

Supplementary Appendix

A Benefit-Harm Analysis of Azithromycin for the Prevention of Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Safa Ahmadian; Don D Sin; Larry D. Lynd; Mark Harrison; Mohsen Sadatsafavi

Table of contents

Appendix 1: Effect of antibacterial resistance on treatment effect	2
Appendix 2: Background incidence of hearing loss	3
Appendix 3: Health State Utility Values (utilities)	4
<i>GOLD grades and exacerbations</i>	4
<i>Hearing impairment</i>	4
<i>Gastrointestinal symptoms</i>	4
Appendix 4: Calculating the rate ratio of exacerbation based on previous patterns	5
Appendix 5: Sensitivity Analyses	6
References	7

Appendix 1: Effect of antibacterial resistance on treatment effect

To model a gradual decline in the efficacy of the treatment through the time horizon, we used a negative exponential equation to calculate the relative risk of exacerbations in each year relative to the base case value.

$$RR = RR_0 \exp(-k(\text{year}-1))$$

With the parameter k controlling the speed of decline in the treatment effect. We estimated the base case value of k as 0.22 based on the results of the efficacy of azithromycin in the first and third year of therapy in the study by Pomares et al.[1] This value was subjected to dedicated threshold analysis.

Appendix 2: Background incidence of hearing loss

We adopted the World Health Organization's definition of hearing loss: bilateral hearing loss of more than the 25 decibels in speech frequency pure-tone averages (the average of hearing sensitivity at different frequencies)[2]. We evaluated studies that used audiometry tests as opposed to less objective methods such as questionnaires to evaluate hearing loss.

A population-based US study[3] reported the prevalence rate of hearing loss for adults age-groups older than 70. Based on the reported data, we parameterised a linear model for the risk of hearing loss as a function of age:

$$\text{hearing prevalence} = \beta_0 + \beta_1 \times \text{Age}$$

with $\beta_0 = -1.169$ (95% CI: -0.173, -2.166) and $\beta_1 = 0.023$ (95% CI: 0.011, 0.035). Ignoring the (negligible) effect of one-year mortality, β_1 is also an estimator of the annual incidence of hearing loss in the general population.

Appendix 3: Health State Utility Values (utilities)

GOLD grades and exacerbations

Baseline utilities for each GOLD grade were taken from the study by Rutten-van Mölken et al. (involving 1,235 COPD patients from 13 different countries[4]). To obtain the disutility associated with exacerbations, we used the data provided by Spencer et al.[5] and modelled the reduction in QALY similar to the approach used by Sadatsafavi et al.[6]. Assuming that each patient had at most one exacerbation in three months, the difference between the baseline utility and the utility weight for a three-month exacerbation period divided by four gave us the average disutility associated with each exacerbation (see the main paper by Sadatsafavi et al. [6] for more details). The variance of the disutility is estimated by summing the variance of the baseline utility and the utility weight in the exacerbation period, assuming the two variables are independent.

Hearing impairment

As EQ-5D may not capture the changes in quality of life due to hearing loss [7].[8], we used the HUI-3 instrument to model the impact of hearing loss on quality of life. Following the same approach as a previous study on the management of hearing loss in adults [9], we assigned an average disutility of 0.187 (95% CI: 0.167-0.207) for hearing loss. However, we assumed that after the first year the use of hearing aids would result in a partial recovery of hearing and an increase of 0.06 (95% CI: 0.044 - 0.073) in quality of life, as reported previously[10].

Gastrointestinal symptoms

To find the disutility related to GI symptoms, we used a comprehensive report on the EQ-5D scores associated with various conditions from US-based samples[11]. Among the list of chronic conditions reported in this study, we identified three relevant conditions, “*stomach function disorder*”, “*other gastroduodenal disorders*”, and “*other intestinal disorders*”, to represent the reported GI symptoms associated with azithromycin use[12]. We pooled the disutility associated with these three conditions using a fixed-effect meta-analysis[13].

