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Once-daily glycopyrronium bromide, a long-acting muscarinic antagonist, for chronic obstructive pulmonary disease: a systematic review of clinical benefit

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Background: Long-acting bronchodilators are central in the pharmacological management of patients with chronic obstructive pulmonary disease (COPD). The aim of this systematic review is to provide an overview of the studies evaluating the safety and clinical efficacy of inhaled glycopyrronium bromide, a novel long-acting muscarinic antagonist, in patients with COPD.

Methods: This study was performed as a systematic literature review.

Results: Inhaled glycopyrronium bromide seems to be a safe and well tolerated long-acting muscarinic antagonist with a fast onset of action. In patients suffering from moderate to severe COPD, glycopyrronium bromide has clinically important effects on level of forced expiratory volume in one second, use of relief medication, percentage of days with no use of rescue medication, daytime dyspnea scores, and probably also on health status. Furthermore, in this group of patients, glycopyrronium bromide has beneficial effects on dynamic hyperinflation and exercise tolerance. Glycopyrronium bromide has been shown to reduce the rate of exacerbations in patients with moderate to severe COPD, but long-term controlled trials with exacerbation rate as the primary outcome variable have not been published yet.

Conclusion: Once-daily inhaled glycopyrronium bromide has characteristics important for use in COPD, including a fast onset of action, sustained 24-hour bronchodilatation, and improvement in exercise tolerance, and therefore appears to have the potential for a significant role in the future management of COPD.

Keywords: chronic obstructive pulmonary disease, glycopyrronium bromide, long-acting bronchodilators

Introduction

The Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD strategy document) recommends the use of long-acting bronchodilators as first-line maintenance therapy for patients with moderate to severe chronic obstructive pulmonary disease (COPD).^{1,2} Clinical studies of patients with COPD show that long-acting bronchodilators have a positive impact on prevention and control of symptoms, severity and rate of exacerbations, quality of life, and exercise capacity.^{1,3,4}

Dyspnea is the hallmark symptom of COPD, and dyspnea is the main reason for patients suffering from COPD seeking medical attention.¹ Dyspnea is probably also the most important cause of COPD-related anxiety and disability.¹ Long-acting bronchodilators reduce lung volumes by a reduction in air trapping and an improvement in emptying of the lungs, which leads to an improvement in dyspnea and

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exercise capacity.^{1,3,5} Long-acting bronchodilators, including β_2 -agonists and antimuscarinic agents, are therefore key elements in the symptomatic management of COPD.

Long-acting anticholinergic agents may be the most effective class of bronchodilators for COPD,^{1,2,6,7} and although tiotropium bromide is the only long-acting anticholinergic bronchodilator marketed for COPD, several others are in various stages of development, including glycopyrronium bromide. Glycopyrronium bromide has been used for years, administered as injections or tablets, as an adjunct in peptic ulcer disorders, to diminish secretions and block cardiac vagal reflexes before surgery, and has now been developed as an inhaled agent for the treatment of COPD. This short review provides an overview of the available clinical studies evaluating the safety and efficacy of inhaled glycopyrronium bromide in patients with moderate to severe COPD.

Materials and methods

A series of systematic searches were carried out and last updated in August 2012, using the database PubMed. The strategy was intended to be broad in order to maximize the capture of citations for peer-reviewed publications relevant to glycopyrronium bromide and COPD. The PubMed searches were carried out using the following algorithm of MeSH terms: glycopyrronium bromide, NVA237, long-acting antimuscarinic agents, indacaterol, salmeterol, formoterol, tiotropium bromide, aclidinium bromide, long-acting bronchodilators, and COPD, and the searches were repeated with these terms in combination with forced expiratory volume in one second (FEV_1), hyperinflation, exercise capacity, dyspnea, health status, exacerbations, and adverse effects. The citation pool was further supplemented from manual assessment of the reference lists in identified reviews and clinical studies of aspects related to long-acting bronchodilators and COPD and from other publications identified as being relevant for further review. All identified randomized studies published in peer-reviewed journals of glycopyrronium bromide for the treatment of COPD are included in the present review.

Results

Activity profile and safety of glycopyrronium bromide

Glycopyrronium bromide (NVA237) is a synthetic quaternary ammonium compound acting as a competitive antagonist by binding to muscarinic receptors in bronchial smooth muscle, thereby inhibiting acetylcholine-induced bronchoconstriction.

