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REVIEW

Aclidinium bromide/formoterol fixed-dose combination therapy for COPD: the evidence to date

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Abstract: The quest for the right combination of bronchodilators with different mechanisms of action such as long-acting muscarinic antagonists and long-acting β-agonists in the management of stable moderate-to-severe chronic obstructive pulmonary disease (COPD) is a topic of intense research activity currently, given the rising morbidity and mortality due to this disease. The fixed-dose combination of aclidinium bromide and formoterol fumarate in a single inhaler seems to offer superior advantages over either drugs given alone or as separate inhalers concurrently. Since the fixed-dose combination needs to be given twice daily, it is likely to achieve control of symptoms most crucial to the quality of life in COPD, namely, the morning hours. This is reflected in significant trough FEV_1 (forced expiratory volume in 1 second) improvements after the dose. This paper reviews the various studies related to this combination put in the perspective of its safety and efficacy and potential benefits over other therapeutic options. However, there is a dearth of data on the long-term safety and efficacy in terms of improvement in lung function. This combination could emerge as an excellent option in the management of stable COPD if data on exacerbation rates and patient-reported outcomes become available from longer-term studies. Moreover, we need some more studies to define the ideal phenotype of COPD best suited for the use of this combination.

Keywords: aclidinium, formoterol, COPD, lung function, bronchodilators, combination therapy

Introduction

Chronic obstructive pulmonary disease (COPD) is a recalcitrant inflammatory disease of the lungs with irreversible and progressive airflow limitation and parenchymal destruction with significant systemic inflammatory components. It is the third most severe disease in terms of mortality and morbidity globally, and the World Health Organization (WHO) predicts that it would step up to the second leading cause of mortality by 2030.[1–6] The disease is manifested by dynamic hyperinflation, and the inflammation in COPD is steroid-nonresponsive. The inhaled corticosteroids (ICS) are the mainstay of treatment across all categories of asthma. However, in COPD, the therapeutic use of ICS is perhaps limited to reducing the rate of frequent exacerbations. The role of steroids in controlling the inflammation in COPD seems to be lacking the same class of evidence as compared to their role in asthma inflammation. Of note, ICS has no effect on dynamic hyperinflation in COPD as compared to the bronchodilators. Therefore, the only treatment that has shown significant merit in COPD management is the bronchodilators.[7] Bronchodilators act by either stimulating β_2 agonist receptors or blocking muscarinic receptors. The long-acting bronchodilators are naturally the preferred drugs due to reduced frequency of dosing, which induces

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better compliance, reducing the symptoms for prolonged duration. The Global Initiative for Chronic Obstructive Lung Diseases (GOLD)[8] guidelines recommend combining the two types of long-acting bronchodilators with differing mechanisms of action if monotherapy is ineffective in controlling the disease. Several combination formulation compounds of long-acting muscarinic antagonists (LAMAs) and long-acting β_2 agonists (LABAs) have been clinically tested or are in the process of formulation, such as glycopyrrolate-formoterol, glycopyrronium-indacaterol, tiotropium-olodaterol, umeclidinium-vilanterol, and aclidinium-formoterol, in the management of obstructive airway disease. The pharmaceutical industries are investing in developing several once- or twice-daily LABA/LAMA combinations to improve COPD treatment in future either as free combinations in different devices or as a fixed-dose combination (FDC) in a single inhaler.[9,10] It is hoped that FDCs could offer advantages of better compliance, adherence, and cost-efficacy in addition to synergistic action of the components in free combinations in separate devices. Table 1 presents recent evidences of the efficacy of these newer LAMAs and LABAs on the onset of action and improvement of trough forced expiratory volume in 1 second (FEV_1) among COPD patients. Table 2 presents results of some LABA and LAMA combinations as free combinations and FDCs.

Formoterol (LABA) and aclidinium bromide (LAMA) have shown significant individual efficacy in COPD management, and combination of these two drugs raises the promise of prospective therapeutic application in the management of COPD, although clinical evidences are still emerging. In this paper, we have taken an approach to revisit the evidences critically how the combination of these drugs could be useful in clinical practice.

Formoterol fumarate – an effective LABA with unique advantages

Formoterol is being used as a preferred bronchodilator in obstructive airway diseases over a long time. It has a stronger affinity to the receptors in contrast to other LABAs such as salmeterol. In a comparative study between salmeterol and formoterol, it was found that formoterol protected against methacholine-induced bronchial hyperresponsiveness in a dose–response manner and that effect was higher than that of salmeterol, which also suggested that salmeterol has properties of a partial agonist of β_2 receptors.[11] Aalbers et al[12] conducted a randomized, controlled study and demonstrated that COPD patients who received 9 and 18 μg formoterol twice a day had reduced symptoms and increased number of symptom-free days; they also found that formoterol at a dose of 4.5 μg or higher could significantly improve lung function in COPD patients. Gross et al[13] also reported that formoterol fumarate delivered through nebulizers had improved lung function and Saint George's Respiratory Questionnaire (SGRQ) score, and compared to any short-acting β_2 agonist or short-acting muscarinic antagonist, formoterol imparts its action within 5 minutes of administration via any metered

Table 1 Comparison of various drugs in development of combination therapy with respect to frequency of dosage, rapidity of action, and quantum of improvement in trough FEV_1

