COST-EFFECTIVENESS OF OMALIZUMAB FOR THE TREATMENT OF SEVERE PEDIATRIC ALLERGIC ASTHMA-RESULTS OF A REAL-LIFE STUDY IN SPAIN

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Abstract

BACKGROUND Severe Pediatric Allergic Asthma (SPAA) induces a huge economic burden in terms of direct, indirect and intangible costs. The use of omalizumab for the treatment of these patients has produced a significant improvement in several clinical outcomes, but at the same time, the cost for the management of the disease has also increased. The aim of this report was to evaluate whether the use of omalizumab is cost-effective. **METHODS** A sample of 426 children with SPAA from the ANCHORS study was used to calculate the Incremental Cost Effectiveness Ratio (ICER) for the avoidance of Moderate to Severe Exacerbations (MSE), and also for the improvement in childhood Asthma Control Test (c-ACT) or the Asthma Control Questionnaire (ACQ5). We retrospectively collected data of health encounters and drug consumption before and up to six years after the beginning of the treatment with omalizumab. **RESULTS** The ICER per avoided MSE was \euro2,107 after one year, and it consistently decreased to \euro656 in those followed up to six years. Similarly, the ICER for the Minimally Important Difference in control tests showed a decrease from \euro2,059 to \euro380 per each 0.5 points of improvement in ACQ5, and from \euro3,141 to \euro2,322 per each 3 points improvement in c-ACT, at years 1 and 6 respectively. **CONCLUSION** The use of OMZ is a cost-effective option for most children with uncontrolled SPAA, mainly those who have frequent exacerbations, showing progressively reduced costs in successive years of treatment.

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ABSTRACT

BACKGROUND

Severe Pediatric Allergic Asthma (SPAA) induces a huge economic burden in terms of direct, indirect and intangible costs. The use of omalizumab for the treatment of these patients has produced a significant improvement in several clinical outcomes, but at the same time, the cost for the management of the disease has also increased.

The aim of this report was to evaluate whether the use of omalizumab is cost-effective.

METHODS

A sample of 426 children with SPAA from the ANCHORS study was used to calculate the Incremental Cost Effectiveness Ratio (ICER) for the avoidance of Moderate to Severe Exacerbations (MSE), and also for the improvement in childhood Asthma Control Test (c-ACT) or the Asthma Control Questionnaire (ACQ5). We retrospectively collected data of health encounters and drug consumption before and up to six years after the beginning of the treatment with omalizumab.

RESULTS

The ICER per avoided MSE was \euro2,107 after one year, and it consistently decreased to \euro656 in those followed up to six years. Similarly, the ICER for the Minimally Important Difference in control tests showed a decrease from \euro2,059 to \euro380 per each 0.5 points of improvement in ACQ5, and from \euro3,141 to \euro2,322 per each 3 points improvement in c-ACT, at years 1 and 6 respectively.

CONCLUSION

The use of OMZ is a cost-effective option for most children with uncontrolled SPAA, mainly those who have frequent exacerbations, showing progressively reduced costs in successive years of treatment.

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KEYWORDS

Severe Pediatric Allergic Asthma, Biologics, Omalizumab, Pharmacoeconomics, ICER, Cost

INTRODUCTION

Asthma is one of the most common chronic diseases in children;(1) prevalence in Europe ranges from 2.2% to 11.9%.(2) Asthma in children accounts for approximately half of asthma-related hospitalizations in Canada, (3) and so it is accountable for huge costs, which are comprehensively very difficult to estimate as they include:

- Direct costs (spent resources) incurred by the health system, society, family and individual patient: healthcare and non-healthcare costs.(4,5)
- Indirect costs (unearned resources) because of productivity losses due to morbidity and mortality, borne by the individual, family, society, or the employer.(4,5)
- Intangible costs, related to impairment of quality of life (QoL), limitation of physical and school activities, with consequences such as depression, fear, grief, stress, anxiety, etc.(5)

In the US, the total direct costs of pediatric asthma in 2013 accounted for $5.9 billion, mainly due to hospitalizations and emergency department visits.(6) In this context, severe asthma accounts for the majority of asthma costs. Most of the proposed definitions for severity include poor symptom control and use of high doses of medication, and many also include frequent exacerbations.(7) Despite its low prevalence (up to 5% of cases), severe forms account for a considerable proportion of the disease-related costs.(7,8) Poor symptom control, in addition, is associated with lower QoL of asthmatic children and their caregivers.(9,10)

