CLINICAL INVESTIGATION

Arformoterol: rationale for use in chronic obstructive pulmonary disease

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Long-acting β-agonists (LABAs) are the standard of care for chronic obstructive pulmonary disease (COPD) patients with advanced disease, those with mild to moderate disease and frequent exacerbations or those with significant dyspnea. Currently available LABAs include salmeterol, formoterol, indacaterol, vilanterol and olodaterol. The bronchodilatory effect of LABAs is mediated via the binding and ligation of the β_2–adrenergic receptor and the lipophilic nature of the LABA compound accounts for their long duration of action. LABAs are available as hand held devices, either as a single agent or combined with a corticosteroid. Proper inhaler technique is necessary for adequate drug delivery but is often difficult to achieve in older patients with significant impairment in cognition, dexterity or ability to generate adequate inspiratory flow rates. Arformoterol, which is an (*R*,*R*) enantiomer of formoterol, is available as a nebulized solution and is clinically equivalent to formoterol or salmeterol. Arformoterol as a nebulized solution provides an alternative to device-based LABAs in select patients.

Keywords: arformoterol • COPD • dyspnea • formoterol • long-acting β-agonist • metered dose inhaler • nebulizer • quality of life • salmeterol • spirometry

Background

Chronic obstructive pulmonary disease (COPD) is characterized by incompletely reversible airflow obstruction and progressive loss of lung function over time. The natural history is interspersed by exacerbations. Affecting >64 million individuals and the fourth leading cause of death worldwide, COPD is predicted to become the third leading cause of death by 2030 [1,2]. The prevalence of COPD increases with age, with up to 15% of adults >65 years diagnosed with COPD [3]. Obstructive lung diseases contribute substantially to the financial burden of healthcare systems with US $49.9 billion estimated in the USA during 2010; 20.9% was directly related to emergency department and acute hospital care [4–6].

Currently, US FDA-approved Long-acting β-agonists (LABAs) include salmeterol, formoterol, indacaterol, vilanterol, olodaterol and arformoterol, an active enantiomer component of formoterol, available as a nebulized solution (Figure 1). The LABAs have received a black box warning related to increased risk of death in asthma patients when used without corticosteroids. However, similar adverse event (AE) warning as a single agent in COPD patients is lacking [7]. COPD treatment guidelines support LABA monotherapy use in moderate to severe COPD [8]. LABAs improve symptoms and, when administered by nebulizer, have higher patient satisfaction than other options [9–11]. However, LABA medications are expensive and can add significant cost burden to both the patient and the healthcare system (Table 1). Appropriate choice of medication and route of administration must be evaluated prior to prescribing medications. In this review, we discuss the rationale of using nebulized arformoterol in the context of other LABAs for select patients with COPD.

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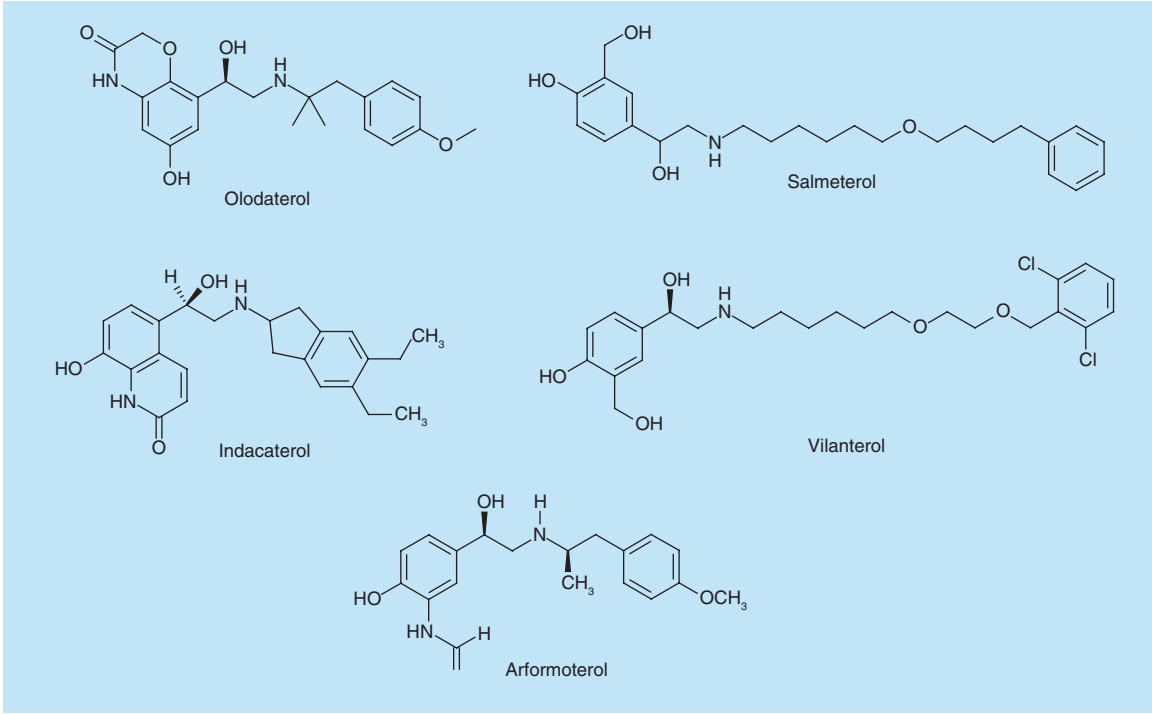