Glycopyrronium bromide binds to all five subtypes of the muscarinic receptor (M_1 – M_5), of which the M_3 receptor located on airway smooth muscle is primarily involved in smooth muscle contraction. Blockade of M_2 receptors attenuates the feedback inhibition of acetylcholine production, and thereby may reduce the bronchodilating effects of an antimuscarinic agent. Furthermore, blocking cardiac M_2 receptors may result in an increase in heart rate. Therefore, the optimal antimuscarinic agent for use in COPD has high affinity for M_1 and M_3 receptors and low affinity for M_2 receptors. Like tiotropium bromide, glycopyrronium bromide has higher selectivity for M_3 receptors than for M_2 receptors, and like both tiotropium bromide and aclidinium bromide, dissociates more slowly from the M_3 receptor than it does from the M_2 receptor.^{8,9} Therefore, glycopyrronium bromide provides bronchodilatation via M_3 blockade long after its less desirable M_2 effects, such as an increased heart rate.^{8–10}

In vitro studies have indicated that glycopyrronium bromide may have a faster onset of action than tiotropium, and this has been confirmed in clinical studies.^{8,11} Glycopyrronium bromide equilibrates four to five times faster with the M_3 receptor than does tiotropium bromide and aclidinium bromide.^{8,11} This more rapid equilibration of glycopyrronium bromide with the M_3 receptor is assumed to underlie its faster onset of action compared with that of tiotropium bromide,⁸ and probably also aclidinium bromide.

Early preclinical and clinical studies have suggested a very favorable safety profile for inhaled glycopyrronium bromide. Sechaud et al¹⁰ investigated the pharmacokinetics of glycopyrronium bromide following single and repeated once-daily inhalation in mild to moderate COPD patients, and reported that the pharmacokinetics of glycopyrronium bromide were consistent between doses and with limited systemic accumulation at steady state after repeated once-daily inhalation. The overall incidence of adverse events was similar in patients treated with glycopyrronium bromide and placebo, apart from a higher frequency of dry mouth in the groups treated with glycopyrronium bromide. No serious adverse events were reported, and no clinically relevant effects were observed on vital signs, electrocardiography, or physical examinations.¹⁰

In a randomized, double-blind, placebo-controlled, parallel-group study, in which 257 patients with moderate to severe COPD were assigned to indacaterol plus glycopyrronium bromide, indacaterol, or placebo, Van de Maele et al¹² investigated the change from baseline in 24-hour mean heart rate versus placebo. A total of 255 patients were

included in the safety analysis, which showed no clinically significant differences between groups in the mean 24-hour heart rate or QTc interval, suggesting a cardiovascular safety profile of both long-acting bronchodilators similar to that of placebo.

The issue of inhaled anticholinergics and risk of major cardiovascular events has been much debated, and a meta-analysis of previously published studies has reported an increased risk of cardiovascular death, myocardial infarction, and stroke in COPD patients treated with inhaled anticholinergics,¹³ but conclusions regarding this point await the findings of ongoing prospective studies. In the clinical studies published so far, cardiac and vascular disorders have been reported at a similar frequency in the glycopyrronium bromide and placebo groups, although, as in other clinical trials of antimuscarinic agents in COPD, patients with any of a number of concomitant diseases, including symptomatic prostatic hyperplasia and narrow-angle glaucoma, were not eligible for inclusion.

Clinical studies of glycopyrronium bromide

FEV₁

Verkindre et al¹⁴ published one of the first double-blind, placebo-controlled trials of glycopyrronium bromide in patients with COPD. The study was conducted in 83 patients (78 patients completed the study) with stable moderate to severe COPD (mean post-bronchodilator FEV₁ 53% predicted). The patients were randomized to glycopyrronium bromide 12.5, 25, 50 or 100 µg, placebo, or tiotropium bromide 18 µg once daily (open-label active comparator) for 7 days. The primary endpoint was mean trough (23–24 hours following dosing) FEV₁ on day 7. Mean trough FEV₁ on days 1 and 7 was significantly higher with all active treatments versus placebo ($P < 0.05$). Glycopyrronium bromide 50 µg and 100 µg and tiotropium bromide showed clinically relevant improvements versus placebo on day 1 (differences 121, 135, and 112 mL, respectively, $P < 0.0001$) and day 7 (differences 131, 142, and 127 mL, respectively, $P < 0.0001$). No clinically significant difference in improvements in FEV₁ was observed between either dose of glycopyrronium bromide and tiotropium bromide, although a statistically significant difference in level of FEV₁ in favor of glycopyrronium bromide was reported. Therefore, this study showed that glycopyrronium bromide once daily was well tolerated and demonstrated rapid and sustained 24-hour bronchodilatation, the latter being at least comparable with tiotropium bromide.