Children aged [?] 6 years with severe persistent allergic asthma (SPAA) not controlled with high-dose inhaled corticosteroids (ICS) plus long-acting beta-agonists (LABA) have the option to receive targeted therapy with omalizumab (OMZ).(1) This monoclonal antibody prevents IgE from binding to the FceRI receptors, avoids the activation and triggering of the allergic cascade, and downregulates the production of IgE.(11) Clinical trials (12–14) and real life studies (15–18) have demonstrated the safety, efficacy and effectiveness of OMZ in pediatric patients, showing a reduction of symptoms, exacerbations, use of rescue medication, medical visits and hospitalizations, and an improvement in QoL.

Although there are some studies analyzing the costs in pediatric asthma,(2,5,8,19,20) the majority of pharmacoeconomic studies involve general population. The specific evaluation in severe pediatric asthma is needed as the use of biologic treatments in children has significantly increased the direct medical costs.

The aim of our study was to evaluate the evolution of direct medical costs related to healthcare resources and medication in a large cohort of children with SPAA treated with OMZ, followed up to 6 years since the beginning of the treatment.

METHODS

We performed the ANCHORS (Asthma iN CHlidren: Omalizumab in Real-life in Spain) study, a retrospective, observational, multicenter study, in real life conditions, designed to evaluate the use OMZ in children with SPAA. Demographic and clinical results of the ANCHORS study have been published elsewhere.(21) Briefly, it included 484 patients aged <18 years with SPAA from 25 Pediatric Allergy and Pulmonology units in Spain, who had been started on OMZ between 2006 and 2018 because of uncontrolled symptoms despite treatment with ICS+LABA and sometimes chronic oral corticosteroids (OCS). Some patients received OMZ as an off-label indication because they did not fulfil the accepted criteria either of age or of levels of serum total IgE, but were judged as lacking other alternatives of treatment.

The primary outcome of the ANCHORS study was the evolution of the annual number of moderate-to-severe exacerbations (MSE), defined as those requiring systemic corticosteroids, emergency visits, and/or hospitalizations, compared to baseline;(21) A secondary outcome was the improvement in asthma control assessed by the validated Childhood Asthma Control Test (c-ACT) or the Asthma Control Questionnaire (ACQ5). Other clinical data, available in the previous publication, were not used for the present report.

The aim of this report was to assess cost-effectiveness of the use of OMZ measuring the costs from the perspective of the National Health System. We calculated the ICER (formula displayed in the figure 1) to avoid an MSE and for significant improvements in results of asthma control tests. The c-ACT values range from 0 to 25, with higher scores associated to better asthma control; conversely, the ACQ5, ranging from 0 to 6, shows better control with lower values. The cut-off points to consider asthma as well controlled are above 20 points in c-ACT, and below 1 point in ACQ5. We evaluated the cost for the clinical Minimally Important Difference (MID) in the control tests, estimated as 3 points for c-ACT and 0.5 points for ACQ5.(22,23)

We collected the number of asthma-related healthcare encounters: unscheduled visits to primary care pediatricians and to specialists, emergency room visits, ward hospitalizations and Pediatric Intensive Care Unit (PICU) admissions. The official cost of each of these encounters differed across centers, so the mean values were used for all of them.

The use of medication was also recorded. It included montelukast, prolonged OCS, bursts of rescue OCS, ICS alone, and ICS+LABA. The daily doses of montelukast were calculated according to age (4 mg for children <6 years, 5 mg for those 6-14 years, 10 mg for those >14 years). The dose of chronic OCS was estimated as 1 mg/kg/day of prednisone for children >6 years and 1 mg/kg/day of prednisolone for those younger. The dose of bursts of OCS was calculated, as per guidelines, at 2 mg/kg/day of prednisone or prednisolone (according to the same age) for three days plus 1 mg/kg/day for three more days. We used the mean weight of boys and girls for age according to the reference by the Faustino Orbegozo Foundation.(24) The actual doses of ICS or ICS+LABA received by each patient were transformed to equivalent doses of budesonide or budesonide+formoterol, used for a harmonized calculation of costs. We used the laboratory sale price (LSP) for drugs, obtained from the Spanish General Council of Official Associations of Pharmacists website.(25) Other drugs, as theophylline, azithromycine or ipratropium bromide, were not included in the analysis due to the limited impact on costs, because of the small number of patients using these drugs, as well as their low price.

