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REVIEW

Ultra Long-Acting β-Agonists in Chronic Obstructive Pulmonary Disease

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Introduction: Inhaled β-agonists have been foundational medications for maintenance COPD management for decades. Through activation of cyclic adenosine monophosphate pathways, these agents relax airway smooth muscle and improve expiratory airflow by relieving bronchospasm and alleviating air trapping and dynamic hyperinflation improving breathlessness, exertional capabilities, and quality of life. β-agonist drug development has discovered drugs with increasing longer durations of action: short acting (SABA) (4–6 h), long acting (LABA) (6–12 h), and ultra-long acting (ULABA) (24 h). Three ULABAs, indacaterol, olodaterol, and vilanterol, are approved for clinical treatment of COPD.

Purpose: This article reviews both clinically approved ULABAs and ULABAs in development.

Conclusion: Indacaterol and olodaterol were originally approved for clinical use as monotherapies for COPD. Vilanterol is the first ULABA to be approved only in combination with other respiratory medications. Although there are many other ULABA's in various stages of development, most clinical testing of these novel agents is suspended or proceeding slowly. The three approved ULABAs are being combined with antimuscarinic agents and corticosteroids as dual and triple agent treatments that are being tested for clinical use and efficacy. Increasingly, these clinical trials are using specific COPD clinical characteristics to define study populations and to begin to develop therapies that are trait-specific.

Keywords: chronic obstructive pulmonary disease, COPD, β-agonist, long-acting β-agonist, LABA, ultra long-acting β-agonist, ULABA

Introduction

Bronchodilating β-agonists have been lynchpins of chronic obstructive pulmonary disease treatment for decades.[1–3] Therapeutic β-agonists preferentially bind β_2 receptors that are expressed abundantly by airway smooth muscle cells.[4] Activation of the β_2 receptor stimulates smooth muscle relaxation and bronchodilation via a cyclic adenosine monophosphate pathway.[5,6] Based upon their therapeutic duration of action, β-agonists are classified as short acting (SABA) (4–6 h), long acting (LABA) (6–12 h), and ultra-long acting (ULABA) (24 h) (Box 1).[7] Ultra-long-acting β-agonists (ULABAs) are of particular interest due to more convenient dosing patterns, the advent of a growing number of nebulized medications, and the ability to use these agents in combination drug therapy.[7,8] The Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD) guidelines recommend daily use of these agents for any patient with active daily COPD symptoms and/or a history of acute exacerbations of COPD (AECOPD).[1] More recently, work has focused on developing therapies specific to clinical COPD phenotypes by utilizing ULABAs in combination with other types of respiratory medications, including muscarinic antagonists and

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Box 1 List of β-Agonists Based Upon Duration of Action

Short-Acting β-Agonists (4–6 h)
• Albuterol • Levalbuterol • Pirbuterol • Terbutaline • Metaproterenol
Long-Acting β-Agonists (12 h)
• Arformoterol • Bambuterol • Clenbuterol • Formoterol • Salmeterol • Protokylol
Approved Ultralong-Acting β-Agonists (24 h)
• Indacaterol • Olodaterol • Vilanterol (in association with other drugs only)

inhaled corticosteroids.[9,10] Additionally, new and innovative delivery systems are being developed to optimize drug delivery to the lungs and improve ease of use.[11,12]

This review will focus on translational and clinical studies that are helping to create a patient-centered approach to COPD treatment. Although several efficacious ULABA formulations are approved and available (indacaterol, olodaterol, and vilanterol), medical chemists continue to design new β-agonist molecules that are being evaluated for possible clinical testing. Another promising area is the development of molecules with both β-agonist and muscarinic antagonist properties. We will begin with an overview of current guidelines which will provide the framework for future drug discovery and salient clinical outcomes expected of ULABAs, discuss the most recent work being performed with ULABAs, including combination therapies, discuss the role of drug delivery in the development of ULABA therapy, and, finally, biochemical advances that may be utilized in the next wave of ULABA agents. Understanding the breadth of science, from bench-side-to-translational-to-clinical will refine how these agents may be used in COPD management.

