Preventing COPD exacerbations with macrolides: A review and budget impact analysis

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Summary
Long-term treatment with macrolides has recently been shown to reduce COPD exacerbations in doses lower than bactericidal doses. This article aims to critically review the international literature relating to the long-term effectiveness and safety of macrolides and to estimate the budget impact of preventing exacerbations with azithromycin in Belgium. Controlled clinical studies focusing on the prevention of COPD exacerbations with long-term macrolide treatment were identified in PubMed, EMBASE, Controlled Trials Registry of the Cochrane Library, and Social Science and Citation Index. The budget impact of preventing exacerbations with azithromycin in Belgium over a one-year period was calculated as the difference between the additional expenditure of annual treatment with azithromycin and the savings in hospital expenditure arising from fewer COPD exacerbations in patients with GOLD stages II–IV. Prevalence and resource use data were derived from the literature and unit cost data from Belgian sources. The literature review suggests that long-term treatment of COPD patients with azithromycin, erythromycin or clarithromycin is effective and safe, and reduces exacerbations and related hospitalizations. However, uncertainty remains about the specific patient population that is most likely to benefit from long-term macrolide treatment, the optimal dose and duration of macrolide treatment, and the potential impact of long-term macrolide treatment on resistance. The budget impact analysis demonstrated that annual hospital savings of €950 million resulting from fewer exacerbations outweighed additional expenditure on azithromycin of €595 million, implying that the prevention of COPD exacerbations with azithromycin is a cost saving strategy in Belgium.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a debilitating disease that affects 5%–10% of the adult population. It is currently the fourth leading cause of death and the World Health Organisation expects it to become the third leading cause of death by 2030. While in the past three decades, mortality due to heart disease and stroke clearly decreased, mortality due to COPD almost doubled. The disease is characterized by exacerbations, periods of increased symptoms often following viral infections that may trigger hospitalization, respiratory failure and death. In addition, these episodes are associated with enhanced progression of the disease.

Prevention of exacerbations is one of the prime treatment goals in COPD. Several medications have been shown to reduce exacerbations including long-acting β2-agonists, inhaled corticosteroids, fixed combinations of these medications, long-acting anticholinergic agents, phosphodies- terase-4 inhibitors and N-acetylcystein. Nevertheless, the reduction in exacerbations obtained in the best of cases, remains limited to 25–30%, even with combinations of the aforementioned agents. Hence, an important unmet need remains.

Macrolides like erythromycin and azithromycin have recently been proposed as agents that reduce exacerbations in doses lower than bactericidal doses. It is at present unclear what the relevant mechanism of action is to explain the reduction of exacerbations observed with macrolides. As these antibiotics exert several immune-modulatory and anti-inflammatory effects, a variety of potential mechanisms of action can be proposed. Macrolides exert a host of effects that collectively limit the tissue damage by neutrophils, including effects on chemo-attractants, inhibition of their oxidant burst, impairment of granulation, and enhancement of the rate of neutrophil apoptosis. They also stimulate the production of antimicrobial β-defensin-1 and β-defensin-2 by epithelial cells. Finally, macrolides stimulate phagocytosis by macrophages and enhance the expression of Mannose receptor on these cells, facilitating the elimination of bacterial organisms. This may be particularly important in COPD patients. Indeed, two observations point to a defective macrophage function in these patients. First, alveolar macrophages of these patients are defective in phagocytosis of apoptotic cells. Second, monocye-derived macrophage phagocytosis of bacteria is also known to be defective in these patients. The potential importance of these effects is even enhanced by the observation that azithromycin may reach very high concentrations in alveolar macrophages, even more so than other macrolides. All of these effects occur clinically at serum concentrations attainable by low dose administration.

The aims of this study are to critically review the international literature relating to the long-term effectiveness and safety of macrolides and to estimate the budget impact of preventing exacerbations with azithromycin in Belgium over a one-year period.

Methods

Literature review

Search strategy

Studies were identified by searching the following electronic databases up to April 2012: PubMed, EMBASE, Controlled Trials Registry of the Cochrane Library, and Social Science and Citation Index. The search strategy was varied and adapted as necessary to suit particular databases. In general, search terms included 'chronic obstructive pulmonary disease', 'chronic bronchitis', 'emphysema', 'acute exacerbation', 'trial', 'effectiveness', 'efficacy', 'clinical outcomes', 'quality of life', 'mortality', 'safety', 'side effect', 'adverse events', 'resistance', 'pharmacotherapy', 'treatment', 'long-term', 'continuous', 'chronic', 'macrolide',
Preventing COPD exacerbations with macrolides

azithromycin’, ‘erythromycin’, ‘clarithromycin’, ‘roxithromycin’, ‘telithromycin’ alone and in combination with each other. Additionally, the bibliography of included studies was checked for other relevant studies.

