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Impacting patient-centred outcomes in COPD: exacerbations and hospitalisations

R. Rodríguez-Roisin

ABSTRACT: Patients with chronic obstructive pulmonary disease (COPD) frequently develop exacerbations, leading to major clinical and healthcare utilisation ramifications. Exacerbations, especially those that result in hospitalisation, are the main cost driver in COPD and frequent exacerbations are associated with increased mortality, impaired health-related quality of life (HRQoL) and perhaps a more rapid decline in lung function over time. Prevention and treatment of exacerbations is, therefore, an important goal of maintenance therapy in COPD.

The impact of tiotropium, a long-acting anticholinergic agent, on exacerbations and associated healthcare utilisation has been studied in five randomised, controlled clinical trials of ⩾6 months' duration involving >5,000 patients.

Analyses of adverse events reports submitted during three long-term efficacy and safety trials showed that tiotropium significantly reduced the incidence of exacerbations and delayed the time to first exacerbation, compared with either placebo or the short-acting anticholinergic agent, ipratropium. More recent prospective data confirmed previous findings.

Collectively, the results of these studies support the role of tiotropium as maintenance therapy in chronic obstructive pulmonary disease, demonstrating that this agent can provide significant reductions in the incidence of exacerbations and associated healthcare utilisation.

KEYWORDS: Bronchodilators, chronic obstructive pulmonary disease, exacerbations, healthcare utilisation, hospitalisation, long-acting anticholinergic agents

Exacerbations of chronic obstructive pulmonary disease (COPD) are a major cause of morbidity and mortality [1]. They are caused or triggered by a variety of factors, including bacteria, viruses and air pollution [2]. There is no standardised and generally accepted definition of an exacerbation; however, it is commonly defined as a sustained worsening of the patient's condition, from the stable state and beyond normal day-to-day variations, that is both acute in onset and necessitates a change in regular medication in a patient with underlying COPD [3]. As well as the burden to the patient, the cost of additional medication and/or hospitalisation for exacerbations adds to the financial cost of treating COPD [4]. In addition, frequent exacerbations are associated with increased mortality [5], impaired health-related quality of life (HRQoL) [6] and a more rapid decline in lung function over time [7].

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines state that one of the goals of effective management is to prevent and treat exacerbations and recommend long-acting bronchodilators, namely anticholinergic agents (tiotropium) and/or β_2-agonists (formoterol or salmeterol), as first-line maintenance treatment in COPD [8]. The aim of this article is to review the currently available data on the effect of tiotropium on exacerbations and associated healthcare utilisation.

EFFECT OF LONG-ACTING ANTICHOLINERGIC AGENTS ON EXACERBATIONS

Tiotropium is a long-acting anticholinergic agent that works through prolonged M_3-receptor blockade. Tiotropium has been consistently shown to have a beneficial impact on lung function and patient-centred outcomes, such as dyspnoea, exercise tolerance, HRQoL and exacerbations in patients with COPD. The impact of tiotropium on exacerbations and associated healthcare utilisation has been studied in five double-blind, controlled, parallel-group, large-scale trials of ⩾6 months' duration involving >5,000 patients (table 1) [9–13].

Six pivotal trials (comprising three pairs) compared the long-term efficacy and safety of tiotropium *versus* placebo [9], the short-acting anticholinergic agent, ipratropium [10], or the long-acting β_2-agonist, salmeterol [11], in patients

CORRESPONDENCE
R. Rodríguez-Roisin
Servei de Pneumologia
Hospital Clinic
Villarroel 170
Barcelona 08036
Spain
Fax: 34 932275455
E-mail: rororo@clinic.ub.es

CONFLICT OF INTEREST STATEMENT
R. Rodríguez-Roisin has lectured for Almirall Prodesfarma (Barcelona, Spain), AltanaPharma (New Jersey, NJ, USA), AstraZeneca (Madrid, Spain), Boehringer Ingelheim (Ingelheim, Germany), Pfizer (New Jersey, NJ, USA) and GlaxoSmithKline (Hertford, UK) and has had consultancy arrangements with Almirall Prodesfarma, AltanaPharma, Boehringer Ingelheim, Pfizer, Chiesi Wasserman (Parma, Italy), GlaxoSmithKline, Laboratoris Dr Esteve SA (Barcelona, Spain) and Novartis (Basel, Switzerland). He has also received research funding from Almirall Prodesfarma, AstraZeneca, Boehringer Ingelheim, Pfizer, GlaxoSmithKline, Laboratoris Dr Esteve SA and Merck SD (Madrid, Spain).