Guideline Based Utilization of ULABAs for COPD

The GOLD guidelines are the preeminent global clinical guidelines for the treatment of COPD.[1] The GOLD guidelines classify ULABAs as long-acting-daily COPD medications for symptomatic patients and/or patients predisposed to COPD exacerbations and do not distinguish ULABA from LABA. The utilization of either LABA or ULABA should not preclude the use of short-acting β-agonists (SABA) for symptomatic control.[1] However, GOLD does not make specific recommendations for the utilization of long-acting β-agonists outside of recommending prescribing drugs that are best tolerated, provide optimal convenience, and are the most efficacious for any given patient. Certainly, the use of a once daily medication, if drug delivery is optimized, is a boon to COPD therapy. Long-acting β-agonists (LABA and ULABA) have been combined with either anticholinergics or corticosteroids in dual combination devices and with both anticholinergics and corticosteroids in triple combination devices.[13] ULABA monotherapy and combination therapy in COPD have been extensively studied and will be reviewed.

As a class, LABA and ULABA therapy in COPD has been shown to improve quality of life metrics and reduce hospitalizations relative to placebo, while seemingly having no effect on exacerbations-as-a-whole and mortality in a combination of 26 studies with approximately 15,000 participants.[14] It should be noted that visual appraisal of the funnel plot in this review suggests that there is some bias towards statistically significant findings in publications as well as reported inconsistencies in the definition of "exacerbation" across studies. Further, the studies mainly focused on salmeterol and formoterol as interventions, which are not ULABAs.[14] Studies of other ULABAs present generally similar but not entirely analogous findings:

Indacaterol

Indacaterol is a ULABA developed by medicinal chemists at Novartis and approved for clinical use by the Federal Drug Administration (FDA) in July 2011. The development, pharmacology, clinical efficacy, and safety profile of indacaterol were reviewed extensively in our previous review of ULABA's.[15] Initial studies in 2006 showed that after 28 days of indacaterol therapy, participants receiving indacaterol (400 mcg and 800 mcg) had a 200 mL to 260 mL, respectively, increase in forced expiratory volume in one second (FEV_1) compared with placebo.[16] Further, in this initial study, indacaterol had no effect on electrocardiographic parameters, adverse events, or tachycardia, with only a mild increase in serum

potassium, glucose, and blood pressure. Other pre-clinical and early clinical trials of indacaterol have been reviewed.[17] Indacaterol improved breathlessness in a meta-analysis of six trials.[18,19] A Cochrane systemic review analyzed 13 trials comparing indacaterol with either placebo or twice daily β-agonist in the treatment of COPD and demonstrated that indacaterol produced statistically and clinically meaningful increases in both lung function and quality of life compared with placebo.[20] A network meta-analysis comparison of monotherapy with LABA's or ULABA's in individuals with COPD showed that indacaterol was the most effective β-agonist monotherapy for moderate-to-severe COPD based upon the effects on spirometry, breathlessness, and COPD exacerbation rates.[21] A similar network meta-analysis of 40 randomized controlled trials showed that indacaterol treatment was associated with a reduction in mortality in fixed (HR 0.28; 95% CI 0.08–0.85) and random effects (HR 0.29; 95% CI 0.08–0.89) models compared with placebo.[22] Indacaterol's safety profile is similar to placebo but side effects may occur with prolonged use.[23]

Dual drug combinations incorporating indacaterol have been examined in the management of COPD. With less frequent medication administration, these combinations seek to improve patient adherence and ease of use. Once daily treatment with indacaterol/glycopyrronium (110/50 mcg once daily) for 24–26 weeks produced greater benefits in lung function, daily symptoms, breathlessness, health-related quality of life, and rescue medication use compared with LAMAs.[24] In a one-year trial, combination indacaterol/glycopyrronium (110/50 mcg once daily) prevented COPD exacerbations more effectively than salmeterol/fluticasone (50/500 mcg twice daily) in individuals who have a high risk of exacerbations.[25] Additionally, indacaterol/glycopyrronium (110/50 mcg once daily) treatment delayed the time to clinically important deterioration (defined as ≥100 mL decrease in FEV1 or ≥4 unit increase in the St. George's Respiratory Questionnaire or a moderate to severe COPD exacerbation) compared with salmeterol/fluticasone (50/500 mcg twice daily) therapy in individuals with moderate to very severe COPD.[26] A 12-week trial comparing indacaterol/tiotropium and umeclidinium/vilanterol in individuals with COPD showed similar improvements in spirometry, dyspnea, St. George's Respiratory Questionnaire, and safety profile.[27] Combination indacaterol/glycopyrronium treatment is well tolerated with a safety profile and adverse effects similar to each of its components.[28]

Most recently, indacaterol/glycopyrronium combination therapy has been evaluated in the de-escalation of triple therapy for COPD. The SUNSET trial showed that individuals with COPD and infrequent exacerbations treated with tiotropium (18 mcg once daily) and salmeterol/fluticasone propionate (50/500 mcg twice daily) who were switched to indacaterol/glycopyrronium (110/50 mcg once daily) experienced small reductions in lung function but no change in COPD exacerbations.[29] However, the greater exacerbation risk in individuals with ≥300 eosinophils suggested that these individuals would obtain greater benefit from triple therapy.