Figure 1. Chemical structures of different long-acting β-agonists.

Chemical structure & mechanism of action of LABAs

Arformoterol, salmeterol, vilanterol, olodaterol and indacaterol are phenylethanolamine derived compounds with side groups that vary in structure and in their interaction with the hydrophobic active site of the receptor complex [12,13]. The important clinical differences seen between LABAs are the receptor selectivity, the time to onset of action and the half-life of the medication (Table 2). Salmeterol, a partial β_2-adrenergic agonist, has a uniquely long lipophilic side chain that anchors the molecule in the membrane exosite, allowing prolonged interaction with the cell receptor [14,15]. Formoterol is moderately lipophilic with an increased ligand available outside the lipid layer, similar to albuterol, which allows for the rapid onset of action seen with both medications [14]. Indacaterol rapidly disseminates into the lipid layer with a twofold higher affinity for lipid rafts along with a high intrinsic efficacy, which may contribute to the rapid onset and long duration of action [12,16,17]. Vilanterol, a LABA structurally similar to salmeterol, has a high β_2-adrenergic receptor affinity, allowing for a more rapid action than salmeterol and with similar potency as formoterol, at least as demonstrated *in vitro* [18,19]. Lastly, olodaterol forms a stable complex with the β_2-adrenergic receptor that has a dissociation half-life of greater than 18 h, which likely accounts for the ultra-long duration of action of this medication [20,21].

β_2-adrenergic agonists exert pleiotropic effects via the β_2-adrenergic associated submembrane Gs complex (Figure 2), adenyl cyclase, and PKA mediated intracellular signaling within cytosol [22]. For example, ligation of the β_2-adrenergic receptor results in the relaxation of airway smooth muscle mediated by upregulation of adenyl cyclase activity, and increased intracellular cAMP, and subsequent decreased smooth muscle myosin light chain kinase activity, resulting in the desired therapeutic bronchodilatory effect. However, a number of studies have indicated that β_2-adrenergic agonists may also have anti-inflammatory properties, for example, inhibition of TNF and vascular leak, *in vitro* [23–25]. This anti-inflammatory property of β_2-adrenergic agonists in airway smooth muscle has been reviewed previously [26] and, similar to the case of bronchodilation mentioned above, appears to be associated with β_2-adrenergic receptor ligation driven increases in intracellular cAMP, which downregulate nuclear transcription and thereby decrease the production of proinflammatory cytokines. This downregulation of proinflammatory cytokines by LABAs may favorably impact treatment in specific COPD subtypes acutely, and for extended durations, particularly during exacerbations.

(*R*,*R*) & (*S*,*S*) formoterol enantiomers

The differential effects of β_2-adrenergic receptor agonists on the airway smooth muscle, the immune system and the inflammatory cascade is thought to be potentially due, in part, to the differences associated with

Table 1. Cost of select β-agonist therapies as a single agent or as combination therapies.