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TABLE 1 The effect of tiotropium on exacerbations and related hospitalisations

First author [ref.]	Comparator	Patients n	Duration weeks	Baseline FEV_1 L	Exacerbations	Associated hospitalisations
CASABURI [9]	Placebo	921	52	1.02	↓	↓
VINCKEN [10]	Ipratropium	535	52	1.25	↓	↓
BRUSASCO [11]	Placebo	1207	26	1.12	↓	NS
BRUSASCO [11]	Salmeterol	1207	26	1.12	NS	NS
NIEWOEHNER [12]	Placebo	1829	26	1.04	↓	↓
DUSSER [13]	Placebo	1010	52	1.37	↓	NS

↓: significant reduction in exacerbation or associated hospitalisation end-points *versus* comparator; NS: no significant reduction in exacerbation or associated hospitalisation end-points *versus* comparator.

with COPD (table 1). Analyses of adverse event reports from these studies showed that tiotropium significantly delayed the time to first exacerbation compared with either placebo or ipratropium [9–11]. Furthermore, tiotropium significantly reduced the percentage of patients experiencing one or more exacerbation, and reduced the number of exacerbations and exacerbation days compared with either placebo or ipratropium [9–11]. Collectively, these results suggest that tiotropium may provide a protective effect against exacerbations.

To test this hypothesis, two prospectively designed trials were initiated [12, 13]. NIEWOEHNER *et al.* [12] evaluated the effectiveness of tiotropium in reducing exacerbations and associated healthcare utilisation. The results of this 6-month study showed that tiotropium reduced exacerbations and may cause healthcare utilisation in patients with moderate-to-severe COPD to fall. Compared with placebo, tiotropium significantly reduced: the percentage of patients experiencing one or more exacerbation by 13% (fig. 1a); the number of exacerbations by 19%; and the exacerbation days by 21% ($p<0.05$ for all). In addition, the time to first exacerbation was significantly longer in patients receiving tiotropium ($p<0.05$; table 1).

Subgroup analyses were also performed to assess the impact of tiotropium on exacerbations according to the following baseline characteristics: age; race; current cigarette smoking; baseline forced expiratory volume in one second (FEV_1); hospitalisation for COPD in the past year; at least one course of systemic corticosteroids for COPD in the past year; at least one course of antibiotics for COPD in the past year; and use at study entry of home oxygen, inhaled corticosteroids, long-acting inhaled β_2-agonists (LABAs) or theophylline. As shown in figure 2, tiotropium fairly uniformly reduced exacerbations compared with placebo for all subsets included in the analyses [12].

In another recent prospective study, exacerbation data were solicited using a grading system that distinguished events by severity [13]. The results of this 1-yr study confirmed previous findings, demonstrating that tiotropium significantly delayed the time to first exacerbation ($p<0.001$), as well as being significantly more effective at reducing the proportion of patients experiencing more than one exacerbation (by 17%; $p<0.01$), the number of exacerbations (by 35%; $p<0.001$) and the number of exacerbation days (by 37%; $p<0.001$) *versus* placebo. Furthermore, tiotropium proved particularly effective