In a randomized, placebo-controlled trial, Vogelmeier et al¹⁵ studied the bronchodilator efficacy of two doses of glycopyrronium bromide (100 µg and 200 µg) versus placebo in patients with moderate to severe COPD (mean post-bronchodilator FEV₁ 53% predicted). Enrolled patients were randomized to treatment with glycopyrronium bromide 100 µg ($n = 92$), glycopyrronium bromide 200 µg ($n = 98$), or placebo ($n = 91$) for 28 days. The primary objective was to evaluate safety, but efficacy measures were included as secondary objectives. Mean trough FEV₁ was significantly higher in patients receiving glycopyrronium bromide compared with those receiving placebo. For glycopyrronium bromide 100 µg, the treatment differences from placebo were 131 mL and 161 mL, respectively, on days 1 and 28 ($P < 0.05$); for glycopyrronium bromide 200 µg, the treatment differences were 146 mL and 151 mL, respectively, on days 1 and 28 ($P < 0.05$). In line with this, peak FEV₁, FEV₁ at all time points up to 24 hours after dosing, and FEV₁ area under the curve (AUC) from 5 minutes to 5 hours after dosing were also significantly higher for both doses of glycopyrronium bromide compared with placebo. Although this study did not include an active comparator, its reported findings support the bronchodilator efficacy of glycopyrronium bromide in patients with moderate to severe COPD.

In a small, randomized, double-blind, placebo-controlled, two-period crossover trial, Fogarty et al¹⁶ studied the bronchodilatory effects of glycopyrronium bromide versus placebo in 33 patients with moderate COPD (mean post-bronchodilator FEV₁ 70% predicted). Only subjects with at least a 5% increase in FEV₁ following inhalation of ipratropium bromide were eligible for the study. Patients were randomized to receive glycopyrronium bromide 50 µg once daily followed by placebo or vice versa for 14 days; the treatment periods were separated by a washout period of 7–14 days. The primary efficacy variable was the standardized FEV₁ AUC between 0 and 24 hours after dosing on day 14. The FEV₁ AUC_{0–24 h} values on day 14 were significantly higher for glycopyrronium bromide than for placebo ($P < 0.001$) with a least squares mean difference of 163 mL between glycopyrronium bromide and placebo. The FEV₁ with glycopyrronium bromide was significantly higher ($P < 0.001$) than for placebo for all AUCs evaluated. On day 14, significant treatment differences were found in mean FEV₁ AUC_{0–5 h} (difference 198 mL, $P < 0.001$), FEV₁ AUC_{0–12 h} (difference 165 mL, $P = 0.001$), and FEV₁ AUC_{12–24 h} (difference 161 mL, $P < 0.001$) versus placebo. Furthermore, all primary analyses for trough FEV₁ comparisons showed a clinically significant effect (predefined threshold exceeded,

ie, 120 mL) at the 5% level, except for the treatment least squares mean difference in trough value for glycopyrronium bromide on day 7 (91 mL). The mean difference in peak FEV₁ values between glycopyrronium and placebo was 208 mL ($P < 0.001$) on day 14 and 173 mL ($P = 0.011$) on day 7, respectively. Therefore, this study supports the notion that glycopyrronium bromide provides significant and sustained 24-hour bronchodilatation in patients with COPD, similar to that provided by tiotropium bromide.¹⁷

In one of the largest published clinical trials of glycopyrronium bromide (The glycopyrronium bromide in COPD airways clinical study 1 [GLOW1]), D'Urzu et al¹⁸ randomized patients with stable moderate to severe COPD (mean post-bronchodilator FEV₁ 54% predicted) to either glycopyrronium bromide 50 µg once daily ($n = 552$) or placebo ($n = 270$) for 26 weeks. Patients were not eligible for the study if they were participating in a supervised pulmonary rehabilitation program. The primary outcome measure was trough FEV₁ at week 12. Least squares mean trough FEV₁ at week 12 was significantly higher in patients receiving glycopyrronium bromide (1.41 L) versus placebo (1.30 L), with a treatment difference of 108 ± 15 mL ($P < 0.001$). Significant improvements in trough FEV₁ were observed at the end of day 1 and sustained through week 26. FEV₁ was significantly improved in the glycopyrronium bromide group versus the placebo group throughout a 24-hour period on day 1, at weeks 12 and 26, and at all other scheduled visits and time points.