Medication	Amount dispensed	Medication cost (US$)
Short-acting β-agonists		
Albuterol nebulizer	25 vials	4–19
Levalbuterol nebulizer	24 vials	62–109
Albuterol/ipratropium nebulizer	30 vials	13–24
Albuterol MDI†	1 inhaler	49–70
Levalbuterol MDI	1 inhaler	58–63
Albuterol/ipratropium SMI	1 inhaler	282–295
Long-acting β-agonists		
Arformoterol nebulizer	30 vials	278–290
Formoterol nebulizer	30 vials	275–302
Salmeterol DPI	1 inhaler	219–230
Formoterol DPI	1 inhaler	217–227
Indacaterol DPI	1 inhaler	198–208
Long-acting β-agonists/inhaled corticosteroids		
Salmeterol/fluticasone DPI	1 inhaler	304–317
Vilanterol/fluticasone DPI	1 inhaler	287–300
Formoterol/budesonide MDI	1 inhaler	272–285

Only US FDA approved formulations reviewed for pricing due to data availability of equivalent dosing of medications. Prices are a range of ten different nationwide pharmacies as of 25/2/2014 [11].
Albuterol inhaler formulations evaluated were ProAir, Ventolin, and Proventil.
DPI: Dry powder inhaler; MDI: Metered dose inhaler; SMI: Soft mist inhaler.

specific enantiomers, and has been previously demonstrated with enantiomers of albuterol [27,28]. Similar to racemic albuterol, which has two enantiomers, the racemic formoterol formulation consists of two enantiomeric forms, (*R*,*R*) and (*S*,*S*), each having two chiral carbon centers around which the substituents are arranged by mass number priority in either a clockwise rotatory order (*R*,*R*), or a counter-clockwise rotatory order (*S*,*S*) [29]. Of note, the R-enantiomer has a substituent order similar to that of endogenous epinephrine made by the adrenal gland; the opposing isomer of epinephrine is not produced in the body (vide supra). Importantly, the order of the substituents determines the binding affinity, such that the (*R*,*R*) configuration demonstrates a thousand times greater affinity for the β_2-adrenergic receptor, as compared with the (*S*,*S*) enantiomer, resulting in a 640-fold greater potency in airway smooth muscle relaxation [30,31]. The two different enantiomers of formoterol also have been shown to have opposing effects on inflammatory mediators: the (*R*,*R*) isomer suppresses GM-CSF in human airway smooth muscle cells, while the (*S*,*S*) isomer increases GM-CSF levels [32]. Thus, it is important to note that this potential effect of the racemic mixture is obviated with administration of the single enantiomer, (*R*,*R*)-formoterol, as arformoterol.

Arformoterol pharmacokinetics

Arformoterol is metabolized in the liver by glucuronidation via the cytochrome P450 pathway. Impaired

Table 2. Comparison of pharmacokinetic and pharmacodynamic properties of β-agonists.

Medication	Time to Change in FEV_1 (min)	Plasma Half-life (h)	β1:β2 selectivity	Ref.
Albuterol	5	4.6	1:27	[13,22]
Arformoterol	7	26	1:150	[22,31]
Salmeterol	48	5.5	1:525	[15,22]
Vilanterol	16	21.3	1:2400	[19,22]
Indacaterol	5	45.5–126	1:16	[17,22]
Olodaterol	5	45	1:65	[21,22]

