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Aclidinium Bromide: Clinical Benefit in Patients with Moderate to Severe COPD

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Abstract: *Background and Aim*: Long-acting bronchodilators are the mainstay of pharmacological treatment for patients with chronic obstructive pulmonary disease (COPD). The aim of this review is to provide an overview of the clinical studies evaluating the safety and efficacy of inhaled aclidinium bromide, a novel long-acting anticholinergic bronchodilator, for the treatment of COPD.

Method: This systematic review explored the efficacy and safety of aclidinium bromide in comparison with placebo and other long-acting bronchodilators for treatment of moderate to severe COPD. Randomised controlled trials were identified through systematic searches of different databases of published trials.

Results: Ten trials (3.922 participants) were included. Aclidinium bromide appears to be a safe and well-tolerated long-acting anti-cholinergic bronchodilator with a relatively fast onset of action. Compared with other long-acting bronchodilators, including tiotropium bromide, aclidinium bromide leads to at least similar clinically important improvements in level of FEV_1, health status, use of rescue medication, and day-time dyspnea scores in patients suffering from moderate to severe COPD. With twice-daily dosing, aclidinium bromide may have clinically important effect on night-time symptom scores in COPD patients, but further studies are needed in order to permit valid conclusions with regard to this point. The effect of aclidinium bromide on exercise tolerance, as assessed by exercise endurance time, and dynamic hyperinflation in patients with moderate to severe COPD seems to be at least comparable to other long-acting bronchodilators, incl. tiotropium bromide and indacaterol. Aclidinium bromide might reduce the rate of exacerbations in COPD patients, but conclusions must await further long-term controlled trials.

Conclusion: Aclidinium bromide has effects on relevant COPD outcome measures, including level of FEV_1, similar to other long-acting bronchodilators, and therefore seems to have the potential for a significant role in the future management of moderate to severe COPD.

Keywords: COPD, aclidinium, long-acting antimuscarinic agents, long-acting, bronchodilators.

INTRODUCTION

The Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD strategy document) recommends maintenance treatment with at least one long-acting bronchodilator for patients with moderate to severe COPD [1]. In general, bronchodilators provide the mainstay of pharmacological treatment of COPD [1,2].

In COPD, long-acting bronchodilators help to prevent and control symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise performance [1,3,4]. Furthermore, inhaled long-acting bronchodilators, including β_2-agonists and muscarinic antagonists, reduce air trapping and improve emptying of the lungs, and by that reduce lung volumes, leading to an improvement in breathlessness and increasing exercise capacity [1,3,5]. Based on studies from recent years, long-acting anticholinergic agents appear to be the most effective bronchodilators for the management of COPD [1,2,6,7]. Currently, the only long-acting anticholinergic bronchodilator marketed for the treatment of COPD is tiotropium bromide, but several others are in various stages of development, including aclidinium bromide.

The aim of this review is to provide an overview of the clinical studies evaluating the safety and efficacy of inhaled aclidinium bromide for the treatment of COPD.

MATERIAL AND METHODS

The general principles of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [8,9] were adopted to perform this review. A series of systematic searches were carried out, last updated October 2012, using the database PubMed, EMBASE, Cochrane Controlled Trials Register, and Clinical Trials.gov using the following algorithm of MeSH terms: Aclidinium bromide, indacaterol, QAB149, glycopyrronium bromide, NVA 237, formoterol, tiotropium, long-acting bronchodilators, and COPD, and the searches were repeated with these terms in combination with FEV_1, hyperinflation, exercise capacity, dyspnoea, health status, quality of life and exacerbations in order to identify published studies. The search was limited to English-language articles. Clinical

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trials published solely in abstract form were excluded because the methods and results could not be fully assessed.