In the GLOW 2 study, Kerwin et al¹⁹ randomized patients with moderate to severe COPD (mean FEV₁ 56% predicted) to either glycopyrronium bromide 50 µg once daily ($n = 525$), open-label tiotropium 18 µg once daily ($n = 267$), or placebo ($n = 268$) for 52 weeks. The primary outcome measure was trough FEV₁ at week 12. Least squares mean trough FEV₁ at week 12 was significantly higher in patients receiving glycopyrronium bromide and tiotropium compared with that in patients receiving placebo, with a treatment difference of 97 mL ($P < 0.001$) and 83 mL ($P < 0.001$), respectively. Furthermore, trough FEV₁ at weeks 26 and 52 was significantly higher for patients treated with glycopyrronium bromide versus placebo and comparable with tiotropium. At these time points, the treatment difference, compared with placebo, in favor of glycopyrronium bromide, was 134 mL and 108 mL, respectively ($P < 0.001$), while the difference in favor of tiotropium was 84 mL and 89 mL, respectively ($P < 0.001$). On day 1, the least squares mean FEV₁ treatment difference for glycopyrronium bromide/placebo and tiotropium bromide/placebo was 87 mL and

45 mL at 5 minutes, respectively, and 143 mL and 78 mL at 15 minutes, respectively ($P < 0.001$). The latter finding further supports the notion that glycopyrronium bromide has a faster onset of action than other inhaled antimuscarinic agents, including tiotropium bromide.

Hyperinflation and exercise capacity

Similar to the studies of indacaterol and tiotropium by O'Donnell et al^{20,21} and a study of aclidinium bromide by Maltais et al,²² a study by D'Urzu et al¹⁸ revealed a significant treatment difference in inspiratory capacity. The inspiratory capacity was significantly higher in patients receiving glycopyrronium bromide than in those receiving placebo at all time points on day 1 and at weeks 12 and 26 (all $P < 0.001$). The glycopyrronium bromide/placebo difference for inspiratory capacity by the end of day 1, week 12, and week 26 was 104 mL, 97 mL, and 113 mL, respectively (all $P < 0.001$). These findings suggest that glycopyrronium bromide, like other long-acting bronchodilators, has a beneficial effect on dynamic hyperinflation in patients with COPD. In line with this, the GLOW2 trial¹⁹ also revealed a significantly higher inspiratory capacity in the glycopyrronium bromide group than in the placebo group, but comparable with that in the tiotropium group.

In the GLOW3 trial, Beeh et al²³ evaluated the effect of once-daily glycopyrronium bromide on exercise tolerance in patients with moderate to severe COPD (mean post-bronchodilator FEV₁ 57% predicted). A total of 108 patients were randomized to glycopyrronium bromide 50 µg once daily followed by placebo or vice versa for 3 weeks, with a 14-day washout period. The primary outcome measure was the effect of glycopyrronium bromide versus placebo on exercise tolerance after 3 weeks of treatment. Exercise tolerance was measured by exercise endurance time during a submaximal constant-load cycle ergometry test. Secondary outcome measures included inspiratory capacity at isotime (refers to the last time point in the ergometry test at which each patient had a valid test result for both treatment periods) and inspiratory capacity at rest. Treatment with glycopyrronium bromide was significantly superior to placebo with respect to exercise endurance time at 3 weeks, and the least squares mean difference between treatment groups was 89 seconds ($P < 0.001$). At the same time point, glycopyrronium bromide also produced statistically significant treatment differences in inspiratory capacity at isotime ($P < 0.001$) and inspiratory capacity at rest ($P < 0.05$). Therefore, the effect of glycopyrronium bromide on exercise tolerance in patients with COPD

appears to be comparable with that of other long-acting bronchodilators.^{20–22,24}

Health status, symptom relief, and use of rescue medication

During the 28-day treatment period in the study by Vogelmeier et al,¹⁵ patients receiving either dose of glycopyrronium bromide (100 µg or 200 µg once daily) used significantly less rescue medication than patients in the placebo group ($P < 0.05$); the change from baseline in the number of puffs of rescue medication was -0.55 and -0.26 , respectively, in groups treated with glycopyrronium bromide 100 µg and 200 µg versus $+0.51$ in the placebo group. In keeping with this, the GLOW1 study¹⁸ showed that use of rescue medication was significantly lower in patients receiving glycopyrronium bromide than in those on placebo ($P = 0.005$), with a between-group difference of 0.46 puffs per day. A reduction in the use of rescue medication was also observed in the GLOW2 trial by Kerwin et al,¹⁹ with a between-group treatment difference of 0.37 puffs per day ($P = 0.039$) and 0.63 puffs per day ($P = 0.003$), respectively, in the glycopyrronium bromide and tiotropium groups.