Inclusion/exclusion criteria
All controlled studies focusing on the prevention of COPD exacerbations by means of long-term treatment with macrolides were selected. Preference was given to randomized controlled trials, but observational studies such as cohort studies and before-and-after studies were also considered. Case series were excluded. Studies had to measure the impact of macrolide treatment on final clinical outcomes (e.g., number of exacerbations, time to first exacerbation, duration of exacerbation, quality of life). Studies that examined the impact on intermediate outcomes such as inflammatory markers were not included.

Studies needed to focus on long-term treatment (arbitrarily set at treatment exceeding three months) of COPD with macrolides and not on short-term treatment of an acute exacerbation. Intermittent treatment was not considered. Long-term treatment was limited to macrolides, given the well-known anti-inflammatory and immunomodulatory properties of macrolides.23

Inclusion was restricted to articles published in peer-reviewed journals. Congress abstracts were not considered because they do not provide sufficient details of methodology and results. The review included studies published between 2000 and 2012. It was considered that any earlier studies would be of limited relevance due to changes in antibiotics, bacterial pathogens and their susceptibility over time.24 Articles could be published in English, Dutch or French.

Assessment of methodological quality
The methodological quality of each study was assessed according to the criteria outlined by the Cochrane Collaboration.25 For each macrolide product, the available evidence was evaluated using the following items of the GRADE system: study design, study quality, consistency, directness and imprecision.26

Data analysis
A standard inclusion and data extraction form was completed for each study. This form enquired about the country of the study, sample, intervention and comparator, study design, effectiveness and safety results, and methodological quality (cfr. supra). This form was filled in by two independent reviewers. Any disagreements were resolved through discussion. Due to the heterogeneity of the studies, a descriptive synthesis of the extracted data was made.

Budget impact analysis
In order to calculate the budget impact of preventing exacerbations with azithromycin in Belgium over a one-year period, the additional expenditure of annual treatment with azithromycin was contrasted with the savings in hospital expenditure arising from a reduced number of COPD exacerbations.

The target population was COPD patients in GOLD stage II (who experience many exacerbations under usual care), patients in GOLD stage III and patients in GOLD stage IV.7 Data on the mean number of hospitalisations due to COPD exacerbations per patient per year with azithromycin or with placebo were derived from Albert et al.16; with azithromycin this amounted to 0.5 hospitalisations per patient per year for GOLD stage II patients, 0.85 hospitalisations for GOLD stage III patients and 0.74 hospitalisations for GOLD stage IV patients; with placebo this amounted to 0.65, 0.96 and 1.03 hospitalisations, respectively. As a result, the reduction in the mean number of exacerbation-related hospitalisations per patient per year with azithromycin as compared to placebo was 0.15 for patients in GOLD stage II, 0.11 for patients in GOLD stage III and 0.29 for patients in GOLD stage IV.16 To calculate the number of Belgian COPD patients in each GOLD stage, population-based prevalence data were taken from the European sites participating in an international study27 and from a Dutch study,28 and applied to the number of Belgian inhabitants.29

Belgian sources were used to obtain the unit cost of a hospitalisation related to COPD exacerbation (inflated to 2012 using Health Index figures) (at a unit cost of €6413)30 and the annual cost of treatment with generic azithromycin 250 mg per day (at a cost of €594 per patient).31 Unit costs reflected third-party payer reimbursement and patient co-payment. The price year was 2012.