To be included, studies had to meet all the following criteria: 1) published in peer-reviewed journal, 2) randomised controlled trial, 2) inclusion of adults aged > 40 years with stable moderate to severe COPD according to the Global Obstructive Lung Disease (GOLD) strategy document (1) or American Thoracic Society/European Respiratory Society (ATS/ERS) guideline criteria, 3) comparison of inhaled aclidinium bromide with placebo, tiotropium bromide, indacaterol, salmeterol, formoterol, or glycopyrronium bromide, and 4) report at least one of the following outcomes: onset of action, trough FEV_1 (24 hours post-dosing) at the end of the treatment period, peak change in FEV_1, inspiratory capacity, exercise capacity, health status assessed with the St. George Respiratory Questionnaire (SGRQ), use of rescue medication, symptom relief (assessed with the transitional dyspnoea index), and exacerbations.

A meta-analysis was not included in the present review, primarily due to the limited number of published clinical trials fulfilling the inclusion criteria.

RESULTS

Of the 114 potential relevant citations identified, 10 trials fulfilled the inclusion criteria (3.922 participants). Participants were stable, but symptomatic at baseline and fulfilled the spirometric criteria for moderate to severe COPD. All included studies were multicentre, randomised controlled trials sponsored by a single pharmaceutical company (Table **1**). Three studies compared aclidinium bromide with tiotropium bromide (and placebo), six studies with placebo, and one study with formoterol.

Table 1. Characteristics of Included Aclidinium Bromide Studies in Patients with Moderate to Severe COPD

Study	Duration (Weeks)	No. of Subjects	Males (%)	Mean Age (Years)	Mean Baseline FEV_1%pred	Smoking History (Pack-Yrs)	Drug and Dose	Main Outcome
Vestbo *et al*. [9]	-	115	69	63	43	48	Acli# 200 µg Tiot¤ 18 µg Plac*	Onset of bronchodilation
Jones *et al*. [10]	 52	843 804	79 62	62 65	53 50	39 58	Acli# 200 µg Plac*	Trough FEV_1 at week 12 and 28
Joos *et al*. [12]	-	17	100	64	49	44	Acli# 100 µg Acli# 300 µg Acli# 900 µg Plac *	Area under the FEV_1 curve
Chanez *et al*. [13]	4	464	83	62	48	45	Acli# 25 µg Acli# 50 µg Acli¤ 100 µg Acli# 200 µg Acli# 400 µg Tiot 18 µg Plac*	Trough FEV_1 on day 29
Singh *et al*. [14]	1	79	59	61	54	51	Acli# 100 µg Acli# 200 µg Acli# 400 µg Form& 12 µg Plac*	Area under the FEV_1 curve
Fuhr *et al*. [15]	2	30	63	58	56	41	Acli# 400 µg Tiot¤ 8 µ Plac*	Area under the FEV_1 curve (0-12/12h)
Kerwin *et al*. [16]	12	561	53	64	54	54	Acli# 200 µg Acli# 400 µg Plac*	Trough FEV_1
Jones *et al*. [17]	24	828	67	62	53	40	Acli# 200 µg Acli# 400 µg Plac*	Trough FEV_1
Maltais *et al*. [18]	6	181	58	65	51	55	Acli# 200 µg Plac*	Exercise endurance time

[#]Aclidinium bromide, [¤]Tiotropium bromide, *Placebo, and [&]Formoterol.

Onset of Action and Safety Profile

Vestbo *et al.* [10] studied, in a double-blind, double-dummy, cross-over design, the percentage of patients with an increase in $FEV_1 \geq 10\%$ above baseline at 30 minutes post dose. Significantly more patients reached the end-point with aclidinium and tiotropium *vs* placebo (49.5% and 51.8% *vs* 13.8%; $p<0.0001$); and aclidinium and tiotropium significantly improved FEV_1 compared with placebo at all measured points from 10 minutes to 3 hours post-dose. The rate of onset of bronchodilation of aclidinium is, based on the present study, at least as fast as for tiotropium.

The safety profile of aclidinium bromide was studied based on pooled data from ACCLAIM/COPD I and ACCLAIM /COPD II by Jones *et al.* [10]. The overall incidence of adverse events was similar in the aclidinium and placebo groups, apart from a higher frequency of dry mouth in the groups treated with aclidinium. In the clinical studies published so far cardiac and vascular disorders were reported at a similar frequency in the aclidinium and placebo groups [11,12].