Olodaterol

Olodaterol was first reported by medicinal chemists at Boehringer Ingelheim in 2010 and approved by the FDA in July 2014. Initially, olodaterol was noted to reverse acetylcholine-induced bronchoconstriction in canines and guinea pigs. This effect persisted for over 24 h, significantly longer than concomitantly tested formoterol.[30] In addition to a prolonged duration of effect, olodaterol has a fast onset of action and high β2-adrenoreceptor selectivity.[31] Initial placebo-controlled, single dose–response studies in individuals with moderate to very severe COPD showed a dose-dependent response in FEV_1 to 2–20 mcg olodaterol.[31] Compared with placebo, olodaterol significantly augmented FEV_1 at 12 h (121 mL to 213 mL based on dose from 2 to 20 mcg) and 24 h (74 mL to 141 mL based on dose from 2 to 20 mcg).[32] In this early study, lung function peaked 2–3 h after all doses and then decreased from 12 to 24 h.[32] Subsequent 12-week studies of once daily 5 or 10 mcg olodaterol in individuals with moderate to very severe COPD showed that both doses of olodoterol significantly improved the FEV1 area under the curve from 0 to 3 hours (FEV_1 $AUC_{0–3}$) and trough FEV1 response compared with placebo with a comparable range and incidence of adverse events.[33] Further studies showed that once-daily 5 or 10 mcg olodaterol improved FEV_1 $AUC_{0–3}$ and trough FEV1 response after 24 weeks compared with placebo in individuals with moderate to very severe COPD and these improvements were comparable to the effect of twice daily formoterol.[34] Although there was no difference in transitional dyspnea index for either olodoterol or formoterol compared with placebo, the St. George's Respiratory Questionnaire[35] total score was significantly improved after olodoterol but not formoterol compared with placebo.[34] Subsequent Phase III clinical trials of olodaterol

in individuals with COPD demonstrated significant improvements in lung function, breathlessness, and quality of life.[36] Studies have generally deemed olodaterol safe based on lack of observed adverse events compared with placebo.[32,33] Cough, nasopharyngitis, and headache are the most frequent side effects.

Olodaterol has been combined with tiotropium to develop a long-acting fixed dose combination ULABA/LAMA medication for COPD management.[37,38] Tiotropium/olodaterol (5/5 mcg once daily) produced greater increases in lung function, health-related quality of life indices, St. George's Respiratory Questionnaire, and breathlessness than either drug alone.[39]

Vilanterol

Medicinal chemists at GSK developed vilanterol, another ULABA. Vilanterol was initially described in a murine model to have a long and potent duration of action along with high β-receptor selectivity.[40] Vilanterol's affinity for the β2-receptor is comparable to salmeterol but greater than olodoterol, formoterol, or indacaterol.[41] In human airway tissue, vilanterol has a faster onset and longer duration of action than salmeterol.[41] To date, vilanterol is only marketed in combination with other COPD/asthma medications. Studies have been performed on vilanterol monotherapy showing increased FEV_1 compared with placebo without an increase in adverse events including electrocardiographic, glucose, or potassium changes.[42] Vilanterol, 25–100 mcg, increased FEV1 as quickly as 5 min after dosing and maintained the increases for up to 24 h in individuals with COPD. A dose-ranging study of vilanterol from 3 to 50 mcg in patients with moderate to severe COPD showed that higher doses of vilanterol, 25 and 50 mcg, produced clinically relevant increases in trough FEV1 (>130 mL) after 28 days compared with placebo.[43] The safety and tolerability profile of vilanterol was similar to placebo.