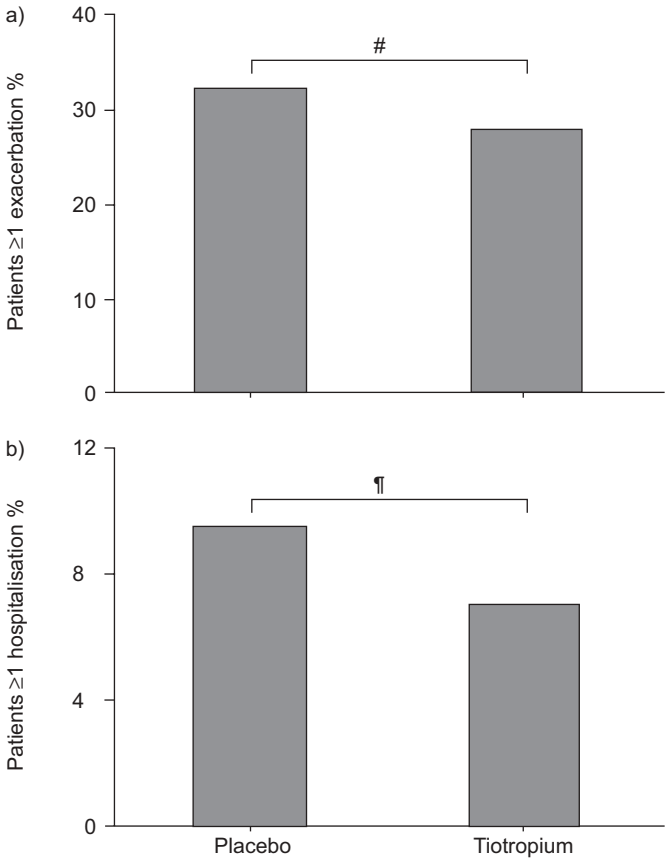

FIGURE 1. Percentage of patients a) experiencing one or more exacerbation and b) one or more chronic obstructive pulmonary disease hospitalisation. #: $p=0.037$; ¶: $p=0.056$. Data taken and modified from [12].

at reducing moderate-to-severe exacerbations. Compared with placebo, tiotropium significantly reduced the percentage of patients experiencing one or more moderate-to-severe exacerbation by 30%, the number of moderate-to-severe exacerbations by 36% and the number of moderate-to-severe exacerbation days by 34% ($p<0.0001$ for all).

The mechanisms by which tiotropium reduces exacerbations remain to be identified. Tiotropium may have a direct anti-inflammatory effect [14]. For instance, because acetylcholine

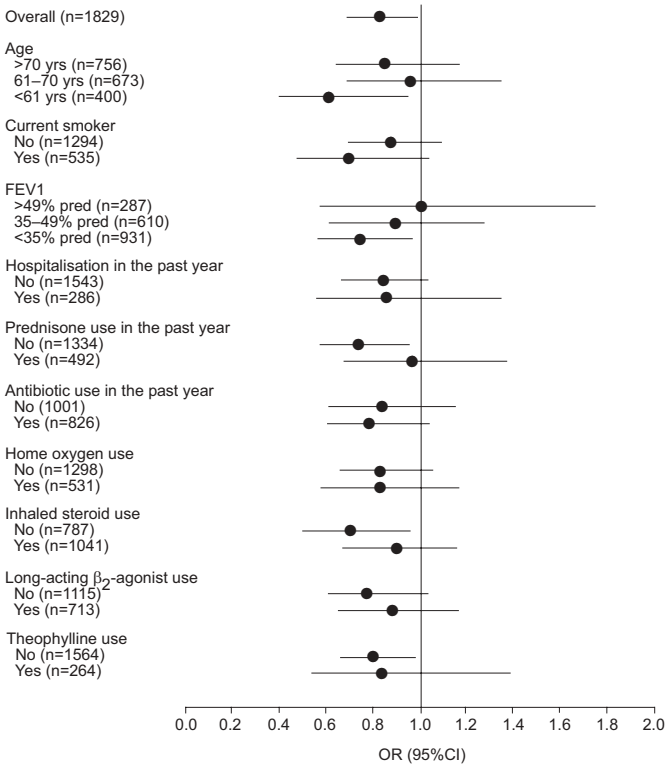

FIGURE 2. Odds ratios (OR; ●) and 95% confidence intervals (CI; ——) for reduction in first exacerbation with tiotropium compared with placebo according to selected baseline characteristics. 0.0–1.0: favours tiotropium; 1.0–2.0: favours placebo. FEV1: forced expiratory volume in one second; % pred: % predicted. Reprinted from [12] with permission from the publisher.

stimulates bronchial epithelial cells to release neutrophil and monocyte chemotactic activity through the muscarinic receptor [15], tiotropium may inhibit this pro-inflammatory response. Alternatively, tiotropium may simply lessen the dyspnoea associated with an exacerbation as a result of the sustained increase in expiratory flow rates and the reduction in lung hyperinflation [16]. For example, whereas patients may have previously perceived an acute deterioration in their condition as an exacerbation and sought emergency care for an exacerbation, after recalibration of their operating lung volumes with tiotropium, their symptoms become better tolerated. The reduction in lung hyperinflation during exacerbations can result in less ventilation–perfusion imbalance, so that patients may be less vulnerable to triggers of exacerbations. The latter may be an additional or complementary mechanism by which tiotropium could reduce exacerbations.