FEV_1

The study by Joos *et al*. [13] enrolled patients with an FEV_1 < 65% of predicted value and bronchodilator reversibility > 12% and 200mL. The mean area under the FEV_1 curve (primaru outcome) over the 0-24 h time interval was 1.58 L for placebo, and 1.72 L, 1.79 L, and 1.82 L for aclidinium 100, 300, 900 µg, respectively ($p<0.001$ *vs* placebo, all doses). The authors concluded that aclidinium bromide 100-900 µg produces sustained bronchodilatation over 24 h in patients with moderate to severe COPD. In keeping with this, the ACCLAIM/COPD I and ACCLAIM/COPD II published by Jones *et al*. [11] revealed a trough FEV_1 at 12 and 28 weeks of aclidinium bromide versus *vs* placebo of 61 ml and 67 ml (both $p<0.001$), and 63 ml and 59 ml (both $p<0.001$), respectively, in the two studies.

Chanez *et al*. [14] aimed at establishing the optimal dose of aclidinium bromide in COPD patients with an FEV_1 of 30 to 65%pred. Aclidinium bromide at doses of 200 µg and 400 µg and tiotropium bromide were statistically significant more effective than placebo in increasing through FEV_1 at day 29. Adjusted mean differences compared with placebo in through FEV_1 for aclidinium were 148 ml (200 µg) and 128 ml (400 µg), and for tiotropium 161 ml. In line with this Singh *et al*. [15] studied, in a double-blind, double-dummy, placebo- and active comparator controlled crossover design, the mean change from baseline in FEV_1 normalised area under the curve $(AUC)_{0\text{-}12}$ on day 7. After 7 days of treatment, aclidinium and formoterol produced statistically significant greater change from baseline in FEV_1 normalised $AUC_{0\text{-}12}$ *vs* placebo; and, furthermore, the study confirmed the twice-daily aclidinium dosing regimen and aclidinium 200 µg and 400 µg as suitable doses for further investigation. Furthermore, the study by Fuhr *et al*. [16] showed that aclidinium bromide 400 µg twice-daily compared with placebo provided clinically meaningful in 24-h bronkodilatation that generally were comparable to the effect of tiotropium bromide, but with statistically significant differences in favour of aclidinium bromide observed in the night-time period.

In the ACCORD I/COPD study including COPD patients with a mean baseline FEV_1 of 47 %pred., Kerwin *et al*. [17] showed that Aclidinium bromide 200 µg and 400 µg significantly improved mean (95%CI) trough FEV_1, compared with placebo, by 86 (45, 127) ml and 124 (83,164) ml, respectively, and peak FEV_1 by 146 (101, 190) ml and 192 (148, 236) ml, respectively ($p< 0.0001$).

From the ATTAIN study of COPD patients with a mean baseline FEV_1 of 53 %pred, Jones *et al*. [18] reported a significant improvement from baseline with aclidinium 200 µg and 400 µg *vs* placebo for trough FEV_1 (99 and 128 ml; $p< 0.0001$) and peak FEV_1 (185 and 209 ml; $p< 0.0001$). Furthermore, the observed improvement in peak FEV_1 on day 1 was comparable with that on week 24.

Exercise Capacity and Hyperinflation

Maltais *et al*. [19] investigated exercise capacity in COPD patients with a mean post-bronchodilator FEV_1 approximately 50%pred, and functional residual capacity ≥ 120%pred. At screening, all patients underwent symptom-limited cycle ergometry with increasing work-load in 10 W increments in order to determine the maximum tolerated workload; and constant work rate cycling exercises at 75% of peak work rate were performed at baseline, day 1, week 3, and week 6 (primary end-point). Patients treated with aclidinium had, compared with placebo, significantly greater improvement in exercise endurance time (mean ± SE of 129 ± 31 s for aclidinium *vs* 13 ± 31 s for placebo). Furthermore, the study by Maltais *et al*. [19] also revealed a significant treatment difference from baseline in trough inspiratory capacity (IC) and IC/total lung capacity, and by that suggesting a beneficial effect on dynamic hyperinflation