The net annual budget impact was calculated as the difference between the annual expenditure of treating Belgian COPD patients in GOLD stages II–IV with azithromycin and savings arising from the reduced number of exacerbation-related hospitalisations with azithromycin as compared to placebo. To assess the robustness of our budget impact estimate to changes in input parameter values, the following sensitivity analyses were conducted: a) number of hospitalisations avoided with azithromycin as compared with placebo ± 50%; b) cost of azithromycin 250 mg per day between €1.63 and €1.68 (in accordance with observed variation in azithromycin prices in Belgium);32 and c) use of azithromycin in patients with a history of frequent COPD exacerbations only, i.e. 22% of patients in GOLD stage II, 33% in GOLD stage III, and 47% in GOLD stage IV.32

Results

Literature review
The literature search generated 39 articles Fig. 1. Articles were excluded if they were published prior to 2000 or if they examined the impact of macrolide treatment on inflammatory markers only. Eight studies were included in the review that focused on the prevention of COPD exacerbations by means of long-term treatment with a macrolide (i.e., azithromycin, erythromycin and clarithromycin).15,16,33–38 One study evaluated treatment with erythromycin and/or clarithromycin, but did not document effectiveness and safety for each antibiotic separately.38 This study was included in both the erythromycin and clarithromycin sections (cfr. infra). No study of the prevention of COPD exacerbations with other macrolide products was identified.

Effectiveness and safety of azithromycin
Three controlled studies investigated the effectiveness and safety of long-term treatment (6–12 months) with azithromycin in addition to usual care in patients with severe
COPD or at high risk of exacerbation. The characteristics and results of these studies are summarized in Table 1.

The highest quality of evidence was derived from a multicentre, double-blind RCT enrolling more than 1100 patients. Patients received azithromycin 250 mg daily for one year or placebo. The findings indicated that long-term treatment with azithromycin decreased time to first exacerbation, exacerbation frequency, number of COPD-related hospitalisations and enhanced quality of life. An acute exacerbation was defined as an increase in respiratory symptoms lasting for at least three days, requiring treatment with antibiotics or systemic steroids. The magnitude of the treatment effect may have been under-estimated given that patient compliance with azithromycin treatment did not exceed 70%. Although hearing decrements were more common with azithromycin, this finding can be questioned as hearing improved to baseline levels within one month after study completion in patients who continued treatment with azithromycin.

A relevant question is whether chronic treatment with azithromycin may cause the development of resistance to macrolides. In this study, no difference was found in the prevalence of resistance to macrolides between the two groups (azithromycin: 52% versus placebo: 57%, \( p = 0.64 \)) in patients who were colonized with respiratory pathogens at the time of enrollment. However, in patients who became colonized with respiratory pathogens in the course of the study, the resistance to macrolides was 81% versus 41% with placebo (\( p < 0.001 \)). The clinical relevance of this resistance is not clear, as no evidence of an increased incidence of acute exacerbations of COPD or pneumonia was found.

In addition, two observational studies administered azithromycin 500 mg three times a week in small numbers of patients (≤20 patients), thereby raising questions about the precision of estimates. Nevertheless, these studies consistently showed that azithromycin treatment reduced the number of exacerbations and the number of related hospitalizations. This effect was already observed after three months of treatment in one study. No serious adverse events were observed with azithromycin in either study.

**Effectiveness and safety of erythromycin**

Three randomised controlled trials and one cohort study demonstrated that long-term treatment (≥6 months) with erythromycin reduced exacerbation frequency, delayed time to first exacerbation and reduced hospitalisations in COPD patients as compared with no long-term antibiotic treatment (see Table 2). Furthermore, less severe exacerbations were observed with erythromycin in one study and erythromycin treatment was associated with a shorter duration of exacerbations in another study. The frequency of adverse events with erythromycin was low in each study. In the one large study with erythromycin, there was no difference in detection rate or resistance of microorganisms between the two groups. However, these studies did not explore the impact of erythromycin treatment on quality of life. Also, there is uncertainty surrounding the precision of estimates given the small number of patients enrolled in these studies. Finally, three out of four studies had been conducted in one centre only.

