, Chung KF, Bouquet J, et al. Omalizumab 011 International Study Group. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy* 2004;34:632–638.
 12. Lanier BQ, Corren J, Lumry W, Liu J, Fowler-Taylor A, Gupta N. Omalizumab is effective in the long-term control of severe allergic asthma. *Ann Allergy Asthma Immunol* 2003;91:154–159.
 13. Braunstahl GJ, Chen CW, Maykut R, Georgiou P, Peachey G, Bruce J. The eXpErience registry: the ‘real-world’ effectiveness of omalizumab in allergic asthma. *Respir Med* 2013;107:1141–1151.
 14. Barnes N, Menzies-Gow A, Mansur AH, Spencer D, Percival F, Radwan A, Niven R. Effectiveness of omalizumab in severe allergic asthma: a retrospective UK real-world study. *J Asthma* 2013;50: 529–536.
 15. Schumann C, Kropf C, Wibmer T, Rüdiger S, Stoiber KM, Thielen A, Rottbauer W, et al. Omalizumab in patients with severe asthma: the XCLUSIVE study. *Clin Respir J* 2012;6:215–227.
 16. Brusselle G, Michils A, Louis R, Dupont L, Van de Maele B, Delobbe A, Pilette C, et al. ‘‘Real-life’’ effectiveness of omalizumab in patients with severe persistent allergic asthma: the PERSIST study. *Respir Med* 2009;103:1633–1642.
 17. Korn S, Thielen A, Seyfried S, Taube C, Kornmann O, Buhl R. Omalizumab in patients with severe persistent allergic asthma in a real-life setting in Germany. *Respir Med* 2009;103:1725–1731.
 18. Cazzola M, Camiciottoli G, Bonavia M, Gulotta C, Ravazzi A, Alessandrini A, Caiaffa MF, et al. Italian real-life experience of omalizumab. *Respir Med*. 2010;104:1410–1416.
 19. Korn S, Schumann C, Kropf C, Stoiber K, Thielen A, Taube C, Buhl R. Effectiveness of omalizumab in patients 50 years and older with severe persistent allergic asthma. *Ann Allergy Asthma Immunol*. 2010;105:313–319.
 20. Grimaldi-Bensouda L, Zureik M, Aubier M, Humbert M, Levy J, Benichou J, Molimard M, et al. Pharmacoeconomics of Asthma and Xolair (PAX) Study Group. Does omalizumab make a difference to the real-life treatment of asthma exacerbations? Results from a large cohort of patients with severe uncontrolled asthma. *Chest* 2013;143:398–405.
 21. López Bastida J, Oliva J, Antoñanzas F, García-Altés A, Gisbert R, Mar J, Puig-Junoy J. Propuesta de guía para la evaluación económica aplicada a las tecnologías sanitarias. *Gac Sanit* 2010; 24:154–170.
 22. Dal Negro RW, Tognella S, Pradelli L. A 36-month study on the cost/utility of add-on omalizumab in persistent difficult-to-treat atopic asthma in Italy. *J Asthma* 2012;49:843–848.
 23. National Institute for Health and Clinical Excellence (NICE). Omalizumab for treating severe persistent allergic asthma (review of technology appraisal guidance 133 and 201) [Online]. 2013 Apr. Available at: <http://www.nice.org.uk/nicemedia/live/14157/63689/63689.pdf>. [last accessed Sep 2013].
 24. Dewilde S, Turk F, Tambour M, Sandström T. The economic value of anti-IgE in severe persistent, IgE-mediated (allergic) asthma patients: adaptation of INNOVATE to Sweden. *Curr Med Res Opin* 2006;22:1765–1776.
 25. Wu AC, Paltiel AD, Kuntz KM, Weiss ST, Fuhlbrigge AL. Cost-effectiveness of omalizumab in adults with severe asthma: results from the Asthma Policy Model. *J Allergy Clin Immunol* 2007;120: 1146–1152.
 26. Juniper EF, Guyatt GH, Cox FM, Ferrie PJ, King DR. Development and validation of the Mini Asthma Quality of Life Questionnaire. *Eur Respir J* 1999;14:32–38.
 27. Comité Ejecutivo GEMA 2009. Guía española del manejo del asma. *Arch Bronconeumol* 2009;45:2–35.
 28. Dilla T, González de Dios J, Sacristán JA. Evaluación Económica en Medicina (I): fundamentos y Metodología. *Evid Pediatr* 2009;5:71.
 29. Chen H, Gould MK, Blanc PD, Miller DP, Kamath TV, Lee JH, Sullivan SD. TENOR Study Group. Asthma control, severity, and quality of life: quantifying the effect of uncontrolled disease. *J Allergy Clin Immunol* 2007;120:396–402.
 30. CGCOF. Consejo General del Colegio Oficial de Farmacéuticos. Base de datos del medicamento [Online]. 2012. Available from: <http://www.portalfarma.com> [last accessed Dec 2012].
 31. R Core Team. 2013. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing.
 32. Sacristán JA, Oliva J, Del Llano J, Prieto L, Pinto JL. Qué es una tecnología sanitaria eficiente en España? *Gac Sanit* 2002;16: 334–343.
 33. van Nooten F, Stern S, Braunstahl GJ, Thompson C, Groot M, Brown RE. Cost-effectiveness of omalizumab for uncontrolled allergic asthma in the Netherlands. *J Med Econ* 2013;16:342–348.
 34. Dal Negro RW, Pradelli L, Tognella S, Micheletto C, Iannazzo S. Cost-utility of add-on omalizumab in difficult-to-treat allergic asthma in Italy. *Eur Ann Allergy Clin Immunol* 2011;43:45–53.
 35. Watson L, Turk F, James P, Holgate ST. Factors associated with mortality after an asthma admission: a national United Kingdom database analysis. *Respir Med* 2007;101:1659–1664.
 36. Löwhagen O, Ekström L, Holmberg S, Wennerblom B, Rosenfeldt M. Experience of an emergency mobile asthma treatment programme. *Resuscitation* 1997;35:243–247.