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Cost-utility of tiotropium for children with severe asthma in patients aged 1–5 years

Short running title: Cost-utility tiotropium

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To the editor

Severe asthma is a disease that affects more than 300 million people worldwide (1). At least 24% of the patients with asthma are classified as severe asthma requiring high doses of inhaled corticosteroids (ICS)-long-acting beta2-agonist (LABA) or ICS-LABA or oral corticosteroids (OCS) (2). New pharmacological alternatives have been developed for patients with severe asthma, among them the addition of long-acting muscarinic antagonists (LAMA), as tiotropium, to the current treatment with ICS-LABA (3). Tiotropium is delivered using a slow and soft-mist, non-breath-actuated, propellant-free inhaler (Respimat Soft Mist Inhaler). The inhaler device delivers the medication dose to the airways independent of the patient's variable inspiratory flow. Tiotropium showed the potential to reduce asthma exacerbation risk in children aged 1–5 years with persistent asthmatic symptoms without differences in frequency of adverse events respect to current treatment in clinical trials and

real-life studies (4,5). Concerns are generated, as to whether if the extra benefit offered by tiotropium outweighs the additional cost compared to therapy with only ICS-LABA in patients aged 1–5 years. This question is even more relevant in developing countries with an increasing prevalence of asthma and constrained healthcare.

We conducted a cost-utility from the societal perspective. We compare standard of Care (SOC) typically defined as a low or medium dose of inhaled corticosteroids in combination with (LABA) long-acting β_2 -agonist and/or leukotriene receptor antagonist (LTRA) , versus once-daily tiotropium 2.5 μg as an add-on to SOC (2). Our Markov model was composed of three mutually exclusive health states: controlled asthma (patient without asthma symptoms), ED visit (exacerbation with an unscheduled visit to the emergency department), and hospitalization (**Figure 1**). Due to heterogeneity in the diagnosis of asthma in children less than 6 years, we made this analysis in a time horizon of 6 years. The model cycle length was of 2 weeks. Half-cycle correction and an annual discounting rate of 5% were applied to both costs and QALY following the recommendation of national guidelines for economic evaluations in Colombia. Data of relative risk (RR) of tiotropium in exacerbations were obtained randomized, double-blind, placebo-controlled, in children aged 1–5 years with at least a 6-month history of persistent asthmatic symptoms (5); while data of transition probabilities and utilities were extracted from a previous local study made in Colombian asthmatic children (6). We extracted all costs of infants less than 18 years of age in Colombia, due to asthma according to the national clinical guideline of asthma in children from a study previously published (7).

The main results are presented in **Table 1**. For SOC and add-on therapy with tiotropium, the total discounted cost per person was US\$ 409 (CI 95% US\$ 400 to US\$ 418), and US\$ 656 (CI 95% US\$ 642 to US\$ 669) respectively. The QALY per person estimated were 19.7 (CI 95% 16.33 to 21.55), and 19.9 (CI 95% 19.53 to 21.75) respectively. The model suggests a potential gain of 0.198 QALY per patient per year on tiotropium, with a difference of US\$ 275 per patient-year respect to SOC. The incremental cost-effectiveness ratio estimated was US\$ 710 in the deterministic model and US\$ 1244 in the probabilistic model. In the deterministic sensitivity analyses, our base-case results were robust to variations of all assumptions and parameters. For none of the variables evaluated, variations within the established ranges led to the incremental cost-effectiveness ratio being higher than the WTP. The

results of probabilistic sensitivity analysis are graphically represented in the cost-effectiveness plane, **figure 2**. This scatter plot shows that compared with SOC, treatment with tiotropium tends to be associated with lower costs and higher QALY. Indeed, 9% of simulations were graphed in quadrant 2 (lower cost, high QALY), 91% in quadrant 1 (high cost, high QALY). Tiotropium becomes cost-effective in 50% of the iterations at a willingness-to-pay (WTP) threshold of US\$ 800.

Our findings suggest that add-on therapy with tiotropium achieves better outcomes at a lower cost compared to standard treatment. To our knowledge, this is the first economic evaluation of tiotropium in the pediatric and specifically preschool population. Our results are in line with previous studies in adults. Hyng et al, using a similar Markov model as our study, the ICER was \$60,074/QALY, indicating that the addition of tiotropium is a cost-effective alternative, in patients poorly controlled asthma with an ICER \$4,078/QALY in frequent SABA users and \$8,332/QALY, on frequent exacerbators (8). As is expected the cost of adult patients and exacerbation rates are different and the magnitude of ICER is lower in children. Willson et al using a six Markov model health states estimate an incremental cost-effectiveness ratio of £21,906 per QALY gained being tiotropium cost-effective in the UK(9). The cost per event of OCS bust, ED visit, or hospitalization were higher five times in the UK than in our study in Colombia; and this can explain the differences in the magnitude of ICER between the studies. Zafari et al, also using a probabilistic Markov model with a 10-year time horizon and from a US societal perspective, found ICER of add-on therapy with tiotropium versus standard therapy, and omalizumab versus tiotropium were \$34,478/QALY, and \$593,643/QALY, respectively (10). Strength of our study is the use of local utilities, and not extrapolated from other populations. Our study has some limitations. We use RR from the literature and not estimated directly from our population. As was mentioned previously, the reliability and robustness of the results were evaluated by sensitivity analyses. Our result only refers to a patient with severe asthma uncontrolled by medium-dosage to high-dosage inhaled corticosteroids plus long-acting β_2 -agonists and cannot be extrapolated to patients with the use of oral daily corticosteroids. Studies of tiotropium in asthma have recruited both allergic and non-allergic asthma patients. In conclusion, add-on therapy with tiotropium was found to be cost-effective when added to usual care 1-6 years with severe asthma who remain uncontrolled despite treatment with low-medium ICS/LABA/LTRA. Our study provides evidence that

should be used by decision-makers to improve clinical practice guidelines and should be replicated to validate their results in other middle-income countries.