**Effectiveness and safety of clarithromycin**

Table 3 indicates that long-term treatment of COPD patients with clarithromycin was investigated in one randomised controlled trial and one cohort study, which provided
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<tr>
<td>Italy</td>
<td>22 patients &gt; 45 years with history of severe COPD and tracheostomy</td>
<td>Standard care (n = 11); standard care plus azithromycin 500 mg 3 times a week for 6 months (n = 11)</td>
<td>Multicentre, open-label RCT</td>
<td>Azithromycin was associated with lower cumulative number of exacerbations after 3 months of treatment when compared to standard care (p = 0.001) and with lower cumulative number of hospitalizations (p = 0.02). A lower rate of first exacerbation (p &lt; 0.001) and of first hospitalization (p = 0.04) occurred with azithromycin when compared to standard care. Azithromycin significantly improved quality of life when compared to standard care. There was no difference in mortality rate.</td>
<td>There were no serious adverse events with azithromycin.</td>
<td>Small number of patients; no blinding of patients, physicians or researchers; high drop-out rate, limiting duration of analysis to 3 months; no evaluation of liver function in context of safety assessment.</td>
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<tr>
<td>US</td>
<td>1142 patients &gt; 40 years with COPD, used supplemental oxygen or systemic glucosteroid in previous year, had gone to emergency room or been hospitalized for COPD exacerbation.</td>
<td>Usual care plus azithromycin 250 mg daily for 1 year (n = 570); usual care plus placebo (n = 572)</td>
<td>Multicentre, double-blind RCT</td>
<td>Median time to first exacerbation was 266 days with azithromycin and 174 days with placebo (p &lt; 0.001). Frequency of exacerbations was 1.48 exacerbations per patient-year with azithromycin and 1.83 with placebo (p = 0.01). Hazard ratio for having an exacerbation per patient-year was 0.73 with azithromycin (95% CI, 0.63 to 0.84; p &lt; 0.001). The mean number of COPD-related</td>
<td>There were no differences in frequency of (serious) adverse events between azithromycin and placebo. Hearing decrements were more common with azithromycin than with placebo (25% vs 20%, p = 0.04).</td>
<td>Hearing decrements can be questioned as hearing improved to baseline levels within 1 month after study completion in patients who (dis) continued azithromycin or placebo; limited therapy compliance (around 67% in both groups); limited drop-out rate (around 10% in both groups).</td>
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<td>Spain</td>
<td>20 patients with severe COPD and frequent exacerbations or chronically colonized by <em>P. aeruginosa</em></td>
<td>Azithromycin 500 mg 3 times a week for 12 months plus triple therapy (long acting anticholinergics, long-term beta-agonists, inhaled corticosteroids); triple therapy</td>
<td>Before-and-after analysis</td>
<td>Azithromycin reduced number of exacerbations (2.8 ± 2.5 vs 6.8 ± 2.8, ( p &lt; 0.001 )), hospitalizations (1.4 ± 1.5 vs 3.6 ± 1.4, ( p &lt; 0.001 )), and cumulative annual days in hospital (25 ± 32.2 vs 43.7 ± 21.4, ( p = 0.01 )).</td>
<td>There were no serious adverse events with azithromycin. One patient stopped azithromycin due to dyspepsia.</td>
<td>Small number of patients; four out of 24 patients did not complete 12-month treatment period and were excluded from analysis; single centre study.</td>
<td>36</td>
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**GRADE assessment:**