Vilanterol has been combined with corticosteroids (fluticasone) and with LAMA (umeclidinium) in dual and triple combinations. Vilanterol/umeclidinium improves lung function, St George's Respiratory Questionnaire scores, and requirement for rescue inhaler use in individuals with COPD.[44–47] Additionally, vilanterol/umeclidinium treatment produced greater improvement in lung function compared with salmeterol/fluticasone.[48]

A randomized, open-label cross-over trial comparing umeclidinium/vilanterol and tiotropium/olodoterol in individuals with COPD, umeclidinium/vilanterol was non-inferior to tiotropium/olodoterol in the primary endpoint, change from baseline in trough FEV1 at week eight.[49] However, umeclidinium/vilanterol produced greater improvements in other measures of lung function as well as reductions in rescue medication use and the COPD Activity Test scores compared with tiotropium/olodoterol.

In a 12-week trial comparing 25 mcg vilanterol and 100/25 mcg fluticasone furoate/vilanterol treatment for 8 weeks in individuals with COPD, the change from baseline trough FEV1 was greater for those receiving combination therapy.[50] Although rescue medication use was similar in the two groups, there was a 42% risk reduction in time to first moderate to severe COPD exacerbation in the combination treatment group. Adverse events were similar with either therapy.

Dual combination treatment with fluticasone furoate/vilanterol compared with placebo increases lung function in individuals with COPD.[51,52] The annual rate of moderate and severe COPD exacerbations, time to first moderate or severe exacerbation, and frequency of exacerbations requiring steroids in individuals with moderate-to-severe COPD treated with fluticasone furoate/vilanterol are reduced compared with those treated with vilanterol alone.[53] The SUMMIT trial randomized over 16,000 participants with COPD to placebo, fluticasone furoate or vilanterol or fluticasone furoate/vilanterol treatment and showed that combination treatment did not affect all-cause mortality or cardiovascular outcomes, but combination and fluticasone furoate alone treatment decreased the rate of FEV_1 decline.[54]

The FULFILL study compared fluticasone furoate/umeclidinium/vilanterol triple combination therapy with budesonide/formoterol dual therapy and showed that triple therapy improved lung function, reported pulmonary symptoms, and quality of life indices.[55,56] A large study of over 10,000 participants with COPD compared combined triple therapy, fluticasone furoate/umeclidinium/vilanterol (100 mcg/62.5 mcg/25 mcg) with fluticasone furoate/vilanterol (100 µg/25 µg) or umeclidinium/vilanterol (62.5 mcg/25 mcg) for 52 weeks and showed triple therapy reduced the rate of moderate or severe COPD exacerbations compared with either dual therapy and the rate of COPD hospitalizations compared with umeclidinium/vilanterol dual therapy.[55]

Equipoise remains in guidelines in regard to the utilization of ULABA agents for bronchodilation in COPD compared with long-acting muscarinic (LAMA) agents. LAMA are preferred as the first choice for bronchodilation

in COPD patients.[1] However, the tenets of patient-directed care and continual reassessment of symptoms and drug delivery suggest that the opportunity for utilization of ULABA monotherapy in COPD certainly exists and may be appropriate in select patients. The differentiating factor is likely drug delivery. Indacaterol is delivered in a dry powder inhaler device that has been associated with a high degree of user error[57] while olodaterol is in a soft mist inhaler that generally improves drug administration and deposition[58] but requires necessary motor and coordination skills to actuate and inspire from the device properly. On the balance, all inhaler devices have some degree of potential for patient error and patient-centered device education and continual reassessment are tantamount in determining the best delivery system to use.

Recent Approaches to ULABA Therapy and Experimental Agents

In recent years, ULABAs in combination with LAMAs have changed the paradigm of COPD therapy. This combination is particularly effective due to the synergistic effect between β receptor stimulation and muscarinic receptor antagonism.[13] These combinations appear to have considerable clinical benefit and provide bronchodilation without the additional potential risk of pneumonia caused by concomitant inhaled corticosteroid use.[25] ULABA/LAMA combination therapy provides bronchodilation and symptom relief with a safety profile similar to either ULABA or LAMA monotherapy,[59] and these agents are powerful tools in the treatment of COPD patients whose disease course is marked by persistent chest symptoms. Other studied ULABAs include:

Trantinerol

Trantinterol or SPFF is a unique ULABA that is based upon a 2-amino-2-phenylethanol scaffold rather than the 2-amino-1-phenylethanol backbone used to develop other ULABA drugs such as indacaterol.[60] SPFF has high affinity and selectivity for the β_2 receptor.[61] It relaxes both untreated and acetylcholine or histamine-precontracted isolated guinea pig trachea strips in a dose-dependent manner with a potency similar to isoprenaline. Evaluation of SPFF enantiomers demonstrates that the (-)- enantiomer has greater affinity for the β_2 adrenergic receptor than either the (±)- or the (+)- enantiomers and is more potent.[62] Subsequent in vivo experiments showed that (-) SPFF inhibited histamine-induced bronchoconstriction in guinea pigs while (+) SPFF did not.[63] At the time of this writing, there are no registered clinical trials investigating SPFF.