The dose of OMZ was that recommended by the manufacturer. Its cost was calculated considering the number of 150 or 75 mg syringes needed by each patient and the frequency of administration. A reduction of 7.5% was applied according to Royal Decree-Law 8/2010.(26)

The unit cost of each health encounter and drug is shown in Table 1. The cost for each patient was calculated multiplying the number of units of used health encounters and drugs by their corresponding cost. We calculated cost in euros of 2018, regardless of the year when it occurred.

Data were retrospectively collected reviewing the electronic medical records of the hospitals and primary care centers. The basal data were those of the year before initiating OMZ treatment; thereafter data were referred to each complete year. The time horizon was the duration of follow-up since the start of treatment in each patient until closure of database.

Results are shown as means and 95% confidence intervals, and medians and interquartile range. As variables had a non-normal distribution, for paired samples, Wilcoxon sign-ranked test for two and Friedman test for three or more groups were used. SPSS 15.0 software program (Chicago, Ill, USA) was used for calculations.

The study was approved by a Central Ethics Committee (Hospital Universitari i Politècnic La Fe, Valencia-Spain), which granted a waiver for informed consent.

RESULTS

We included 484 patients who started treatment, but 58 did not complete the first year of treatment, leaving 426 (263 males/163 females; mean age 11.1±2.9 years) available for assessment. The results shown are those of patients with actual data. As these were retrospectively collected, missing results were frequent and some patients were excluded from some results.

The number of MSE showed an 86% decrease in year 1 of treatment with OMZ (from 7.86 to 1.08), and there was a further gradual decrease up to 96% in year 6 (0.33) (Table 2). A marked improvement in the values of control tests exceeding the MIDs appeared in the first year and increased thereafter (Table 2).

The cost of health encounters is shown in Figure 2 and Table E1. There was a decrease of more than 93% in the cost of health encounters since the first year (Figure 3), especially for hospitalizations and even more for PICU admissions (only one in year 1 and none thereafter).

There was a decrease in all types of drugs of pharmacologic treatment (other than OMZ) since year 1, except for ICS (Figure 4 and Table E2). For these there were increases some of the years as some patients receiving ICS+LABA were switched to ICS alone.

There were quite a few missing values in some variables, as shown in Tables E1 and E2, especially in unscheduled visits to the primary care pediatrician. Tables E3 and E4 display the same results as above for only the patients with complete data in all variables of health encounters and drugs; the results show the same decreasing tendency.

Figure 4 and Table 2 show the costs of health encounters plus medication per patient, and the increase of costs, compared to baseline, due to OMZ. There was an increase of \euro9,823 in costs in the first year when OMZ was added; that amount gradually decreased to \euro4,715 in year 6 even though there was further clinical improvement. The mean ICER per avoided MSE was \euro2,107 (95%CI 1,652 to 2,562) (median 1,472) (median \euro369) in year 6. Likewise, the ICER for MIDs in control tests showed a decrease from year 1 (\euro2,059) to year 6 (\euro380) per each 0.5 points of improvement in ACQ5, less marked for c-ACT (\euro3,141 and \euro2,322 per each 3 points improvement in years 1 and 6 respectively).

DISCUSSION

Several published clinical trials demonstrate that OMZ is able to improve the clinical condition and QoL of many children with SPAA uncontrolled with conventional treatment.(12–14) It has also proved to be effective in real-life studies,(15–18) including ours,(21) which is used for the present report.

OMZ is recommended in guidelines as an add-on therapy in the last step of treatment, mainly due to its higher cost compared to other drugs.(1) In patients with good response to OMZ, the rest of treatments are usually tapered or even withdrawn, either on medical recommendation or, quite often, by the patients themselves when they consider they do not need it. The improved clinical status is also reflected in the reduction of health encounters and the improvement of control tests scores.