Therapies	Manufacturer	Dosage	Time to onset	Trough FEV_1 (difference from placebo)
LABA				
Formoterol[14]	Merck[a]	Twice daily 4.5 μg (MDI) and 12 μg (DPI)	5 min	50–90 mL
Indacaterol[48]	Novartis	Once daily 150 and 300 μg (EU) (DPI)	5 min	130–180 mL ($P<0.001$)
Indacaterol[48]	Novartis	Once daily 75 μg (US) (DPI)	5 min	≥120 mL ($P<0.001$)
Olodaterol[49]	Boehringer Ingelheim	Once daily 5 and 10 μg (Respimat®)	Not available	61–132 mL ($P<0.01$)
Vilanterol[50]	GSK	Once daily 25 and 50 μg (DPI)	Median 6 min	137–165 mL ($P<0.001$)
LAMA				
Aclidinium[18,51]	Almirall/Forest Laboratories	Twice daily 200–400 μg (DPI)	10–30 min	86–124 mL ($P<0.0001$)
Glycopyrronium[52,53]	Novartis	Once daily 50 μg (DPI)	5 min	91–108 mL ($P<0.001$)
Glycopyrrolate[52]	Pearl Therapeutics	Twice daily 36 μg (MDI)	5 min	Statistically superior to placebo ($P<0.0001$)
GSK233705[54]	GSK	Twice daily 200 μg	Not available	130 mL ($P<0.001$)
Tiotropium[55]	Boehringer Ingelheim	Once daily 18 μg (DPI) and 5 μg (SMI)	15 min	120–150 mL ($P<0.001$)

Notes: [a]Other companies are developing formoterol as part of a fixed-dose combination. Adapted from Tashkin DP, Ferguson GT. Combination bronchodilator therapy in the management of chronic obstructive pulmonary disease. *Respir Res*. 2013;14:49.[56]

Abbreviations: FEV_1, forced expiratory volume in 1 second; MDI, metered dose inhaler; DPI, dry powder inhaler; SMI, Soft Mist™ inhaler; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; EU, European Union.

Table 2 Currently available LABA and LAMA combinations

Combination	Reference	Reported results
Free combinations		
GSK233705: 20 or 50 μg BID; salmeterol: 50 μg BID	Beier et al[57]	Larger mean increases from baseline trough FEV_1 vs placebo with 20 μg GSK233705 + salmeterol (203 mL) and 50 μg GSK233705 + salmeterol (215 mL) vs monotherapy with tiotropium (101 mL) or salmeterol (118 mL).
Tiotropium: 18 μg QD; arformoterol: 15 μg BID	Tashkin et al[58]	Greater improvement in FEV_1 $AUC_{0–24}$ from baseline with combination (0.22 L) vs monotherapy with either arformoterol (0.10 L) or tiotropium (0.08 L); $P<0.001$.
Tiotropium: 18 μg QD; formoterol: 20 μg BID	Hanania et al[59]	FEV_1 $AUC_{0–3}$ greater with combination (1.57 L) vs tiotropium alone (1.38 L); $P<0.0001$.
		Reduced use of rescue medication vs tiotropium alone; $P<0.05$.
Tiotropium: 18 μg QD; formoterol: 12 μg BID	Tashkin et al[60]	Greater improvement in FEV_1 $AUC_{0–4}$ from baseline with combination (0.34 L) vs tiotropium alone (0.17 L); $P<0.001$.
		Dyspnea significantly improved with combination at week 8 (1.86) vs tiotropium alone (1.01); $P=0.013$.
		Reduced use of rescue medication vs tiotropium alone; $P<0.04$.
Tiotropium: 18 μg QD; formoterol: 10 μg BID	Vogelmeier et al[61]	Improvement in FEV_1 2 h postdose after 24 weeks with combination vs formoterol alone ($P=0.044$).
Tiotropium: 18 μg QD; salmeterol: 50 μg BID	van Noord et al[62]	Improved average FEV_1 (0–24 h) with combination (0.142 L) vs monotherapy with either tiotropium (0.07 L) or salmeterol (0.045 L); $P<0.0001$. Combination associated with clinically relevant improvements in TDI focal score ($P<0.001$).
Fixed-dose combinations		
Glycopyrrolate: 36 and 72 μg BID; formoterol: 9.6 μg BID (Pearl Therapeutics)	Reisner et al[63]	Increase in FEV_1 $AUC_{0–12}$ on day 7 with combination compared to monotherapy with either of the components, tiotropium, and placebo ($P<0.0001$).
Glycopyrrolate: 36 and 72 μg BID; formoterol: 9.6 μg BID (Pearl Therapeutics)	Reisner et al[64]	Higher morning pretrough and peak IC with combination vs placebo ($P<0.0005$ and $P<0.005$, respectively) or tiotropium monotherapy ($P<0.05$ for all comparisons).
Glycopyrronium: 50 μg QD; indacaterol: 300 μg QD (Novartis)	van Noord et al[65]	Improved trough FEV_1 with combination: 0.226 L difference in trough FEV_1 vs placebo ($P<0.001$).
		Greater peak FEV_1 with combination (1.709 L) vs 300 μg indacaterol (1.579 L) and 600 μg indacaterol (1.573 L); $P<0.0001$ for both comparisons.
Glycopyrronium: 100 μg QD; indacaterol: 600 μg QD (Novartis)	Van de Maele et al[66]	Increased trough FEV_1 with combination (1.61 L) vs indacaterol monotherapy 300 μg (1.46 L); $P<0.05$.
Glycopyrronium: 50 μg QD; indacaterol: 110 μg QD (Novartis)	Bateman et al[67]	Improved trough FEV_1 with combination vs placebo (0.20 L mean difference), indacaterol (0.07 L), glycopyrronium (0.09 L), and tiotropium (0.08 L) monotherapy; $P<0.001$.
		Improved TDI score with combination vs placebo (mean difference, 1.09); $P<0.001$ and tiotropium (0.51 mean difference); $P<0.05$.
		Improved SGRQ score with combination vs tiotropium (–2.13 mean difference); $P<0.05$.
		Reduced use of rescue medication with combination vs monotherapies (–0.30 to –0.54 mean difference); $P<0.05$.
Glycopyrronium: 50 μg QD; indacaterol: 110 μg QD (Novartis)	Vogelmeier et al[68]	Improvement in trough FEV_1 with combination vs salmeterol/fluticasone (mean difference 0.103 L); $P<0.0001$.
		Improvements in TDI score with combination vs salmeterol/fluticasone (mean difference 0.76); $P=0.003$.
		Lower use of rescue medication with combination vs salmeterol/fluticasone (–0.39 puffs/day); $P=0.019$.
Glycopyrronium: 50 μg QD; indacaterol: 110 μg QD (Novartis)	Dahl et al[69]	Combination increased FEV_1 and FVC vs placebo over a 52-week period; $P<0.001$.
Tiotropium: 5 μg QD; olodaterol: 2, 5, and 10 μg QD (Boehringer Ingelheim)	Maltais et al[70]	Higher peak FEV_1 for all doses of combination investigated vs tiotropium alone ($P\leq0.05$); higher trough FEV_1 response with tiotropium + olodaterol 5/10 μg vs tiotropium alone ($P=0.034$).