Declarations:

Ethics approval and consent to participate: This study was approved by the Institutional Review Board of University of Antioquia (2015-4690)

Consent for publication: Not Applicable

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References.

1. To T, Stanojevic S, Moores G, Gershon AS, Bateman ED, Cruz AA, et al. Global asthma prevalence in adults: findings from the cross-sectional world health survey. BMC Public Health. 2012;12:204.
2. Asthma Gf. Global Strategy for Ashtma Management and Prevention 2021 [06/05/2021]. Available from: <https://ginasthma.org/>.
3. M. Sunther, K. Marchon, A. Gupta, Tiotropium in the Management of Paediatric & Adolescent Asthma: Systematic Review, Paediatric Respiratory Reviews (2020), doi: <https://doi.org/10.1016/j.prrv.2020.08.003>
4. Kerstjens HA, Moroni-Zentgraf P, Tashkin DP, Dahl R, Paggiaro P, Vandewalker M, et al. Tiotropium improves lung function, exacerbation rate, and asthma control, independent of baseline characteristics including age, degree of airway obstruction, and allergic status. Respir Med. 2016;117:198-206.

5. Vrijlandt EJLE, El Azzi G, Vandewalker M, Rupp N, et al. Safety and efficacy of tiotropium in children aged 1-5 years with persistent asthmatic symptoms: a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med*. 2018 Feb;6(2):127-137
6. Rodriguez-Martinez CE, Sossa-Briceno MP, Castro-Rodriguez JA. Cost-utility analysis of the inhaled steroids available in a developing country for the management of pediatric patients with persistent asthma. *J Asthma*. 2013;50(4):410-8.
7. Rodriguez-Martinez CE, Sossa-Briceno MP, Castro-Rodriguez JA. Metered-dose inhalers vs nebulization for the delivery of albuterol in pediatric asthma exacerbations: A cost-effectiveness analysis in a middle-income country. *Pediatr Pulmonol*. 2020;55(4):866-73.
8. Hong SH, Cho JY, Kim TB, Lee EK, Kwon SH, Shin JY. Cost-Effectiveness of Tiotropium in Elderly Patients with Severe Asthma Using Real-World Data. *J Allergy Clin Immunol Pract*. 2020.
9. Willson J, Bateman ED, Pavord I, Lloyd A, Krivasi T, Esser D. Cost effectiveness of tiotropium in patients with asthma poorly controlled on inhaled glucocorticosteroids and long-acting beta-agonists. *Appl Health Econ Health Policy*. 2014;12(4):447-59.
10. Zafari Z, Sadatsafavi M, Mark FitzGerald J, Canadian Respiratory Research N. Cost-effectiveness of tiotropium versus omalizumab for uncontrolled allergic asthma in US. *Cost Eff Resour Alloc*. 2018;16:3.

Table 1. Cost- effectiveness of Tiotropium

	Cost (\$)	Difference (\$)	QUALYs	difference	C/E (\$)	ICER (\$)
Tiotropium	656		19.9		33	1.244
SOC	409	247	19.7	0.198	21	

Figure 1. Markov model

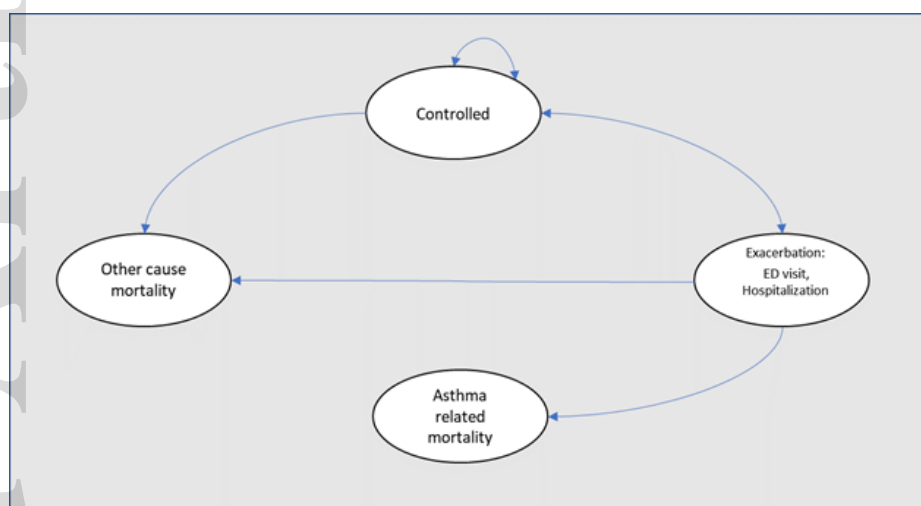


Figure 2. Cost effectiveness plane