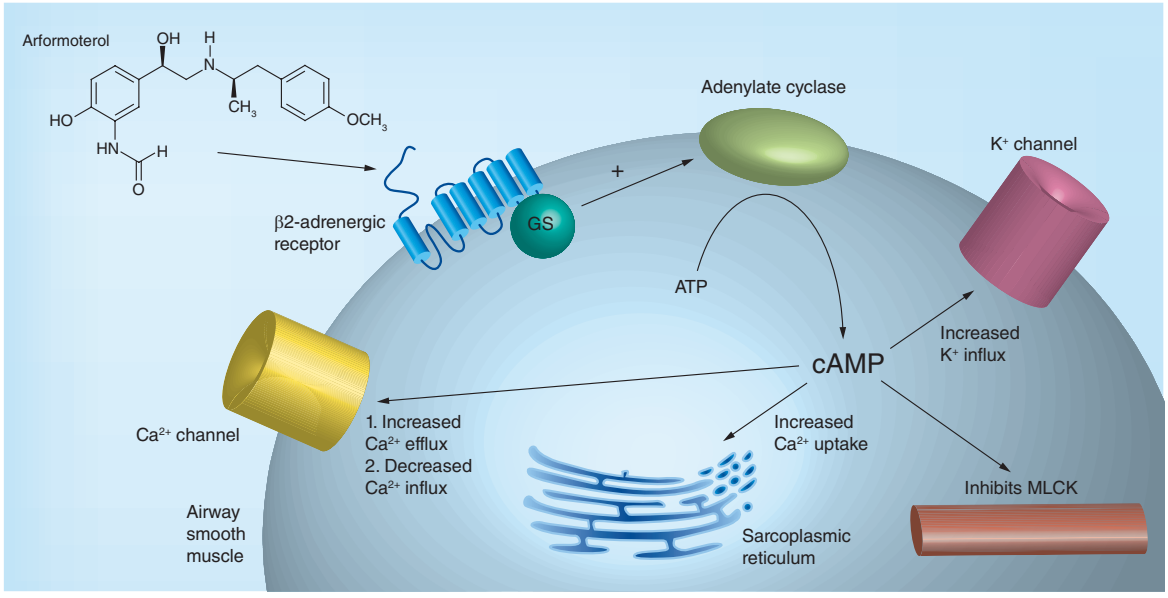

Figure 2. Classic β2-adrenergic receptor mechanism of action.
Ca2+: Calcium; K+: Potassium; MLCK: Major light chain kinase.

hepatic function prolongs the half-life of the drug up to 2.4-fold [31]. Combination (*R*,*R*) and (*S*,*S*) isomer formulations, however, exhibit prolonged metabolism *in vitro* compared with either isomer alone [33]. The prolonged metabolism of the (*S*,*S*) isomer may account for the higher toxicity seen with formoterol [30]. Metabolism of arformoterol is not affected by renal impairment or age, which may be an important consideration for the typically older population of COPD patients.

The onset of bronchodilatory action of arformoterol is similar to that of formoterol. The average time to peak change in forced expiratory volume in 1 s (FEV_1) is 10 min [34]. Time to peak plasma concentration from absorption is 1 h with a terminal half-life of 26 h [30,31]. The short onset of action, long half-life and nebulized preparation make arformoterol a suitable candidate as both a rescue and a maintenance drug.

Administration & dosing selection

Arformoterol inhalation solution is supplied as a 2 ml unit dose vial, containing 15 µg of arformoterol (22 µg of arformoterol tartrate equivalent). Drug delivered to the lungs depends upon patient factors, anatomy of the oropharynx, nebulizer type used, and compressor performance. The mean delivered dose using a PARI DURANEB 3000 compressor® at a mean flow rate of 3.3 l/min with mouthpiece is approximately 4.1 µg (27.6% of the dose within the vial) [35] compared with formoterol dry powder inhaler (DPI), which ranges from 7.2 to 9.6 µg per dose at a flow rate of 40–60 l/min [38].

Based on initial studies that demonstrated similar serum concentrations for 15 µg twice daily (b.i.d.) arformoterol nebulized (1.1 h, 6.5 pg/ml) and 12 µg b.i.d. formoterol DPI (0.9 h, 6.2 pg/ml), a 15 µg initial dosing was used as baseline for evaluation of different dosing strategies [35]. Four dosages were tested for efficacy: 15 µg twice a day, 25 µg twice a day, 30 µg once daily and 50 µg once daily. Comparison of 15 µg and 25 µg arformoterol dosage showed greater improvement in FEV_1 with the 25 µg dose, but this dose had a 10% higher overall AE rate and 4% more myocardial ischemic events than the 15 µg dose [39].

Panettieri *et al.* compared the efficacy of arformoterol 15 µg b.i.d. to arformoterol 30 µg once daily [40]. The daily dosing had a 40% initial improvement of FEV_1 area under the curve over the first 12 h, but FEV_1 declined significantly over the following 12 h. Ultimately, the area under the curve of improvement in FEV_1 over 24 h was similar between the two regimens. A similar result was seen in a higher once daily dosing of 50 µg of arformoterol. Based on these trials, arformoterol 15 µg twice daily was approved due to the optimal benefit of stable improvement in FEV_1 and the least AE rate in this dose.

Clinical studies of arformoterol

Two randomized, placebo-controlled trials of arformoterol and one head-to-head comparison with formoterol have been conducted, with similar baseline patient characteristics (Table 3). Phase III trials of arformoterol included GOLD class III COPD patients with an average predicted FEV_1 of 40% and patients tended to be older with significant smoking history or those who continued to smoke. Interestingly, a substantial proportion of patients had a significant bronchodila-

tor response ranging from 12.1 to 21.1% during baseline lung function testing, similar to the ranges of 10 and 22% seen in the landmark TORCH and UPLIFT trials, respectively [41,42].

In an initial Phase II study, the percent increases in peak and trough FEV_1 from baseline with arformoterol were 20.9 and 19.1%, respectively, compared with 22.1 and 16.0% with formoterol, respectively (Table 4), suggesting equivalence between the two drugs [35]. The change in peak FEV_1 from baseline was 0.30 and 0.26 l and 12-h trough improvement was 0.10 and 0.09 l for arformoterol and formoterol, respectively [39].