(*Continued*)

Table 2 (*Continued*)

Combination	Reference	Reported results
Tiotropium: 1.25, 2.5, and 5 μg QD; olodaterol: 5 and 10 μg QD (Boehringer Ingelheim)	Aalbers et al[71]	Significant improvements in FEV_1 for all doses of combination vs olodaterol alone, with evidence of a dose-dependent response.
Umeclidinium (GSK573719): 500 μg QD; vilanterol: 25 μg QD (GSK)	Feldman et al[72]	Adverse-event rate of 26%, with no single adverse event reported in >1 patient. Combination similar to placebo in terms of cardiac parameters. Greater change from baseline in trough FEV_1 and FEV_1 from 0 to 6 h postdose with combination vs placebo.

Note: Adapted from Tashkin DP, Ferguson GT. Combination bronchodilator therapy in the management of chronic obstructive pulmonary disease. *Respir Res*. 2013;14:49.[56]
Abbreviations: LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; BID, twice a day; FEV_1, forced expiratory volume in 1 second; QD, once a day; AUC, area under the curve; TDI, Transition Dyspnea Index; IC, inspiratory capacity; SGRQ, St George's Respiratory Questionnaire; FVC, forced vital capacity.

dose inhaler or dry powder inhaler.[14] There is a huge body of evidence suggesting the salvaging properties of formoterol in COPD in clinical practice, which is beyond the scope of this review. However, because of its acute and prolonged action, formoterol provides one of the best LABA options to be used in various combination therapies.

The new LAMA: aclidinium bromide – pharmacology and clinical evidences

Chemical composition

Aclidinium is a quaternary ammonium derivative of a (3*R*)-quinuclidinol ester containing two thiophene rings, and the chemical signature of aclidinium bromide is (3*R*)-3-y-1-(3-phenoxypropyl)-1-azoniabicyclo[2.2.2] octane bromide.[15,16] The compound was developed by Almirall S.A. (Barcelona, Spain) and Forest Laboratories (New York, NY, USA). It is a muscarinic antagonist and has high binding affinity for the M3 receptor. Although it has a long duration of action and preliminary safety profile, quaternization of its tertiary amino function imparts a low oral bioavailability and low blood–brain barrier permeability,[17] thereby reducing systemic exposure, especially via the inhaled route, and this has made it a drug of choice with low side effect profile compared to other muscarinic antagonists such as tiotropium.[16]

Physiological effects

Aclidinium has a high kinetic selectivity for M3 receptors in preference to other types of muscarinic receptors and is recommended as twice-a-day (BID) therapy in clinical practice. Some detailed analyses of the kinetics and receptor-binding activities have elucidated interesting results.[17] Although the half-life of aclidinium at muscarinic receptors in guinea pig lung was found shorter when compared to tiotropium (29 hours vs 34 hours), aclidinium had a faster onset of action.[18] In an in vitro study on isolated guinea pig trachea, Gavaldà et al[18] had shown that the onset of action of aclidinium ($t_{1/2}$ =6.8±1.5 minutes; t_{max} =35.9±8.2 minutes) was faster than that of tiotropium ($t_{1/2}$ =13.6±2.7 minutes; t_{max} =61.2±10.6 minutes), but similar to that of ipratropium ($t_{1/2}$ =5.1±1.5 minutes; t_{max} =24.1±3.5 minutes) (Figure 1). In their study, they reported that when compared to tiotropium, aclidinium had significantly faster hydrolysis, with an extremely short half-life in human plasma (2 minutes).[19] Another recent report has reconfirmed this previous finding and has shown that aclidinium had a shorter plasma half-life than glycopyrronium (2 minutes vs 12 hours).[20] This rapid plasma clearance of aclidinium suggests lower systemic and central nervous system side effects profile compared to other LAMAs.[18] The systemic side effects of any drug remains a major concern in COPD because of its elderly population predominance with an increased propensity to comorbidities such as cardiovascular disease and altered metabolic profile.