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Notes: ‘CI’ = confidence interval; ‘COPD’ = chronic obstructive pulmonary disease; ‘RCT’ = randomized controlled trial.
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<tr>
<td>Japan</td>
<td>109 patients with COPD treated with sustained release theophylline</td>
<td>Erythromycin 200–400 mg per day for 12 months ( n = 55 ); no active treatment, ( \text{i.e.} ) riboflavin 10 mg per day ( n = 54 )</td>
<td>Prospective open-label RCT</td>
<td>Relative risk of experiencing exacerbation in control group as compared with erythromycin group was 4.71 (95% CI, 1.53 to 14.5; ( p = 0.007 )). Total number of exacerbations was lower in erythromycin group than in control group ( p &lt; 0.0001 ). More severe exacerbations were observed in control group than in erythromycin group ( p = 0.0007 ). More patients were hospitalized due to exacerbations in control group than in erythromycin group ( p = 0.0007 ).</td>
<td>One patient experienced anorexia and diarrhea in erythromycin group</td>
<td>Small number of patients; no blinding of patients, physicians or researchers; single centre study.</td>
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<td>Japan</td>
<td>123 elderly patients with COPD</td>
<td>Macrolide therapy (erythromycin, ( n = 23 ); clarithromycin, ( n = 26 )) for mean follow-up of 43 months ( 12–193 ) months; no antibiotic ( n = 78 )</td>
<td>Retrospective multicentre cohort study</td>
<td>Number of patients with exacerbation frequency of 1.5 times per year or more in macrolide group (4.4%) was lower than in control group (15.4%) ( p = 0.01 ). Number of patients with hospitalization frequency of 0.75 times per year or more in macrolide group (4.4%) was lower than in control group (14.1%) ( p = 0.04 ). Use of macrolides was related to low frequency of exacerbations ( p = 0.02 ) and hospitalization ( p = 0.04 ).</td>
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<td>Some differences in baseline characteristics between macrolide and control group (risk for selection bias); small number of patients in macrolide group.</td>
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<td>UK</td>
<td>109 elderly patients with moderate-to-severe COPD, most of them were taking inhaled steroids</td>
<td>Erythromycin 250 mg twice daily for 1 year ( n = 53 ); placebo ( n = 56 )</td>
<td>Double-blind RCT</td>
<td>Median exacerbation frequency was 2 with placebo and 1 in erythromycin group ( p = 0.006 ). Median time to first exacerbation was 271 days in erythromycin group versus 89 days with placebo ( p = 0.020 ). Rate ratio for exacerbations in erythromycin group as compared with placebo was 0.648 (95% CI, 0.489 to 0.859; ( p = 0.003 )). Median duration of exacerbations with placebo was 13 days, and 9 days in erythromycin group ( p = 0.036 ).</td>
<td>No differences in adverse events were observed between erythromycin and placebo, and frequency of adverse events was low in both groups.</td>
<td>Small number of patients (lower than that required by sample size calculation); 22% drop-out rate; single centre study.</td>
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inconsistent results.\textsuperscript{33,38} On the one hand, based on a retrospective cohort study in which 26 patients were treated with clarithromycin, long-term treatment reduced exacerbation and hospitalisation frequency.\textsuperscript{38} Conversely, a double-blind randomised controlled trial observed no differences in clinical outcomes between clarithromycin and placebo.\textsuperscript{33} However, this may be expected due to the short duration of treatment and the low dose of clarithromycin. It should also be noted that baseline demographic and clinical characteristics were not comparable between clarithromycin and placebo groups. Finally, these studies provided limited data on the safety of long-term clarithromycin treatment.

**Budget impact analysis**

By applying European prevalence data to Belgium, there were 848,333 COPD patients in GOLD stage II; 132,208 patients in GOLD stage III and 22,035 patients in GOLD stage IV in 2012. The additional expenditure of annual treatment with azithromycin was contrasted with the savings in hospital expenditure arising from a reduced number of COPD exacerbations. Annual treatment of Belgian COPD patients in GOLD stages II\textDash{}IV with azithromycin generated additional expenditure of €595 million, but was associated with hospital savings of €950 million resulting from fewer exacerbations. Therefore, the budgetary savings of preventing COPD exacerbations with azithromycin in Belgium over a one-year period was estimated to amount to €355 million.

The sensitivity analyses indicated that the budget impact estimates were sensitive to changes in the absolute number of exacerbation-related hospitalisations per patient per year avoided with azithromycin as compared to placebo: when the number of avoided hospitalisations increased by 50%, the budgetary savings with azithromycin rose to €830 million, but when the number of avoided hospitalisations fell by 50%, long-term treatment of COPD patients with azithromycin would cost an additional €120 million. When the cost of azithromycin 250 mg per day varied between €1.63 and €1.68, the budgetary savings with azithromycin ranged from €336 to €355 million. Finally, when the use of azithromycin was restricted to patients with a history of frequent COPD exacerbations, budgetary savings amounted to €87 million.

**Discussion**

The literature review suggests that long-term treatment of COPD patients with azithromycin, erythromycin or clarithromycin is in general effective and safe. Macrolide treatment appears to reduce exacerbations and related hospitalizations. However, a number of issues relating to long-term macrolide treatment remain unresolved.

First, existing studies have employed different patient inclusion criteria, so that it is not possible to identify a patient population that is most likely to benefit from long-term macrolide treatment. Intuitively, we would expect that patients who retain high exacerbation rates, despite conventional therapy with long-acting bronchodilators and inhaled steroids, would be the best candidates for such
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<td>Some differences in baseline characteristics between macrolide and control group (risk for selection bias); small number of patients in macrolide group.</td>
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<td>UK</td>
<td>67 patients with moderate-to-severe COPD taking inhaled corticosteroids</td>
<td>Clarithromycin 500 mg once daily for 3 months (n = 31); placebo (n = 36)</td>
<td>Double-blind RCT</td>
<td>Clarithromycin did not improve health status, sputum bacterial numbers or exacerbation rate as compared to placebo.</td>
<td>In clarithromycin group, 1 patient had gastrointestinal upset.</td>
<td>Small number of patients; low dose of clarithromycin and short treatment duration; some differences in baseline characteristics between groups (risk for selection bias); 10% drop-out rate.</td>
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**GRADE assessment**

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Notes: ‘COPD’ = chronic obstructive pulmonary disease; ‘RCT’ = randomized controlled trial.
therapy. However, it is at present not clear whether treatment effects would be larger in these patients.