When compared with salmeterol, peak improvement in FEV1 was 6% higher in arformoterol 15 µg b.i.d. dosing and FEV1 was improved, but less pronounced, at the 12 h trough [43]. A trend towards greater improvements in FEV_1 from baseline was noted in patients with severe versus moderate COPD [34]. There was an increased peak FEV_1 change from a baseline of 21.2% in arformoterol versus 15.1% with salmeterol [43]. The increased FEV_1 response with arformoterol reversed at 12 h to 14.6% improvement in FEV_1 versus 15.5% with salmeterol [34]. It is clear that simple elimination half-life opposes what is seen in the Phase III studies and may be related to a more stable binding to the receptor seen with salmeterol [44].

A tachyphylactic effect is seen over time during the first 12 weeks in the arformoterol Phase III trials, which is similar to the alternate studies with LABA medications, but this decline in medication efficacy appears to plateau during weeks 13–26. The number of subjects with improvement in FEV_1 >10% at 12 weeks dropped by 10–15% with arformoterol when compared with the response to the first dose. Interestingly, the salmeterol group had a similar number of patients with and FEV_1 response, but this group had a decline in FEV_1 response by 26–29.8% over the 12-week study period [34,43]. This much more dramatic fall in FEV_1 response over the 12-week period with salmeterol is poorly understood and needs further study. Efficacy studies of arformoterol to date are up to 1 year. Data on long term efficacy of arformoterol is lacking.

Quality of life & endurance testing

Only two Phase III studies reported quality of life measures for 15 µg arformoterol b.i.d. [45,46]. Patients using arformoterol showed statistically significant improvement in the Transitional Dyspnea Index of 0.97 from baseline versus 0.36 with salmeterol and no difference when compared with formoterol (Table 5). Similarly, no significant difference was noted in the St. George's Respiratory Questionnaire between the two study groups. In summary, these studies showed a trend toward improved quality of life with LABA

Table 3. Baseline demographics of patients with chronic obstructive pulmonary disease in efficacy studies of arformoterol.

Author (year)	Treatment	Dose (µg b.i.d.)	Sample size (n)	Age (mean years ± SD)	Baseline predicted FEV_1 (mean % ± SD)	Baseline FEV_1 (mean l ± SD)	Actively smoking (%)	>30 packs/year smoking (%)	FEV_1 reversibility (mean % ± SD)	Ref.
Baumgartner *et al.* (2007)	Arformoterol	15	124	62.0 ± 9.1	40.2 ± 12.4	1.2 ± 0.4	43.3	87.2	16.6 ± 13.5	[43]
	Salmeterol	42	118	63.4 ± 8.8	41.6 ± 13.2	1.3 ± 0.4	34.7	86.1	20.7 ± 15.9	
	Placebo	N/A	111	63.1 ± 8.4	40.6 ± 12.6	1.3 ± 0.5	43.4	88.8	16.2 ± 15.4	
Hanrahan *et al.* (2008)	Arformoterol	15	234	62.6 ± 8.9	40.2 ± 13.0	1.2 ± 0.5	45.5	87.2	17.0 ± 14.2	[39]
	Salmeterol	42	246	62.8 ± 8.8	40.9 ± 13.0	1.2 ± 0.5	41.0	87.2	21.1 ± 16.3	
	Placebo	N/A	229	63.2 ± 8.9	41.3 ± 12.2	1.3 ± 0.5	49.1	88.4	17.2 ± 13.7	
Hanania *et al.* (2010)	Arformoterol	15	149	65.4 ± 9.0	40.9 ± 13.6	1.2 ± 0.5	51.0	84.6	12.7 ± 30.9	[34]
	Formoterol	12	147	63.9 ± 7.8	41.2 ± 11.5	1.2 ± 0.4	40.0	87.8	12.1 ± 0.3	

b.i.d.: Twice daily; FEV_1: Forced expiratory volume in 1 s.

Table 4. Clinical efficacy of arformoterol as measured by change in forced expiratory volume in 1 s in patients with chronic obstructive pulmonary disease.