Appendix 4: Calculating the rate ratio of exacerbation based on previous patterns

To estimate exacerbation rates conditioned on previous 12-month history, we analysed data from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study, which was a three-year prospective cohort study of GOLD II-IV patients where exacerbation was a prespecified end-point[14]. We used data from the second year of ECLIPSE to calculate rate multipliers conditional on the exacerbation patterns in the previous year. We included patients who were followed for at least 360 days both in the first and the second year. The average rate of moderate and severe exacerbations in the second year was calculated for four subgroups with different patterns of exacerbations in the first year: patients with no exacerbations, with at least one moderate or severe exacerbations (base case), with at least two moderate or severe exacerbations or patients who have had two or more moderate or at least one severe exacerbations (frequent exacerbators[15]).

The rate ratios of exacerbations were then estimated for each subgroup relative to the base case rates. The same analysis was done to estimate the rate ratios of severe exacerbations, separately. The following table provides the estimate of rate ratios:

<i>Table 1. Rate ratio of exacerbation by 12-month history pattern</i>		
	Total exacerbations_no. (95% CI)	Severe exacerbations_no. (95% CI)
No exacerbations in the first year	0.16 (0.14-0.17)	0.16(0.12 - 0.20)
≥1 moderate/severe exacerbations in the first year	1	1
≥ 2 moderate or ≥ 1 severe exacerbation in the first year	1.25 (1.16-1.33)	1.36 (1.17 - 1.58)
≥ 2 moderate/severe exacerbations in the first year	1.3 (1.2 - 1.4)	1.26 (1.07 - 1.48)

Appendix 5: Sensitivity Analyses

In the first sensitivity analysis, we assumed that azithromycin does not result in any excess risk of cardiac death. In the second analysis, we followed a Cochrane systematic review, and set the base case value of the treatment effect to a pooled estimate of the relative rate of 0.69 [95% CI: 0.54,0.89] for exacerbations among COPD patients receiving prophylactic macrolide therapy compared with those who do not[16]. In the next analysis, we repeated the results for the case that hearing loss was also measured by EQ-5D (in the main analysis hearing loss disutility was based in HUI3 values). We used the value of 0.006 (95% CI: 0.0059-0.0061) reported by Sullivan et al.[17]. In the fourth and the fifth sensitivity analyses, we estimated the result for different values of discount rates: 0% and 5%. In two other analyses, we first limited the time horizon to 1-year, as in MACRO study, and then expanded the follow-up to 35 years which is assumed as a life-time, considering the average age of 65 in the model.

In the last analysis, we modeled non-adherence to azithromycin over and above the adherence rate observed in the empirical studies informing our model. Based on findings from a global survey of antibiotic use, we modeled an annual probability of 14.9% for discontinuation. To model this, we added three states to the original Markov model, representing patients who permanently discontinue azithromycin without experiencing adverse events.[18]

The net QALYs gained for all scenarios are represented in table 2.

Table 2. Expected net QALY gain and probability of positive net QALY in different scenarios.

	Expected net QALY gain per 100 patients	Probability of net QALY > 0
No excess risk of cardiovascular death	18.3 (6.1-29.8)	99.8%
Treatment effect of 0.69	21.2 (2.5-37.9)	98.9%
Using EQ-5D to estimate disutility related to hearing loss	22.5(11.3-33.8)	99.6%
5% discount in net QALY	16.0 (6.3 – 26.2)	99.8%
No discount in net QALY	22.3 (7.8-36.7)	99.8 %
Time horizon of 1 year	2.1 (0.9-3.5)	99.9%
Time horizon of 35 (life-long)	18.8 (5.8-31.5)	99.8%
Annual Non-adherence rate of 14.9%	12.9 (3.4-22.0)	99.6%