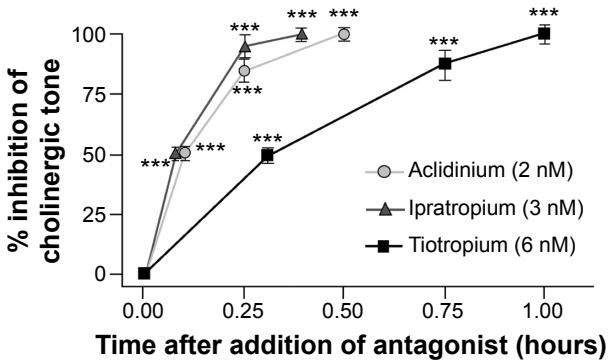

Figure 1 Onset of action of aclidinium, ipratropium, and tiotropium in isolated guinea pig trachea.
Notes: Contraction was induced with 10 μM carbachol and allowed to plateau before the addition of antagonists. Onset was defined as the time from antagonist addition to achieve inhibition of 50% ($t_{1/2}$) or 100% (t_{max}) of the contraction. Data are reported as mean ± SE; n=5–7. ***$P<0.001$ compared with first observational time point. Copyright © 2009. Reproduced from The American Society for Pharmacology and Experimental Therapeutics. Gavaldà A, Miralpeix M, Ramos I, et al. Characterization of aclidinium bromide, a novel inhaled muscarinic antagonist, with long duration of action and a favorable pharmacological profile. *J Pharmacol Exp Ther*. 2009;331(2):740–751.[18]
Abbreviation: SE, standard error.

Antimuscarinics are known to have significant cardiac side effects as a class effect.[21] However, cardiac effects associated with aclidinium are much lower compared to other currently available antimuscarinics. In one study, tiotropium was shown to induce a significant increase in heart rate lasting for 6 hours, while aclidinium-induced increased heart rate lasted barely for 2.5 hours (Figure 2).[18] Another preclinical cardiovascular safety study of the use of aclidinium further exemplified the lower side effects of aclidinium in comparison with tiotropium.[22]

Efficacy and safety of aclidinium: evidence from studies

Extensive clinical studies have been conducted to determine the efficacy of aclidinium in COPD. Aclidinium bromide has demonstrated significant bronchodilator potential in obstructive airway diseases.[23–33] However, discussion on each of those studies is out of the scope of this paper. A Phase I trial showed that low to very high doses of aclidinium increased specific airway conductance (sG_{aw}) of healthy adult individuals in a dose-dependent manner (Figure 3).[26] Apart from its direct action on bronchoconstriction, aclidinium has been shown to contribute to a number of other favorable outcomes in obstructive airway diseases. Aclidinium has been found to reduce carbachol- and tobacco smoke-induced overexpression of MUC5AC,[34] resulting in minimized secretion of mucin from goblet cells in COPD patients.[35,36] Some of the major causes of exacerbation in COPD patients are exposure to airborne allergens and other environmental insults. These aeroallergens trigger an inflammatory response, which cannot be relieved by bronchodilators. Aclidinium, however, seems to be a better option than the other conventional bronchodilators because of its possible additional anti-inflammatory action. In a preclinical study, aclidinium has been shown to reduce *Aspergillus fumigatus*-induced eosinophil trafficking in bronchoalveolar lavage of mice in addition to complete abrogation of methacholine-induced increased airway resistance.[37] This demonstrates significant additional clinical advantage of aclidinium in COPD as *Aspergillus* is a very ubiquitous saprophytic fungus.

A couple of Phase II and Phase III clinical trials investigated the safety aspects of the administration of aclidinium bromide in COPD patients. The ACCORD I (AClidinium in Chronic Obstructive Respiratory Disease I) study recruited 561 patients in that Phase III trial and stated that administration of 200 and 400 µg aclidinium (BID) significantly improved bronchodilation, health status, and symptoms in moderate-to-severe COPD patients and that both the doses were well tolerated without untoward adverse effects for 12 weeks.[38] Two more studies by Fuhr et al[29] (Phase IIb trial) and Jones et al[30] (Phase III trial – the ATTAIN (Aclidinium To Treat Airway obstruction In COPD patieNts) study) also strongly advocated the administration of 200 and 400 µg aclidinium twice daily as safe doses in management of moderate-to-severe COPD. Later, Gelb et al[31] and Beier et al[32] also stated that either of the two doses (200 and 400 µg) of aclidinium twice daily was well tolerated by moderate-to-severe COPD patients. However, the safety and efficacy

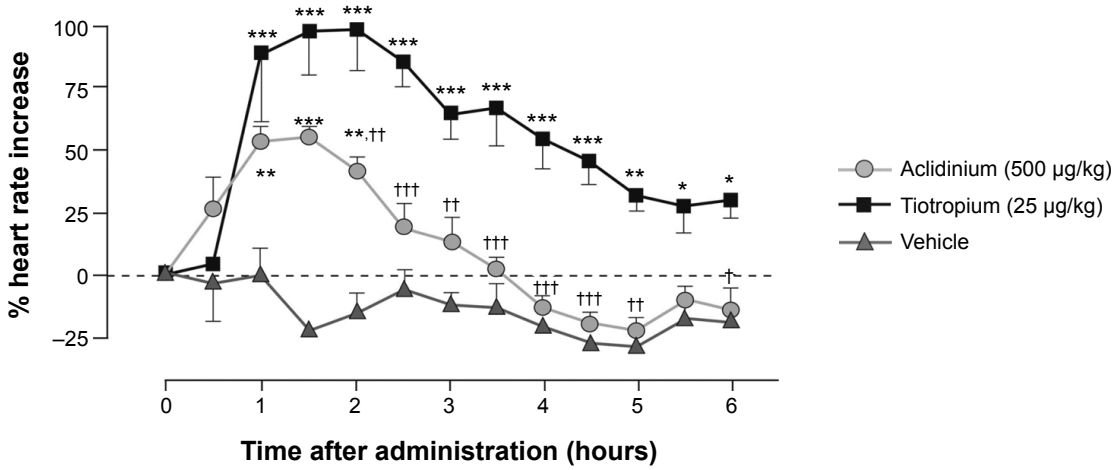

Figure 2 Effect of aclidinium and tiotropium on heart rate in conscious beagle dogs.