The use of OMZ causes a substantial increase in direct costs in the first year. Thus, the mean ICER to avoid an MSE (main objective of this report) was \euro2,107 euros (median \euro998). We have not data

in children for comparison, but in two studies in adult patients in our country, the ICER varied from \euro1,488 to \euro1,712 euros per avoided MSE with the same criteria we used.(27,28) When these studies included indirect costs, not available in our patients, the figures decreased to \euro1,130 and \euro1,607 euros, reductions of 24% and 6% respectively. In two studies in adults, the figures per avoided exacerbation were \euro1,789 and \euro2,244 euros, including indirect costs.(29,30) Importantly, our ICER cost of \euro2,107 euros was progressively reduced to \euro657 euros (median \euro369) in year six of treatment.

In other studies, the ICER for improvement in asthma control tests was higher than that for avoided exacerbations.(27–29) This also happened in our case, where the ICER to achieve the MIDs ranged from \euro3,141 in year 1 to \euro2,321 in year 6 for the c-ACT, and from \euro2,059 in year 1 to \euro380 in year 6 for the ACQ5. Cost in the first year for c-ACT were higher (\euro3,555 to \euro4,569, even including indirect costs) in the studies of adults available for comparisons.(27–29)

There are studies evaluating the costs for Quality Adjusted Life Years (QALY), in adults and adolescents,(31,32) and only one in children.(33) The costs for studies in the USA show very high figures, from US$75,319 (34) to US$821,000 (35) per QALY, whereas in the study in children, in China, that cost was calculated also as high as US$211,217.(45) (33) The cost was much lower in Europe, \euro56,847 in Italy (36) and that a cost of \euro30,000 to \euro45,000 per QALY would be an affordable price in Spain.(37) We have no data about quality of life in our patients, so we can only speculate that at least the cost for QALY would decrease in successive years, given the reduction of costs in the variables we evaluated.

There are several limitations in our study. We collected data retrospectively and there were missing data for some variables, especially regarding health encounters. When calculating the sum of variables (health encounters and medication) patients with missing data could not be included, leading to a lower number for analyses. As this was a multi-center study, the asthma control tests were not performed uniformly, and the number of available patients was even lower.

In addition, it should be noted that in order to harmonize costs, considering the variability between researchers, centers and patients, budesonide and formoterol were used as the gold standard, obtaining an approximate cost when calculating the equivalence to budesonide and formoterol in cases in which another ICS and/or LABA were taken. There may also be different budesonide products with different prices, depending on the inhalation mechanism. Furthermore, the cost of spacer chambers, possible treatment adherence failures, and inflation were not considered.

The cost of personnel for administering OMZ was not included either, nor were expenses for transportation. Although at the time of our study the home administration of OMZ was not yet authorized, it is foreseeable that nowadays these costs would diminish. The number of adverse effects of OMZ were low and mainly mild, as shown in the previous publication.(21) We were not able to calculate costs associated to them, a common situation in other studies, and this can be another limitation of our report.

This is the first study in a pediatric population in Europe to estimate these costs. One strength of our report is that it was a real-life study, with a long duration, a large sample of patients, and actual data, not extrapolated from theoretical evaluations. We found decreasing costs for OMZ, due to increasing intervals between administrations, an approach not based on clinical studies, but common practice across different hospitals, with no previous agreement, based on clinical individual assessment by attending physicians. The improvement was found since year 1 and the costs further decreased along the following years. The decrease in costs may be also partly due to withdrawal of OMZ in non-responders.

Indirect costs could not be collected. As health encounters diminished 95-99% from the basal ones, all the associated expenses for transportation, missing school days, missing workdays of the family or expenses for caregivers would be saved, reducing ICER to a greater extent.

CONCLUSION

The use of OMZ is a cost-effective option for most children with uncontrolled SPAA, mainly those who have frequent exacerbations, showing progressively reduced costs in successive years of treatment.

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LEGEND OF FIGURES

Figure 1

Formula for the calculation of the Incremental Cost-Effectiveness Ratio (ICER)

Figure 2

Cost of health encounters per patient from Baseline to year 6 (in

Figure 3

Cost of anti-asthmatic drugs per patient from Baseline to year 6 (in agonists; OC: oral corticosteroids; OMZ: Omalizumab.

Figure 4

Left axis: Costs of health encounters plus medication per patient from Baseline to year 6 (in \euro of 2018). Right axis (red): Number of MSE per patient from Baseline to year 6. ACQ5: Asthma Control Questionnaire; c-ACT: Childhood Asthma Control Test; CI: confidence interval; MSE: moderate/severe exacerbations

Figure 1. Formula for the calculation of the Incremental Cost-Effectiveness Ratio (ICER)

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Figure 2. Cost of health encounters per patient.