Abediterol

Abediterol is a novel, long-acting β_2 agonist synthesized by medicinal chemists at Almirall.[64] Its affinity for the human β_2 receptor is greater than salmeterol, formoterol, and indacaterol with high specificity and full agonist function. The onset of action is approximately 7.4 min with a prolonged duration of action. In guinea pig acetylcholine bronchoprovocation testing, abediterol was a more potent bronchoprotectant than formoterol, indacaterol, or salmeterol and had a prolonged protective effect.

In the initial study of abediterol in humans, 48 healthy men inhaled abediterol in a randomized, parallel, single-blind placebo-controlled single-dose escalation protocol.[65] Albediterol increased specific airway conductance (sGaw) and reduced airway resistance (Raw) at 24 and 36 h after inhalation. The most common adverse events were palpitations and tremor without clinically significant changes in serum potassium or glucose.

In a dose-ranging randomized, crossover, placebo-controlled study in 62 patients with mild to moderate asthma who were being treated with an ICS, spirometry was performed 36 h after single doses of 0.313, 0.625, 1.25, or 2.5 mcg abediterol.[66] Abediterol stimulated a dose-dependent increase in peak FEV_1 compared with placebo, comparable to the effect of 400 mg salbutamol. Additionally, the peak and trough FVC and the FEV_1 area under the curve for time periods 0–6, 0–12, and 0–24 h were significantly increased compared with placebo. In a similar study of 70 individuals with GOLD stage II/III COPD, single doses of 0.625, 2.5, 5, or 10 mcg Abediterol were compared with 150 mg indacaterol or placebo.[67] Spirometry was performed 36 h after medication administration. All doses of abediterol induced significant increases in trough FEV_1 compared with placebo and 2.5, 5, and 10 mcg abediterol increased trough FEV_1 compared with indacaterol. Adverse events were similar between all the treatment groups.

A randomized, double-blind, crossover, phase IIa trial compared three doses of abediterol (5, 10, and 25 mcg) with salmeterol and placebo added to an inhaled corticosteroid in a stable dose regimen in 25 individuals with mild to moderate persistent asthma.[65] Compared with both placebo and salmeterol, all three doses of abediterol stimulated significant increases in trough FEV_1 that were

sustained for 36 h. Other spirometric measurements including FVC, peak expiratory flow, and $FEF_{25–75}$ also improved. Dose-dependent mild to moderate adverse effects including tremor, restlessness, and nervousness were noted in those receiving abediterol. Slight decreases in serum potassium and increases in serum glucose and heart rate were noted.

An ascending-dose, crossover study evaluated spirometry after 2.5, 5, and 10 mcg abediterol given once daily for a week compared with placebo in men with stable asthma was performed.[68] Both peak and trough FEV_1 on day 7 were increased for all doses. Abediterol was associated with a dose-dependent increase in the proportion of participants experiencing tremor and nervousness. As with SPFF, there are no ongoing trials of abediterol at the time of this writing.

Milveterol (TD-3327; GSK 159797)

Milveterol was developed through the creation of dimeric arylethanolamines with varying linkers based upon the albuterol scaffold.[69] In the BEAS-2B endogenous cell line, it has a β_2 pEC_{50} of 9.3±0.3 and intrinsic activity 87±9%. Milveterol provides both short- and long-term protection in an in vivo guinea pig bronchoconstriction model.

In a study of 38 patients with mild asthma, a single inhalation of GSK159797 achieved the targeted FEV_1 increase over the 24-h study period without cardiovascular toxicity.[70] An inhaled dry powder preparation of 10 and 20 mcg GSK159797 significantly elevated FEV_1 through 24 hours in a placebo-controlled, dose-ascending crossover trial with 20 participants with mild-to-moderate asthma.[71] No results from either of these trials have been posted on ClinicalTrials.gov at the time of this writing.