Author (year)	Treatment	Dose (μg b.i.d.)	Peak change in FEV_1 (mean % ± SD)	Change in FEV_1 trough (mean % ± SD)	Ref.
Kharidia *et al.* (2008)	Arformoterol Formoterol	15 12	20.9 ± 13.3 22.1 ± 11.2	19.1 ± 14.9 16.0 ± 12.7	[35]
Baumgartner *et al.* (2007)	Arformoterol Salmeterol	15 42	21.2 ± 13.2 15.1 ± 13.8	13.8 ± 21.0 15.1 ± 20.4	[43]
Hanrahan *et al.* (2008)	Arformoterol Salmeterol	15 42	21.9 ± 14.6 13.9 ± 11.6	14.6 ± 20.9 15.5 ± 18.6	[34]
Hanania *et al.* (2010)	Arformoterol Formoterol	15 12	24.6 ± 25.5 21.7 ± 22.9	8.2 ± 25.5 7.5 ± 20.4	[39]

b.i.d.: Twice daily; FEV_1: Forced expiratory volume in 1 s.

but the magnitude of change did not meet the minimal improvement required for a clinically meaningful change in either score [47,48].

Treatment with LABA medications can improve exertional capacity. A study evaluating GOLD stage II COPD subjects found arformoterol use resulted in significant improvement in exercise time with both treadmill use and with the cycling testing of 157s and 110 s, respectively [49]. The extent of oxygen desaturation improved by 2.8% during the treadmill test, although no change in desaturation was seen when cycling. In a 26 week trial, arformoterol increased the 6-min walk distance (6MWD) from baseline at dosing trough by 8.2 m, a result not statistically different from formoterol's improvement of 18.3 m [39]. Immediately post dose, there was no change in 6-min walk distance with either medication at the end of the study.

General safety

Side effects of LABAs include tremor, nervousness, dizziness, hypertonia, insomnia, hypokalemia, hyperglycemia and paresthesias. Initial Phase II studies report 28.6–37.1% of COPD patients experienced AEs with large variation related to imprecise AE definition in the earlier study [35]; later studies used more clearly defined AE reporting with a significantly higher rate of 67.4–90.5% (Table 6). Despite AE, rates of withdrawal due to AEs were <10.1%, less than placebo, salmeterol and formoterol comparators. A majority of AEs were "respiratory related," with similar rates as that of placebo and included nasopharyngitis, hoarseness, cough, chest congestion and shortness of breath. The AE profile for arformoterol was similar to those for other LABAs. Arformoterol decreased potassium up to 0.2 mEq/l and increased glucose concentration up to 26 mg/dl, a result identical to salmeterol that did not require intervention. In general, when compared with formoterol and salmeterol, arformoterol had a similar rate of AE as expected from treatment with LABAs.

Increasing concerns are being raised regarding the risk of cardiovascular events in COPD patients initiated on LABA, particularly since cardiovascular disease is common in this population [36]. Cardiovascular complications were specifically evaluated in a Phase III analysis [37]. Subjects receiving arformoterol have high incidence of atrial tachycardia that remained stable over a 12 week study period as assessed by Holter monitor [37], and the rate of serious arrhythmia was similar with other β agonists (Table 6). There appeared to be no increased risk of ischemia or serious cardiac arrhythmias when evaluated against placebo and salmeterol. Overall, cardiovascular comorbidities are common in the COPD population, and LABAs appear to have a favorable risk–benefit profile, although they should be

Table 5. Effect of arformoterol on dyspnea scores and quality of life measures in patients with chronic obstructive pulmonary disease.

Author (year)	Treatment	Dose (μg b.i.d.)	TDI score change from placebo mean (95% CI)	SGRQ score change from placebo mean (95% CI)	Ref.
Baumgartner *et al.* (2007)	Arformoterol Salmeterol	15 42	0.97U (0.25 to 1.69) 0.36U (-0.40 to 1.12)	-1.62U (-3.85 to 0.61) -3.18U (-5.44 to -0.92)	[43]
Hanrahan *et al.* (2008)	Arformoterol Formoterol	15 12	1.40U (0.90 to 2.00) 1.40U (0.90 to 2.00)	-3.70U (-6.40 to -1.00) -6.80U (-8.90 to -4.70)	[34]

SGRQ scores range from 0 to 100. SGRQ change ≥4 is considered clinically relevant [47].
TDI scores range from –9 to 9. TDI change ≥1 is considered clinically relevant [48].
b.i.d.: Twice daily; SGRQ: St. George's Respiratory Questionnaire; TDI: Transition Dyspnea Index.

Table 6. Adverse event rates seen in Phase II and III studies using arformoterol in patients with chronic obstructive pulmonary disease.