Notes: Animals were anesthetized in order to deliver the nebulized compounds or vehicle and were allowed to regain consciousness. The effect on heart rate of a dose 100 times higher than that used to achieve submaximal bronchodilation was assessed continuously up to 6 hours and expressed as a percentage change from baseline heart rate. Data are reported as mean ± SE; n=4 for aclidinium and tiotropium; n=3 for vehicle. *$P<0.05$, **$P<0.01$, ***$P<0.001$ compared with vehicle; †$P<0.05$, ††$P<0.01$, †††$P<0.001$ compared with tiotropium.

Abbreviation: SE, standard error.

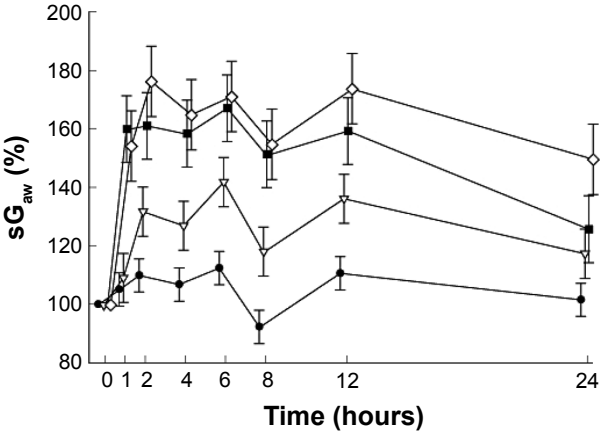

Figure 3 Mean (± SE) changes in sG_{aw} (%) over 24 hours as a percentage of baseline value.
Notes: Placebo (—●—), 50 mg aclidinium bromide (—▽—), 300 mg aclidinium bromide (—■—), 600 mg aclidinium bromide (—◇—). © 2010 The Authors. Journal compilation © 2010 The British Pharmacological Society. Reproduced from Schelfhout VJ, Ferrer P, Jansat JM, et al. Activity of aclidinium bromide, a new long-acting muscarinic antagonist: a phase I study. *Br J Clin Pharmacol*. 2010;69(5):458–464.[26]
Abbreviations: sG_{aw}, specific airway conductance; SE, standard error.

of aclidinium were significantly established before (2011) by Jones et al[39] when the investigators reviewed pooled evidences from two Phase III clinical trials (ACLidinium CLinical trial Assessing efficacy and safety In Moderate to severe COPD patients – the ACCLAIM study).

Aclidinium bromide/formoterol fixed-dose combination therapy – evidences from clinical trials

In a very recent study, Cazzola et al[40] probed the therapeutic effects of aclidinium and formoterol combination on isolated human bronchial experiments. Interestingly, the combination model indicated a synergistic action at the low doses of aclidinium and formoterol in inducing smooth muscle relaxation in acetylcholine-induced bronchial contraction. The combination therapy induced more additive response compared with the expected additive response of the individual drug (in segment bronchi: +18.4%±2.7%; $P<0.05$ vs expected effect; in bronchioles: +19.7%±0.9%; $P<0.05$ vs expected effect). This is one of the very few published preclinical studies on aclidinium/formoterol combinations that clearly highlights the bronchodilation potential of the combination formulation at different doses.

Almirall S.A. and Forest Laboratories have developed a aclidinium bromide/formoterol fumarate FDC. These two companies have been conducting a series of Phase II and Phase III clinical trials to establish the clinical efficacy of the combination. These clinical trials included parallel arms including monotherapy by either of the two drugs (aclidinium and formoterol) at various doses and placebo to compare the efficacy, tolerance, and safety of the combination drug.[41] Although many of those trials have been completed, results are yet to be published. Table 3 elucidates the list of the trials that looked into different aspects of this combination drug in the management of COPD.

Apart from the aforementioned clinical trials, there are some studies that merit discussion, as some results are available in the form of published abstracts. Sliwinski et al[42] reported a dose–response clinical trial that was aimed to assess the efficacy, safety, and pharmacokinetics of three different doses of formoterol (6, 12, and 18 µg) combined with aclidinium bromide 200 µg and compared against aclidinium bromide 200 µg monotherapy and formoterol 12 µg monotherapy.[42] This was a large study in which treatment was administered daily for 4 weeks to 566 stable moderate-to-severe COPD patients. The investigators reported that aclidinium combined with formoterol exhibited greater improvements in pulmonary parameters than did either drug alone or placebo, and all combinations were significantly superior to placebo ($P<0.001$) and to both the monotherapies ($P<0.001$).[42] Another Phase IIa clinical trial by Magnussen et al[43] was designed to investigate the pharmacokinetics, safety, tolerability, and lung function efficacy of aclidinium bromide and formoterol combination delivered through different inhalers.[43] In that randomized, single-blinded, crossover study, 24 moderate-to-severe COPD patients obtained either an FDC of aclidinium bromide (200 µg) and formoterol (12 µg) once daily through Genuair® (Almirall S.A.), or formoterol (12 µg) twice daily through Aerolizer® or, once daily through two different inhalers (Aerolizer® and Genuair®, Almirall S.A.).[43] Each of the 4-day treatment periods was separated by a 7-day washout period, and all four treatments were found to be safe and well tolerated and improve the lung function.