Health Status, Symptom Relief, and Use of Rescue Medication

Chanez *et al*. [14] reported a decrease in the total St. George Respiratory Questionnaire (SGRQ) score, and by that improved, from baseline with all doses of aclidinium. The percentage of patients with meaningful improvement in SGRQ total score ≥ 4 points from baseline ranged from 53% in the 400 µg group to 64% in the 100 µg group; the improvements in SGRQ score were mainly due to changes in the symptom and impact components. Data, however, on corresponding improvements among patients treated with placebo and tiotropium, and by that makes it extremely difficult to draw valid conclusions with regard to the effect on health status. Furthermore, statistically significant increases in Transition Dyspnoea Index (TDI) were also reported for aclidinium 100 µg and 400 µg compared with placebo, but no exact data were reported, including whether the minimal clinical significance were reached, and no statistically significant difference compared with placebo were observed in any treatment group in the magnitude of the effort component. Overall, there were no significant differences between active treatment and placebo in the mean number of days with self-reported symptoms of dyspnoea, cough, wheeze, sputum or daily doses of rescue salbutamol. In contrast to this, Singh *et al*. [15] reported that daily use of relief medication was lower with all doses of aclidinium and with formoterol compared with placebo; treatment difference in number of daily puffs of relief

medication was up to -0.48 for aclidinium ($p<0.05$) and -0.67 for formoterol ($p<0.05$).

The ACCLAIM/COPD I study [11] showed that significantly more patients receiving aclidinium had an improvement in SGRQ total score ≥ 4 units compared with placebo at all measured time points, although the percentage of patients achieving this improvement was 48% and 40%, respectively for aclidinium and placebo, appears lower than in the study by Chanez *et al*. [14]. Furthermore, in the ACCLAIM/COPD II study [11], no significant difference in percentage of patients achieving an improvement in SGRQ total score ≥ 4 units was found between aclidinium (39%) and placebo (33%) at week 52. In line with this, the ACCLAIM/COPD I study [11] showed that compared with placebo significant more patients treated with aclidinium exceeded the minimal clinical important difference (MCID) for TDI focal score at 52 weeks (aclidinium 56% *vs* placebo 38%; $p< 0.0001$), whereas no significant difference in TDI focal score was found in the ACCLAIM/COPD II study, possibly due to the very high drop-out rate in the latter study. Overall, no general significant differences between aclidinium and placebo was observed in the two studies reported by Jones *et al*. [11] with regard to daily symptom scores or use of rescue medication. The ATTAIN study [18] showed a significant improvements in health status, assessed by SGRQ, daily use of relief medication, and TDI focal score in patients treated with aclidinium compared with placebo.

Fuhr *et al*. [16] reported a significant decline in use of relief medication with both aclidinium and tiotropium compared with placebo, with no significant difference between aclidinium and tiotropium. Furthermore, compared with placebo, aclidinium significantly reduced breathlessness ($p=0.026$) and cough ($p=0.039$); night-time COPD symptom score, assessed on a scale from 0 to 4, were significantly reduced by aclidinium compared with placebo at day 15 ($p=0.049$), whereas no significant change was observed with tiotropium [16]. In line with this, the study by Kerwin *et al*. [17] reported a significant reduction in frequency of night-time symptoms, including breathlessness and wheezing, severity and impact of breathlessness and cough on night-time activity, impact of breathlessness on early morning activity, and frequency of night-time awakenings.

Exacerbations

Jones *et al*. [10] reported from the ACCLAIM/COPD II study that fewer in the aclidinium group experienced a moderate (defined as treatment with antibiotics and/or systemic corticosteroid) or severe (defined as hospitalisation) exacerbation compared with those in the placebo group (33% *vs* 40%; $p=0.0046$); and that aclidinium significantly delayed the time to first moderate or severe exacerbation. However, in the ACCLAIM/COPD I study [10], the proportion of patients having a moderate or severe exacerbation was similar in the aclidinium and placebo groups (27% *vs* 26%). The study by Kerwin *et al*. [17] observed a trend towards a reduction in moderate to severe COPD exacerbation rates with aclidinium compared with placebo, although the study was not powered to assess exacerbation frequency. The ATTAIN study [18] reported, compared with placebo, a lower rate of exacerbations in patients treated with aclidinium.