Author (year)	Treatment	Any AE (%)	Respiratory AE (%)	Arrhythmia (%)	Ischemia (%)	Withdrew due to AE (%)	Ref.
Baumgartner *et al.* (2007)	Arformoterol Salmeterol Placebo	67.4 68.8 72.0	39.0 38.2 37.8	2.1 7.6 7.0	0.0 1.4 0.7	5.7 9.0 9.8	[43]
Hanrahan *et al.* (2008)	Arformoterol Salmeterol Placebo	70.1 74.5 74.7	40.3 43.4 39.9	4.4 3.1 5.5	0.7 0.7 1.4	7.5 7.9 9.1	[37]
Hanania *et al.* (2010)	Arformoterol Formoterol	67.8 66.7	– –	3.4 3.4	0.7 1.4	10.1 8.2	[39]
091-060*	Arformoterol Salmeterol	90.5 88.3	– –	8.3 6.4	2.1 3.4	22.2 17.0	–
091-061*	Arformoterol Formoterol	67.8 66.7	– –	– –	– –	– –	–
091-080*	Arformoterol Placebo	72.9 68.2	– –	– –	– –	– –	–

*Numerical studies are unpublished pharmaceutical trial data.
AE: Adverse event.

used judiciously. Further studies with long-term follow up of arformoterol will help answer the potential adverse cardiovascular effects due to sustained atrial tachycardia.

Acute COPD exacerbations

The natural history of patients with COPD is interspersed with exacerbations associated with significant health care expenditure and adverse impact on quality of life. Generally, the frequency and severity of acute exacerbations of COPD increase with disease severity. GOLD guidelines emphasize the importance of mitigating the exacerbation risk for each individual patient. Studies evaluating single agent LABA therapy showed minimal to no improvement in acute exacerbation of COPD rates; however, combined LABA and inhaled corticosteroid therapy reduced acute exacerbations with greatest benefit in subjects with more severe COPD [50]. Minimal to no improvement in rates of acute exacerbation of COPD was seen with formoterol [46,51]. However, arformoterol compared with placebo showed a modest reduction in the rate of acute exacerbations of COPD, by 3.3 and 2.9% in studies by Baumgartner *et al.* and Hanrahan *et al.*, respectively (Table 7) [34,43]. Compliance and adequate drug deposition are important in order to reap clinical benefit from inhaler therapies, so future studies should examine the role of nebulized LABA on quality of life and rates of exacerbations in older adults with severe COPD and poor peak inspiratory flow rate (PIFR). Preliminary results presented in abstract form at a national meeting suggest the potential benefit of arformoterol use during hospitalization for acute exacerbation in reducing 30-day readmission, although this was based on an administrative database without comparison to other available LABAs as control [52]. This benefit may be related to slow recovery of the PIFR and improved delivery by nebulizer in the postexacerbation state [53]. The role of arformoterol in COPD exacerbation may be related to the ability to deliver the medication during a period where the PIFR is below what is needed to adequately use handheld devices. As hospitals are receiving higher penalties for 30-day readmission rates, adequately powered studies of arformoterol are needed to evaluate its role reducing not only in 30-day readmission but also the overall rates of severe exacerbation requiring acute care hospitalizations.

Nebulized arfomoterol as an advantage for COPD treatment

In general, COPD is a disease of older adults with multiple comorbidities. Currently available hand held inhaler delivery systems for LABA administration include metered dose inhaler (MDI) and dry powder inhaler (DPI) formulations. The efficacy of inhaled medicine is directly proportional to the drug delivered to the distal airways. In older adults, multiple factors such as arthritis, weakness, poor manual dexterity, and visual or cognitive impairment limit a patient's ability to use these devices. MDI use requires a carefully coordinated breath and inhaler activation. Up to a third of older adults are unable to execute this maneuver accurately, resulting in pharyngeal deposition of the medication [54].

Table 7. Effect of arformoterol on acute exacerbation of chronic obstructive pulmonary disease.

Author (year)	Treatment	Dose (μg b.i.d.)	Duration of study (days)	COPD exacerbations (%)	AECOPD change from placebo (%)	Ref.
Baumgartner *et al.* (2007)	Arformoterol	15	84	13.5	-3.3	[43]
	Salmeterol	42	84	13.9	-2.9	
Hanrahan *et al.* (2008)	Arformoterol	15	84	12.2	-2.9	[34]
	Salmeterol	42	84	14.2	-0.9	
Hanania *et al.* (2010)	Arformoterol	15	182	32.2	N/A	[39]
	Formoterol	12	182	22.4	N/A	
091-080*	Arformoterol	15	180	23.3	-4.7	–
091-061*	Arformoterol	15	180	25.5	N/A	–
	Formoterol	12	180	18.4	N/A	
091-060*	Arformoterol	15	365	19.7	N/A	–
	Salmeterol	42	365	17.4	N/A	

Numerical studies are unpublished pharmaceutical trial data.
AECOPD: Acute exacerbations of COPD; b.i.d.: Twice daily; COPD: Chronic obstructive pulmonary disease.