The efficacy and long-term safety of aclidinium bromide/formoterol fumarate combination therapy in the management of COPD has been advocated in two recently published large-scale clinical trials – the AUGMENT COPD study and the ACLIFORM-COPD (ACLIdinium FORMoterol-COPD) study. Aclidinium/formoterol fUmarate combination for investiGative use in the treatMENT of moderate-to-severe COPD (AUGMENT COPD) study (trial registration id: NCT01437397) was a 24-week double-blind study in which 1,692 patients with stable COPD were equally randomized to twice-daily treatment with an FDC of aclidinium 400 µg/

Table 3 Recent clinical trials of aclidinium/formoterol fixed-dose combination therapies

Study	Dosage	Primary end point	Coprimary end points	Study period and present status
Interventional pilot study (Phase II) [NCT00706914]	Aclidinium bromide/formoterol fumerate FDC QD	Symptomatic differences between treatment groups after 4 weeks of treatment	Differences between groups in change in pulmonary function test results after 4 weeks of treatment	June 2008–September 2011; results not published
Dose-finding clinical trial (Phase II) [NCT00626522]	Aclidinium bromide/formoterol fumerate FDC QD	Pulmonary function tests	Pharmacokinetics and safety	February 2008–July 2010; results not published
Interventional efficacy trial [NCT01049360]	2 FDCs of aclidinium bromide/ formoterol fumerate BID	Change from baseline in normalized FEV_1 after 14 days of treatment AUC_{0-12} measurement over 12 h after morning dose of drug at day 14	The secondary efficacy assessments were the change from baseline in morning predose FEV_1 and the change from baseline in morning peak FEV_1, both at day 14 on treatment	January 2010–September 2011; results not published
Interventional dose-finding study [NCT01078623]	2 FDCs of aclidinium bromide/ formoterol fumerate BID	FEV_1 AUC 0–12 h after day 14	Morning predose FEV_1 and morning peak FEV_1 after day 14	March 2010–November 2010; study not published
Interventional study [NCT01551888]	Aclidinium/formoterol 400 μg/12 μg FDC (BID) for 4 days, then QD on day 5 via the Genuair®	Area under the formoterol plasma concentration–time curve over the dosing interval at steady state Maximum formoterol plasma concentration at steady state	Area under the formoterol plasma concentration–time curve over the dosing interval following a single dose Maximum plasma concentration of formoterol following a single dose	March 2012–August 2012; no study result published
Interventional study (Phase III) [NCT01437540]	FDCs of aclidinium bromide/ formoterol fumerate BID (high dose)	AE recording: number of patients to experience a TEAE Vital signs: number of patients to experience a PCS change in pulse rate, systolic and diastolic blood pressure, body temperature, or body weight ECGs: number of patients to experience potentially clinically significant changes in ECG from baseline Clinical laboratory measures: number of patients to experience a PCS change in clinical laboratory values for hematology, chemistry, urinalysis, or theophylline	Not listed	September 2011–April 2013; results not published
Interventional study (Phase III) [NCT01572792]	2 FDCs of aclidinium bromide/ formoterol fumerate (low-dose ACL200/FOR12 μg; high-dose ACL400/FOR12 μg, BID)	Safety and tolerability: AE, clinical laboratory parameters, vital sign measurement, and ECG parameters	Not listed	April 2012–June 2013; results not published
Interventional study (Phase III) [NCT01908140]	Aclidinium bromide 400 μg/formoterol fumarate 12 μg BID for 24 weeks	Peak FEV_1 at week 24	TDI focal score at week 24	July 2013–September 2014; results not published

Notes: Information of the clinical trials was obtained from the United States clinical trial registry (available at https://clinicaltrials.gov; last accessed on February 2, 2015). Searching of clinical trial database with the keywords – aclidinium + formoterol + COPD yielded 12 results, and among those aclidinium-formoterol FDC was used in ten studies only. We selected those ten studies and incorporated eight unpublished studies into this table. The other two studies are published (viz, the AUGMENT-COPD Study and the ACLIFORM-COPD Study).

Abbreviations: FDC, fixed-dose combinations; QD, once a day; FEV_1, forced expiratory volume in 1 second; ACL, aclidinium; BID, twice a day; AE, adverse event; TEAE, treatment emergent adverse event; PCS, potentially clinically significant; ECGs, electrocardiograms; FOR, formoterol; TDI, Transition Dyspnea Index; COPD, Chronic obstructive pulmonary disease; AUC, area under the curve.