In the GLOW1 study by D'Urzu et al,¹⁸ patients receiving glycopyrronium bromide had a significantly greater transition dyspnea index focal score at week 26 (1.84) compared with patients receiving placebo (0.80). The observed treatment difference of 1.04 exceeded the minimal clinically important difference of one point. Furthermore, patients treated with glycopyrronium bromide were 1.7-fold more likely to have at least a one-point improvement in transition dyspnea index focal score compared with those on placebo ($P = 0.001$). Furthermore, patients treated with glycopyrronium bromide had a significantly lower (ie, better) St George's Respiratory Questionnaire score at week 26 (39.50) than patients treated with placebo (42.31). The treatment difference was -2.81 , which was statistically significant, but did not reach the minimal clinically important difference of ≥ 4 points. The percentage of patients achieving a ≥ 4 point reduction in St George's Respiratory Questionnaire score was significantly greater with glycopyrronium bromide than with placebo (56.8% and 46.3%, respectively, odds ratio 1.58, $P = 0.006$). Similar findings with regard to transition dyspnea index focal score and St George's Respiratory Questionnaire score were reported from the GLOW2 trial,¹⁹ although the statistically significant treatment difference in transition dyspnea index focal score did not reach the minimal clinically important difference (glycopyrronium bromide versus placebo 0.81 and tiotropium versus placebo 0.94, respectively).

Exacerbations

In the GLOW1 trial,¹⁸ acute exacerbations of COPD were in line with those in previously published studies,²⁵ being classified as of moderate severity if they required treatment with systemic corticosteroids or an antibiotic and severe if they also required hospitalization. A previous history of acute exacerbations of COPD was not an inclusion criterion (79% of the enrolled patients had no history of moderate or severe exacerbation in the year prior to screening). Time to first moderate or severe COPD exacerbation was a secondary outcome measure. During the 26-week study period,¹⁸ 93 of 532 patients (17.5%) in the glycopyrronium bromide group had at least one moderate or severe COPD exacerbation, compared with 63 of 260 patients (24.2%) in the placebo group. Glycopyrronium bromide significantly reduced the risk of COPD exacerbations in terms of time to first moderate or severe COPD exacerbation by 31% compared with placebo (hazards ratio [HR] 0.69, confidence interval [CI] 0.50–0.95, $P = 0.023$). Furthermore, a significant reduction was also observed in the risk of a COPD exacerbation leading to hospitalization in the glycopyrronium bromide group versus placebo (HR 0.35, CI 0.14–0.86, $P = 0.022$). A significant reduction was also observed in the percentage of hospitalizations due to an exacerbation of COPD (1.7% and 4.2%, respectively, odds ratio 0.34, $P = 0.024$) with glycopyrronium bromide versus placebo.

In the GLOW2 trial,¹⁹ glycopyrronium significantly reduced the risk of exacerbations (defined as in the GLOW1 trial) in terms of time to first moderate or severe exacerbation by 34% compared with placebo (HR 0.66, 95% CI 0.52–0.85, $P = 0.001$) over 52, thereby demonstrating results comparable with tiotropium, which provided a 39% risk reduction versus placebo (HR 0.61, 95% CI 0.46–0.81, $P = 0.001$). Further, a 35% reduction was observed in the rate of moderate to severe COPD exacerbations in the glycopyrronium group compared with that in the placebo (0.54 versus 0.80 per year, relative risk 0.66, CI 0.50–0.87, $P = 0.003$).

Conclusion

Based on the available evidence, glycopyrronium bromide (NVA237) is a safe and well tolerated long-acting anticholinergic bronchodilator with a fast onset of action. In patients suffering from COPD, glycopyrronium bromide has clinically important effects on FEV₁, use of relief medication, daytime dyspnea scores, and probably also on health status. Furthermore, treatment with glycopyrronium bromide improves exercise tolerance in patients with moderate to severe COPD, as assessed by exercise endurance time and

inspiratory capacity, suggesting a beneficial effect on dynamic hyperinflation, comparable with that of other long-acting bronchodilators, including tiotropium bromide, indacaterol, and aclidinium bromide. Glycopyrronium bromide has been shown to reduce the rate of exacerbations in patients with moderate to severe COPD, but long-term controlled trials with exacerbation rate as the primary outcome variable have not been published yet. In conclusion, glycopyrronium bromide may have a potentially significant role in the future management of moderate to severe COPD.

Disclosure

CSU has served on advisory boards for Novartis.

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