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Figure 3. Cost of anti-asthmatic drugs per patient.

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Figure 4. Costs of health encounters plus medication per patient

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REFERENCES

1. GINA committee. Global Strategy for Asthma Management and Prevention 2022 Update [Internet]. Global Initiative for Asthma. 2022. p. 225. Available from: http://www.ginasthma.org

2. Van Den Akker-Van Marle ME, Bruil J, Detmar SB. Evaluation of cost of disease: Assessing the burden to society of asthma in children in the European Union. Allergy Eur J Allergy Clin Immunol. 2005;60(2):140–9.

3. CIHI. Asthma Hospitalizations Among Children and Youth in Canada: Trends and Inequalities — Chartbook | CIHI. https://www.cihi.ca/en/document/asthma-hospitalizations-among-children- and-youth-in-canada-trends-and-inequalities. 2018.

4. Jo C. Cost-of-illness studies: concepts, scopes, and methods. Clin Mol Hepatol. 2014;20(4):327–37.

5. Ferrante G, La Grutta S. The burden of pediatric asthma. Front Pediatr. 2018;6(June):1–7.

6. Perry R, Braileanu G, Palmer T, Stevens P. The Economic Burden of Pediatric Asthma in the United States : Literature Review of Current Evidence. Pharmacoeconomics [Internet]. 2019;37(2):155–67.

7. Ahmed H, Turner S. Severe asthma in children — a review of definitions , epidemiology , and treatment options in 2019. Pediatr Pulmonol. 2019;54(6):778–87.

8. Blasco Bravo AJ, Perez-Yarza EG, Lazaro y de Mercado P, Bonillo Perales A, Diaz Vazquez CA, Moreno Galdo A. Coste del asma en pediatria en Espana : un modelo de evaluacion de costes basado en la prevalencia. An Pediatr (Barc). 2011;74(3):145–53.

9. Chipps BE, Haselkorn T, Rosen K, Mink DR, Trzaskoma BL, Luskin AT. Asthma Exacerbations and Triggers in Children in TENOR : Impact on Quality of Life Study. J Allergy Clin Immunol Pract. 2018;6(1):169-176.e2.

10. Cano-Garcinuno A, Bercedo-Sanz A, Mora-Gandarillas I, Callen-Blecua MT, Castillo-Laita JA, Forns-Serrallonga D, et al. Association between quality of life in parents and components of asthma control in children. J Asthma. 2014;51(10):1089–95.

11. Palomares O, Sanchez-Ramon S, Davila I, Prieto L, de Llano LP, Lleonart M, et al. dIvergEnt: How IgE axis contributes to the continuum of allergic asthma and anti-IgE therapies. Int J Mol Sci. 2017;18(6):1–14.

12. Milgrom H, Berger W, Nayak A, Gupta N, Pollard S, McAlary M, et al. Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). Pediatrics. 2001;108(2):E36.

13. Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF, et al. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. J Allergy Clin Immunol. 2009;124(6):1210–6.

14. Busse W, Morgan W, Gergen P, Mitchell H, Gern J, Liu A, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. N Engl J Med. 2011;364(11):1005–15.

15. Deschildre A, Marguet C, Salleron J, Pin I, Rittie JL, Derelle J, et al. Add-on omalizumab in children with severe allergic asthma: A 1-year real life survey. Eur Respir J. 2013;42(5):1224–33.

16. Deschildre A, Marguet C, Langlois C, Pin I, Rittie J-LL, Derelle J, et al. Real-life long-term omalizumab therapy in children with severe allergic asthma. Eur Respir J. 2015 Sep;46(3):856–9.

17. Licari A, Castagnoli R, Denicolo C, Rossini L, Seminara M, Testa G, et al. Omalizumab in Children with Severe Allergic Asthma: The Italian Real- Life Experience. 2017;36–42.

18. Brodlie M, McKean MC, Moss S, Spencer DA. The oral corticosteroid-sparing effect of omalizumab in children with severe asthma. Arch Dis Child. 2012 Jul;97(7):604–9.

19. Szefler SJ, Zeiger RS, Haselkorn T, Mink DR, Kamath T V., Fish JE, et al. Economic burden of impairment in children with severe or difficult-to-treat asthma. Ann Allergy, Asthma Immunol. 2011;107(2):110-119.e1.