formoterol 12 µg (ACL400/FOR12 FDC), FDC aclidinium 400 µg/formoterol 6 µg (ACL400/FOR6 FDC), aclidinium 400 µg, formoterol 12 µg, or placebo. All the drugs were administered by a multidose dry powder inhaler (Genuair®/Pressair®, Almirall S.A.).[44] The primary end points of this study were change from baseline to week 24 in 1-hour morning postdose FEV_1 (FDCs vs aclidinium) and change from baseline to week 24 in morning predose (trough) FEV_1 (FDCs vs formoterol), while the secondary end points were change from baseline in SGRQ total score and improvement in Transition Dyspnea Index (TDI) focal score at week 24. The study also assessed the safety and tolerability of the FDCs. The study was completed in 2012. In accordance to the results, COPD patients treated with ACL400/FOR12 FDC or ACL400/FOR6 FDC had exhibited greater 1-hour postdose improvement in FEV_1 from baseline than did those patients who received aclidinium alone (108 and 87 mL, respectively; $P<0.001$). Similarly, patients who received ACL400/FOR12 FDC had a significant ($P=0.01$) 45 mL improvement in trough FEV_1 than did those who received formoterol 12 µg alone, although ACL400/FOR6 FDC showed only an insignificant 26 mL change over formoterol alone. Both the ACL/FOR FDCs induced rapid bronchodilation with significant improvement in FEV_1 within 5 minutes of the morning dose on day 1 than aclidinium alone or formoterol alone or placebo (Figure 4A). FEV_1 at 3-hours postdose at week 24 also showed results similar to what was observed on day 1 (Figure 4B). Both SGRQ total and TDI focal scores also showed significant improvement at the end of the study in the ACL400/FOR12 FDC group over placebo with differences over placebo exceeding the minimal clinically important difference of ≥4 points and ≥1 unit, respectively. The investigators concluded that treatment with twice-daily aclidinium 400 µg/formoterol 12 µg FDC could help provide rapid and sustained bronchodilation over monotherapy with either drugs, which also helped in improving dyspnea and the health status of the COPD patients.[44] This was a conventional clinical trial and there were hardly any limitations in the study design.

Another study published interesting outcomes of aclidinium bromide/formoterol FDC therapy, which had end points similar to those of the aforementioned study.

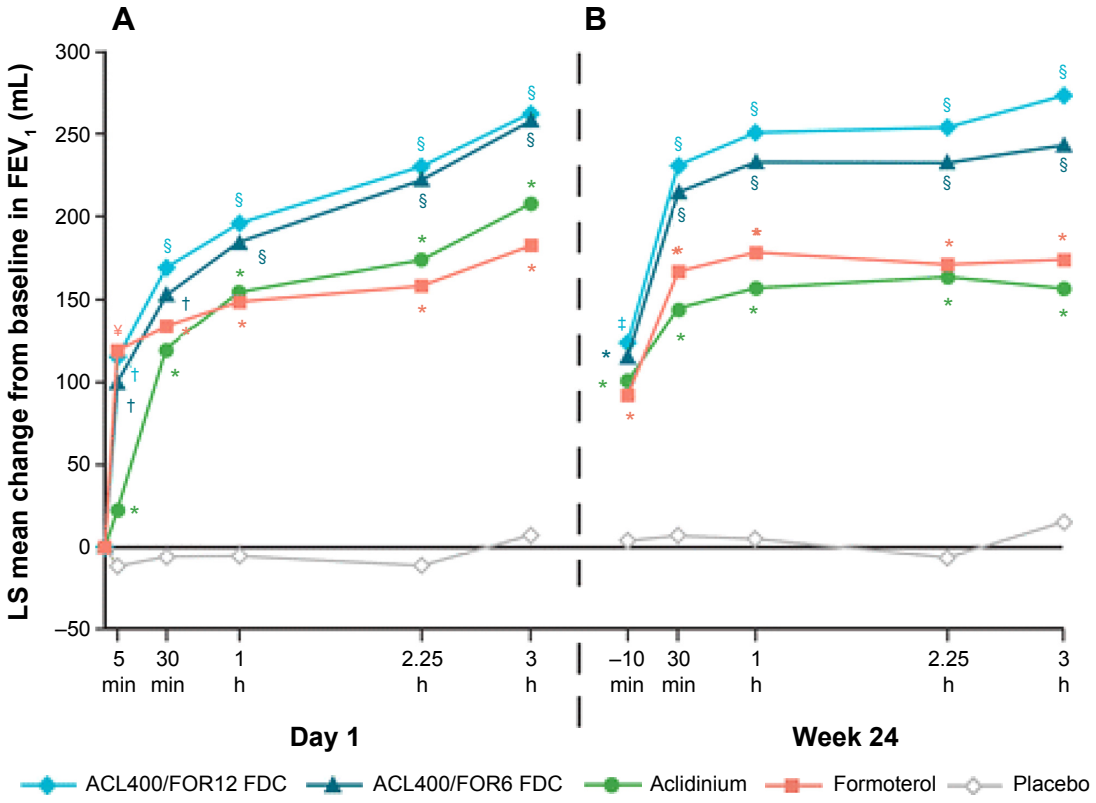

Figure 4 Mean changes from baseline in FEV_1 0–3 hours (**A**) on day 1 and (**B**) at week 24.

Notes: Analyses were based on a mixed model for repeated measures. *$P<0.05$ vs placebo; †$P<0.05$ vs aclidinium and placebo; §$P<0.05$ vs aclidinium, formoterol, and placebo; ¥$P<0.05$ vs aclidinium/formoterol FDC 400/6 µg and placebo. No significant differences between the two FDCs at any time point. Reproduced from D'Urzo AD, Rennard SI, Kerwin EM, Mergel V, Leselbaum AR, Caracta CF; AUGMENT COPD Study Investigators. Efficacy and safety of fixed-dose combinations of aclidinium bromide/formoterol fumarate: the 24-week, randomized, placebo-controlled AUGMENT COPD study. *Respir Res*. 2014;15(1):123.[44]

Abbreviations: ACL, aclidinium; FOR, formoterol; LS, least squares; FEV_1, forced expiratory volume in 1 second; FDCs, fixed-dose combinations; ACL400/FOR12 FDC, FDC of aclidinium 400 µg and formoterol 12 µg; ACL400/FOR6 FDC, FDC of aclidinium 400 µg and formoterol 6 µg.