References

- 1 Pomares X, Montón C, Bullich M, *et al.* Clinical and Safety Outcomes of Long-Term Azithromycin Therapy in Severe COPD Beyond the First Year of Treatment. *Chest* 2018;**153**:1125–33. doi:10.1016/j.chest.2018.01.044
- 2 World Health Organization. *Global costs of unaddressed hearing loss and cost-effectiveness of interventions*. 2017. <http://apps.who.int/iris/bitstream/10665/254659/1/9789241512046-eng.pdf> (accessed 12 Aug 2020).
- 3 Lin FR, Thorpe R, Gordon-Salant S, *et al.* Hearing Loss Prevalence and Risk Factors Among Older Adults in the United States. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences* 2011;**66A**:582–90. doi:10.1093/gerona/qlr002
- 4 Rutten-van Mólken MPMH, Oostenbrink JB, Tashkin DP, *et al.* Does Quality of Life of COPD Patients as Measured by the Generic EuroQol Five-Dimension Questionnaire Differentiate Between COPD Severity Stages? *Chest* 2006;**130**:1117–28. doi:10.1378/chest.130.4.1117
- 5 Spencer M, Briggs AH, Grossman RF, *et al.* Development of an Economic Model to Assess the Cost Effectiveness of Treatment Interventions for Chronic Obstructive Pulmonary Disease: *PharmacoEconomics* 2005;**23**:619–37. doi:10.2165/00019053-200523060-00008
- 6 Sadatsafavi M, Ghanbarian S, Adibi A, *et al.* Development and Validation of the Evaluation Platform in COPD (EPIC): A Population-Based Outcomes Model of COPD for Canada. *Med Decis Making* 2019;**39**:152–67. doi:10.1177/0272989X18824098
- 7 Barton GR, Sach TH, Avery AJ, *et al.* A comparison of the performance of the EQ-5D and SF-6D for individuals aged ≥ 45 years. *Health Econ* 2008;**17**:815–32. doi:10.1002/hec.1298
- 8 Grutters JPC, Joore MA, van der Horst F, *et al.* Choosing between measures: comparison of EQ-5D, HUI2 and HUI3 in persons with hearing complaints. *Qual Life Res* 2007;**16**:1439–49. doi:10.1007/s11136-007-9237-x
- 9 Cost-effectiveness analysis: early versus delayed management of hearing loss - Hearing loss in adults - NCBI Bookshelf. <https://www.ncbi.nlm.nih.gov/books/NBK536562/> (accessed 11 Sep 2020).
- 10 Barton GR, Bankart J, Davis AC, *et al.* Comparing Utility Scores Before and After Hearing-Aid Provision: Results According to the EQ-5D, HUI3 and SF-6D. *Applied Health Economics and Health Policy* 2004;**3**:103–5. doi:10.2165/00148365-200403020-00006
- 11 Sullivan PW, Ghushchyan V. Preference-Based EQ-5D Index Scores for Chronic Conditions in the United States. *Med Decis Making* 2006;**26**:410–20. doi:10.1177/0272989X06290495
- 12 Li H, Liu D-H, Chen L-L, *et al.* Meta-Analysis of the Adverse Effects of Long-Term Azithromycin Use in Patients with Chronic Lung Diseases. *Antimicrob Agents Chemother* 2014;**58**:511–7. doi:10.1128/AAC.02067-13
- 13 Harrer, M., Cuijpers, P., Furukawa, T.A., & Ebert, D. D. (2019). *Doing Meta-Analysis in R: A Hands-on Guide*. Protect Lab. https://bookdown.org/MathiasHarrer/Doing_Meta_Analysis_in_R/ (accessed 27 Aug 2020).
- 14 Hurst JR, Vestbo J, Anzueto A, *et al.* Susceptibility to Exacerbation in Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2010;**363**:1128–38. doi:10.1056/NEJMoa0909883
- 15 Singh D, Agusti A, Anzueto A, *et al.* Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease: the GOLD science committee report 2019. *Eur Respir J* 2019;**53**. doi:10.1183/13993003.00164-2019

- 16 Herath SC, Normansell R, Maisey S, *et al.* Prophylactic antibiotic therapy for chronic obstructive pulmonary disease (COPD). *Cochrane Database of Systematic Reviews* Published Online First: 30 October 2018. doi:10.1002/14651858.CD009764.pub3
- 17 Sullivan PW, Lawrence WF, Ghushchyan V. A National Catalog of Preference-Based Scores for Chronic Conditions in the United States: *Medical Care* 2005;**43**:736–49. doi:10.1097/01.mlr.0000172050.67085.4f
- 18 Pechère J-C, Hughes D, Kardas P, *et al.* Non-compliance with antibiotic therapy for acute community infections: a global survey. *International Journal of Antimicrobial Agents* 2007;**29**:245–53. doi:10.1016/j.ijantimicag.2006.09.026