DISCUSSION AND CONCLUSION

Aclidinium is a potent and selective muscarinic antagonist with subnanomolar affinity for all receptor subtypes ($M_{1\text{-}5}$). Aclidinium dissociates, like tiotropium, more slowly from the M_3 receptor than it does from the M_2 receptor; the M_3 $t_{½}$ is approximately 6 times its M_2 $t_{½}$, and by that providing bronchodilatation *via* M_3 blockage long after its less desirable M_2 effects, such as tachycardia [20].

Regarding inhaled anti-muscarinic agents and risk of major cardiovascular events meta-analysis of previously published studies suggest an increased risk of cardiovascular death, myocardial infarction and stroke in COPD patients treated with inhaled anti-cholinergic drugs [12], but conclusions regarding this point awaits on-going prospective studies. However, with regard to aclidinium bromide, the clinical studies published so far have reported cardiac and vascular disorders at a similar frequency in the aclidinium and placebo groups [11], similar to what have previously been reported from other studies of long-acting antimuscarinic agents in patients with COPD [6,12,21].

Aclidinium bromide is, based on the available evidence, a safe and well-tolerated long-acting anti-cholinergic bronchodilator with a relatively fast onset of action. In patients suffering from COPD, aclidinium bromide has clinically important effects on level of FEV_1, health status, use of relief medication, and day-time dyspnea scores. Aclidinium bromide may have clinically important effect, with twice-daily dosing, on night-time symptom scores in COPD patients, but further studies are needed in order to permit conclusions with regard to this point.

Similar to the study by Maltais *et al*. [18], O'Donnell *et al*. [21] studied exercise endurance time in COPD patients treated with either indacaterol or placebo (mean post-bronchodilator FEV_1 approximately 60%pred), and reported a difference between treatment groups in exercise endurance time of 111 s. In line with this, O'Donnell *et al*. [21] have also previously shown a difference between treatment groups in exercise endurance time of 105 s in COPD patients treated with tiotropium *vs* placebo (mean post-bronchodilator FEV_1 44%pred). Although the minimal important clinical difference (MCID) in duration of constant work rate cycle ergometry is not definitively established, the MCID proposed by Casaburi [22] is 105 s. The effect of treatment with aclidinium in COPD on exercise endurance time therefore seems to at least comparable to the effect of other long-acting bronchodilators. In keeping with the study by Maltais *et al*. [19], studies by O'Donnell *et al*. [20, 21] of indacaterol and tiotropium, respectively, have previously shown an improvement in IC and IC/total lung capacity ratio, and the study by Maltais *et al*. [18], therefore, further supports the assumption that long-acting bronchodilators have a beneficial effect on dynamic hyperinflation in patient s with COPD. The treatment effect of aclidinium bromide on exercise tolerance, as assessed by exercise endurance time, and dynamic hyperinflation in patients with moderate to severe COPD seems, although based on limited evidence, to be at least comparable to other long-acting bronchodilators, incl. tiotropium bromide and indacaterol.

Aclidinium bromide might reduce the rate of exacerbations in patients with moderate to severe COPD [10], although the ACCLAIM/COPD II study [10] did not reveal a reduction in the proportion of patients having at least one exacerbation in the group treated with aclidinium bromide. The very low proportion of patients experiencing an acute exacerbation of COPD in the ACCLAIM/COPD II is remarkable because 58% of the patients enrolled reported at least one COPD exacerbation in the year prior to inclusion in the study. Long-term controlled trials with exacerbation rate as the primary outcome variable are therefore necessary in order to further explore the effect of aclidinium bromide on COPD exacerbation rate.

In conclusion, aclidinium bromide has effects on relevant COPD outcome variables at least similar to that of other long-acting bronchodilators, including tiotropium, and therefore seems to have the potential for a significant role in the future management of moderate to severe COPD.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflicts of interest.

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