The ACLIFORM-COPD study (NCT01462942) was a double-blind, randomized, parallel group, active- and placebo-controlled, multicenter study conducted at 193 centers in 22 countries.[45] In this study, patients with stable, moderate-to-severe COPD were randomized with a double-blind treatment of twice-daily aclidinium/formoterol FDC 400/12 µg or FDC 400/6 µg, aclidinium 400 µg and formoterol 12 µg or placebo. All medications were administered via a breath-actuated, multiple-dose dry powder inhaler (Genuair®/Pressair®, Almirall S.A.). The investigators reported that when compared to aclidinium monotherapy, both the FDCs of aclidinium and formoterol led to significant improvements in 1-hour post-dose FEV_1 from baseline (125 mL in ACL400/FOR12 [95% CI: 90–160, $P<0.001$] and 69 mL in ACL400/FOR6 [95% CI: 34–105, $P<0.001$]). The results were very close to what the other group had shown (108 and 87 mL, respectively).[44] Changes in trough FEV_1 in the FDC groups in contrast to the formoterol alone were found to be 85 mL (95% CI: 51–119; $P<0.001$) and 53 mL (95% CI: 19–87; $P<0.01$), respectively, which were higher than those observed in the other study. In addition to that, ACL400/FOR12 and ACL400/FOR6 provided significant improvements in TDI focal score compared with placebo (1.29 units [95% CI: 0.73, 1.86; $P<0.001$] and 1.16 units [95% CI: 0.59, 1.73; $P<0.001$], respectively (Figure 5)). This study also concluded that both the FDCs of aclidinium and formoterol significantly improved bronchodilation when compared with monotherapy, without any additional risk.[45]

Discussion

These clinical trials have strongly advocated the potential therapeutic advantages of the use of aclidinium/formoterol FDC therapies, as they are superior to either drugs alone and safe over long periods of time. What could be next? The latest update by GOLD[8] also does not settle all the questions. A new combination therapy always raises the concern of efficacy and safety.[46] The efficacy of aclidinium + formoterol in reducing exacerbations would need a 6- or 12-month-long trial. Patient-reported outcomes also would require large multicentric trials possibly involving all phenotypes of COPD. It is definitely a great challenge to formulate the right LABA/LAMA combination that could be delivered along with a corticosteroid, and here the evidence of safety and efficacy of aclidinium/formoterol combination raises a potential option to be delivered as a triple-drug therapy (either separately or as a mixture with ICS) in the management of COPD globally, although such combination therapies need to be tested in patients with frequent exacerbations. Although it may be assumed that such combination therapies would help improve the quality of life of the patients and increase the patient adherence, the availability of such drugs is still very limited.[47]

Conclusion

The FDC of aclidinium bromide and formoterol fumarate holds the promise of round-the-clock control of symptoms of stable moderate-to-severe COPD with significant lung function improvement. However, the effect of this combination in reducing risk of exacerbations in relevant phenotypes of COPD and in improving patient-reported outcome measures and health-related quality-of-life measures in the long term remains to be established. It is worth waiting for further investigations of this FDC and also potentially its

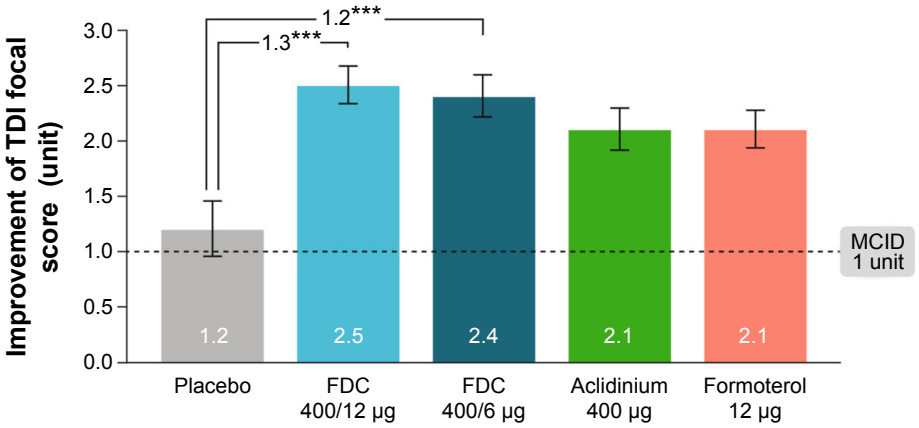

Figure 5 Improvement in TDI focal score at 24 weeks (ITT population).
Notes: Data are presented as least squares means (SE). ***$P<0.001$ vs placebo. Reproduced from Singh D, Jones PW, Bateman ED, et al. Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study. *BMC Pulm Med*. 2014;14:178. http://creativecommons.org/licenses/by/4.0/.[45]
Abbreviations: FDC, aclidinium/formoterol fixed-dose combination; ITT, intent-to-treat; MCID, minimum clinically important difference; SE, standard error; TDI, Transition Dyspnea Index.

incorporation into triple-drug therapy as a free combination or single-inhaler FDC.

Disclosure

The authors report no conflicts of interest in this work.

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