DPI devices are commonly used in COPD treatment but they do have drawbacks. DPI delivered medications require a PIFR of 30–60 l/min and 17% of patients find the device difficult to use. Impairment in PIFR may be due to diaphragmatic weakness or age-related change to the respiratory system that places the patient below the threshold of effective drug delivery [55]. These devices are expensive, and this cost may be wasted if patients are unable to obtain adequate medication delivery due to low PIFR. Particularly in severe COPD, patients may by unable to produce adequate PIFR at baseline or during an exacerbation. Testing a patient's PIFR may allow clinicians to provide a more beneficial and ultimately cost-effective medication choice.

Nebulized therapy has the advantage of requiring minimal coordination, dexterity, or inspiratory flow rate. Drug delivered via nebulization is perceived to provide quick bronchodilatory effect and has shown to improve patient compliance, resulting in improvement in symptoms and quality of life [56]. However, there is no outcome difference between nebulizer and appropriately used MDI treatment with long-acting medications [57]. The major drawback of the nebulizer use is the time required to deliver the medication, which averages approximately 6 min during the studies [35], the need for a power source and the regular maintenance of the equipment to avoid contamination. In addition, the size of the nebulizer makes it less portable. However, a subset of patients who prefer nebulizer use, although poorly described in the studies, may be those with difficulty using a MDI or with poor PIFR. Improved evaluation of patients prior to medication choice will provide the best cost-effective option for treatment of COPD patients.

Future perspective

The most recent Global Initiative for COPD recommends a 'step up' plan in management of patients with COPD. Monotherapy with short-acting muscarinic antagonists (SAMAs) or short-acting β-adrenergic agonists (SABAs) is the preferred first line treatment in patients with mild to moderate disease. In severe disease, long-acting muscarinic antagonists (LAMAs) or long-acting β-adrenergic agonists (LABAs) are added as maintenance therapy to reduce the risk of exacerbations and improve quality of life [58]. The future of management of COPD is combination of LABA and LAMA as we move away from the use of inhaled steroid [59]. As of 2014, two LABA/LAMA combinations are approved. Recently approved by the FDA in the USA is a combination DPI of vilanterol and umeclidinium; approved in Europe was another combination containing indacterol and glycopyronium in a DPI device. There are currently no nebulized LAMA medications; however, Phase III trials are currently underway using a glycopyrrolate solution.

Conclusion

Arformoterol is the active isomeric component of formoterol with a similar overall safety profile to other LABAs. As the medical community shifts towards improving overall quality of care, providing the drug delivery modality with the highest patient derived benefit will be a key to managing patients with COPD. Evaluation of PIFR and the inhaler technique in outpatient practices would be paramount in making the right inhaler choice for the patient. PIFR measurement may become a standard practice prior to prescribing DPI medications, particularly for insurance purposes

given the cost of these drugs. Arformoterol's availability as a nebulized solution along with its rapid onset of action makes it an attractive option in COPD management of patients with poor hand eye coordination and poor peak inspiratory flow rate.

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Executive Summary

- Arformoterol is the active enantiomer of formoterol and is delivered by nebulizer therapy twice a day to achieve similar dosing potency as currently approved formoterol.
- Arformoterol has similar efficacy and overall safety when compared with other long-acting β-agonists (LABAs).
- Newer LABA preparations appear to be superior to salmeterol, and there is considerable debate about the effect of β_2-adrenergic agonists on inflammation and clinical significance.
- Chronic obstructive pulmonary disease (COPD) management is moving away from inhaled corticosteroids and LABA combinations towards initial therapy with LABA and/or long-acting muscarinic antagonist medications.
- Nebulized LABA therapy has a role in patients with poor peak inspiratory flow rate due to severe COPD and in patients with inability to appropriately use hand held devices.
- Regular evaluation of inhaler technique and peak inspiratory flow rate in the clinical setting would help guide the clinician on appropriate delivery system selection for medical treatment of patients with COPD.

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