EFFECT OF INHALED CORTICOSTEROIDS AND/OR LABAs ON EXACERBATIONS

To put the effect of tiotropium on exacerbations into context, the responses shown must be compared with those observed using other drugs. Inhaled corticosteroids (ICS) and LABAs have also been shown to reduce COPD exacerbation rates. For instance, in the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE) study, fluticasone propionate significantly reduced the median yearly exacerbation rate by 25% compared with placebo ($p<0.05$) [17]. However, a *post hoc* analysis showed that this effect was restricted to patients with more severe airflow limitation (*i.e.* FEV_1 <50% predicted) [18].

A number of studies have assessed whether the combination of a LABA, such as salmeterol or formoterol, and an ICS reduces the rate of exacerbations compared with single-agent therapy [19–21]. Compared with placebo, both salmeterol and fluticasone alone significantly reduced the number of exacerbations (by 20% and 19%, respectively; $p<0.01$ for both). However, the combination of both agents provided a greater reduction in the number of exacerbations *versus* placebo (25% reduction, $p<0.0001$) [19]. Similarly, compared with placebo, two studies have shown that the combination of formoterol and budesonide provided a greater reduction in the number of severe exacerbations *versus* either placebo (23–24% reduction, $p<0.05$ for both studies) or formoterol alone (23–25% reduction, $p<0.05$ for both studies) [20, 21].

IMPACT OF LONG-ACTING ANTICHOLINERGIC AGENTS ON HEALTHCARE UTILISATION

A reduction in the incidence of exacerbations or an increase in the time to first exacerbation is likely to reduce healthcare utilisation, which, in turn, should reduce the cost of COPD management. Indeed, in the long-term studies, tiotropium was shown to significantly delay the time to first hospitalisation compared with ipratropium [10], and reduce the percentage of patients with one or more hospitalisation and the number of both hospitalisations and hospitalisation days compared with placebo [9].

One of the co-primary end-points in the study by NIEWOEHNER *et al.* [12] was the percentage of patients with a COPD-related hospitalisation. Although tiotropium reduced the percentage of patients who experienced one or more hospitalisation due to a COPD exacerbation by 26% *versus* placebo, the difference between the groups did not reach statistical significance ($p=0.056$; fig. 1b) [12]. In the same study, however, tiotropium was shown to significantly reduce the number of hospitalisations for a COPD exacerbation and other healthcare events attributable to COPD exacerbations, such as unscheduled clinic visits and days of antibiotic treatment ($p<0.05$ for all) [12].

Similarly, another more recent study showed that tiotropium significantly reduced healthcare utilisation *versus* placebo, as indicated by significant reductions in the use of concomitant respiratory medications, antibiotics and oral steroids, and the number of unscheduled physician contacts ($p<0.05$ for all) [13]. The study was not powered to detect a reduction in hospitalisations due to COPD exacerbations. However, compared with placebo, tiotropium resulted in numerically fewer hospitalisations and hospital days due to COPD, but the differences between the groups were not statistically significant. Because hospitalisation is a large contributor to the cost of COPD, the use of tiotropium as a component of usual-care therapy may reduce the economic burden of this disease. Reducing physician visits and use of concomitant medications are also of economic benefit.

CONCLUSIONS

Exacerbations of chronic obstructive pulmonary disease can lead to costly, clinically significant consequences. Hence, interventions that reduce the frequency or severity of

exacerbations are a highly desirable medical need. The weight of evidence from randomised, controlled clinical trials supports the role of tiotropium as a maintenance therapy in chronic obstructive pulmonary disease, in demonstrating that this agent can provide significant reductions in the incidence of exacerbations and associated healthcare utilisation.

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