20. Chen W, Tavakoli H, FitzGerald JM, Subbarao P, Turvey SE, Sadatsafavi M. Age trends in direct medical costs of pediatric asthma: a population-based study. Pediatr Allergy Immunol. 2021;

21. Nieto Garcia A, Garriga-Baraut T, Plaza Martin AM, Nieto Cid M, Torres Borrego J, Del Mar Folque Gimenez M, et al. Omalizumab outcomes for up to 6 years in pediatric patients with severe persistent allergic asthma. Pediatr Allergy Immunol. 2021 Jul;32(5):980-991.

22. Schatz M, Kosinski M, Yarlas AS, Hanlon J, Watson ME, Jhingran P. The minimally important difference of the Asthma Control Test. J Allergy Clin Immunol. 2009 Oct;124(4):719-23.e1.

23. Juniper EF, Svensson K, Mork A-C, Stahl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med. 2005 May;99(5):553–8.

24. The Faustino Orgegozo Foundation. ESTUDIOS, TABLAS Y GRAFICAS DE CRECIMIENTO [Internet]. Available from: http://www.fundacionorbegozo.com/product-showcase/tablas/

25. Spanish General Council of Official Associations of Pharmacists [Internet]. 2022. Available from: https://botplusweb.portalfarma.com

26. Head of State of Spain. Extraordinary measures to reduce the public deficit - Amended by the Royal Decree-Law 9/2011. [Internet]. BOE-A-2010-8228 - BOE-A-2011-14021. 2010. p. 4–56. Available from: https://www.boe.es/eli/es/rdl/2010/05/20/8/con

27. Vennera MDC, Sabadell C, Picado C. Duration of the efficacy of omalizumab after treatment discontinuation in "real life" severe asthma. Thorax. 2018 Aug; 73(8):782-784.

28. Entrenas Costa LM, Casas-Maldonado F, Soto Campos JG, Padilla-Galo A, Levy A, Alvarez Gutierrez FJ, et al. Economic Impact and Clinical Outcomes of Omalizumab Add-On Therapy for Patients with Severe Persistent Asthma: A Real-World Study. PharmacoEconomics - open. 2019 Sep;3(3):333–42.

29. Martinez-Moragon E, Climent M, Chiner E, Fernandez-Aracil C, Sanchez-Toril F, Lluch-Tortajada I. Effectiveness and pharmacoeconomic analysis of the treatment of severe asthma with omalizumab in clinical practice. Farm Hosp. 2019 May;43(3):101–9.

30. Arrobas A, Barbosa MP, Rabiais S, Vandewalle B, Felix J. Cost-effectiveness of omalizumab in real world uncontrolled allergic asthma patients. Pulmonology. 2021;27(2):124–33.

31. Levy AN, Garcia A Ruiz AJ, Garcia-Agua Soler N, Sanjuan MVH. Cost-effectiveness of omalizumab in severe persistent asthma in Spain: a real-life perspective. J asthma. 2015 Mar;52(2):205–10.

32. 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 Oct;49(8):843–8.

33. Zhou H, Lu Y, Wu B, Che D. Cost-effectiveness of omalizumab for the treatment of inadequately controlled severe allergic asthma in Chinese children. J Asthma. 2020 Dec 3 [cited 2018 Dec 27];57(1):87–94.

34. Sullivan PW, Li Q, Bilir SP, Dang J, Kavati A, Yang M, et al. Cost-effectiveness of omalizumab for the treatment of moderate-to-severe uncontrolled allergic asthma in the United States. Curr Med Res Opin. 2020 Jan;36(1):23–32.

35. 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 Nov;120(5):1146–52.

36. Canonica GW, Colombo GL, Rogliani P, Santus P, Pitotti C, Di Matteo S, et al. Omalizumab for Severe Allergic Asthma Treatment in Italy: A Cost-Effectiveness Analysis from PROXIMA Study. Risk Manag Healthc Policy. 2020;13:43–53.

37. De Cock E, Miravitlles M, Gonzalez-Juanatey JR, Azanza-Perea JR. Threshold value of the cost for life-years gained by adopting health technologies in Spain: Evidence from a literature review. Pharmacoeconomics - Spanish Res Artic. 2007;4(3):97–107.

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