Second, there is also uncertainty surrounding the optimal dose and duration of macrolide treatment. It would be particularly interesting to investigate whether doses below 250 mg azithromycin daily or equivalent doses of other macrolides, would also produce effects. Third, no study has carried out a direct comparison between long-term treatment with one macrolide product and long-term treatment with another macrolide. Fourth, the possible adverse events associated with long-term macrolide treatment need to be investigated in more detail.39 So far, side effects appear acceptable. Fifth, it is not clear whether long-term treatment with a macrolide could lead to restricting or abandoning other medication (e.g. inhaled corticosteroids).

Finally, the question needs to be asked whether long-term treatment with macrolides may induce resistance to these antibiotics. At present, the data in the literature appear conflicting.15,16 More studies on this important topic are required. A particularly important question is whether possible changes in resistance pattern may increase the incidence of infections clinically.

It should be noted that the use of macrolides such as erythromycin and clarithromycin may raise the risk of serious ventricular arrhythmias and the risk of cardiovascular death.40–43 A recent retrospective cohort study has suggested that a five-day course of azithromycin also increases the risk of cardiovascular death.44 However, the authors acknowledged that this observational study was not able to control for confounding factors that are associated with azithromycin use and an increased risk of cardiovascular death. Furthermore, the literature points to the minimal cardiotoxicity of azithromycin.45

Although this fell outside the scope of this literature review, the reader should note that there is also limited clinical evidence about long-term intermittent therapy of COPD patients with moxifloxacin and about long-term treatment with inhaled antibiotics (e.g. inhaled tobramycin). Extensive experience with the latter was obtained in patients with cystic fibrosis.46,47 These treatments appear to reduce exacerbations in COPD patients as well, but these initial results need to be validated by future research.24

To date, to the best of the authors’ knowledge, no economic evaluation has calculated the cost-effectiveness of long-term treatment with a macrolide in the prevention of COPD exacerbations. It is hypothesised that cost-effectiveness will mainly depend on the additional costs of long-term macrolide treatment and on savings arising from fewer exacerbation-related hospitalisations. In this respect, a 2010 audit of COPD care across Europe included 499 Belgian patients admitted to hospital and described their demographic characteristics as follows: median age of 68 years (37% of patients were younger than 65 years), mean height of 166 cm, mean weight of 68 kg, BMI of 24.8, Charlson index of comorbidity of 1.0, 44% of patients were smokers, 51% were former smokers and 5% had never smoked.48

Our simplistic budget impact analysis demonstrated that hospital savings from fewer exacerbations outweighed additional expenditure of annual treatment with azithromycin in COPD patients in stages II–IV, implying that the prevention of COPD exacerbations with azithromycin is a cost saving strategy in Belgium. As is expected, the sensitivity analysis showed that the budget impact estimate depends on the absolute number of avoided hospitalisations with azithromycin as compared with placebo. The number of avoided hospitalisations in our budget impact analysis was derived from a multi-centre, double-blind RCT, which possibly under-estimated the treatment effect of azithromycin in light of the limited compliance of the enrolled patient population with azithromycin.16 Changes in input parameters associated with the cost of azithromycin treatment and the size of the patient population confirmed that long-term treatment of COPD patients with azithromycin is cost saving, thus supporting the generalizability of our results. However, the reader should note that this budget impact analysis did not account for adverse events or possible changes in resistance patterns associated with long-term treatment with azithromycin. Also, in the absence of data, it was not possible to consider the budget impact of changes in the number of physician visits related to COPD exacerbations.

Conflict of interest

Financial support for this research was received from TEVA. The study sponsor did not have a role in the study design, in the collection, analysis and interpretation of data, in the writing of the manuscript, or in the decision to submit the manuscript for publication. The authors have no conflicts of interest that are directly relevant to the content of this manuscript.

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