TD-5471

TD-5471 was developed by modification of the 4-aminophenethylamine linking group of the milveterol scaffold.[72] In the guinea pig trachea assay, it has a slow onset of action with pEC_{50} of 8.7±0.1. TD-5471's selectivity for the human β_2-adrenergic receptor is comparable to formoterol with a β_2 pEC_{50} of 9.4±0.4, intrinsic activity of 83±9%, and functional selectivity β_2/β_1 of 56 and β_2/β_3 of 100. TD-5471 demonstrated both short- and long-term bronchoprotection in a guinea pig model of in vivo intravenous acetylcholine-induced bronchoconstriction. As with the above, there are no ongoing trials of TD-5471

TD-4306

Further evaluation and modification of milveterol and TD-5471 through the addition of amine moieties and scaffold modification led to the development of the dibasic β_2 agonist, TD-4306.[73] TD-4306 has a β_2 pED50 of 10.1, and 70% intrinsic activity in the BEAS endogenous cell line assay. In the in vivo guinea pig bronchoprovocation model, TD-4306 provided significantly greater, dose-dependent bronchoprotection than salmeterol. TD-4306 has reduced enteral bioavailability in both rats and dogs. Again, there are no ongoing trials of this agent.

PF-610355

PF-610355 was developed by medicinal chemists at Pfizer who were attempting to synthesize novel, once daily inhaled β_2 agonists.[74] PF-610355 has a β_2 EC50 of 0.26 nM and is approximately 4-fold more potent than salmeterol with a prolonged duration of action in the in vitro guinea pig trachea contraction model.[74] In an in vivo canine intravenous acetylcholine bronchoprovocation model, PF-610355 was an equipotent bronchodilator compared with formoterol and more potent than salmeterol. It has low systemic bioavailability with poor absorption through both the intestine and the lungs and is metabolized predominantly through CYP3A4.

A single dose of 450 mcg PF-610355 had a more durable effect on specific airway conductance (sGAW) than either placebo or salmeterol (16.4 h and 9.8 h) longer duration, respectively, in healthy male volunteers.[74,75] In a two-week trial, PF-610355 was well tolerated.[74,76] An analysis of 10 clinical studies enrolling 579 healthy volunteers and individuals with asthma and COPD using pharmacokinetic/pharmacodynamic modeling suggested that 19% of individuals with COPD treated with 280 mcg of PF-610355 would increase heart rate by 20 or more beats/minute compared with 8% of those receiving placebo.[77] Further development of this agent has been discontinued.

AZD 3199

Medicinal chemists at AstraZeneca synthesized a family of dibasic des-hydroxy β2 receptor agonists and selected AZD3199 for further evaluation based upon enhanced duration of action and efficacy.[78] AZD3199 has greater than 1500-fold binding selectivity for β_2 receptors compared with β_1 and β_3 receptors, a pEC_{50} of 7.9±0.12, and intrinsic activity in isolated guinea pig tissue comparable

to indacaterol and formoterol with a rapid onset of action and prolonged duration of effect.

Single ascending dose studies using nebulizer delivery and multidose studies using dry powder delivery in healthy participants with either mild-to-moderate persistent asthma or moderate-to-severe COPD showed AZD3199 was rapidly absorbed and had a prolonged half-life of up to 142 h.[79] It was well tolerated with mild dose-dependent reductions in serum potassium levels and increases in heart rate. In a double-blind, placebo-controlled, randomized, cross-over, single-dose study in mild-to-moderate asthma, the bronchodilating effects of inhaled AZD3199 delivered by dry-powder inhaler augmented peak FEV_1 and maintained bronchodilation at 24 h with 480 and 1920 mcg doses when compared with placebo.[80] Throat irritation, tachycardia, and lower serum potassium levels were noted at the highest dose. In a 4-week randomized, double-blind placebo-controlled study of individuals with moderate-to-severe COPD, the efficacy and safety of AZD3199 was compared with formoterol and placebo.[81] Peak and trough FEV_1 and peak FVC were increased, in comparable fashion to formoterol, compared to placebo without dose response. AZD3199 reduced patient-reported symptoms including breathlessness and total symptom burden as well as Clinical COPD Questionnaire and Saint George's Respiratory Questionnaire scores. Adverse events were mild and dose-related. There are no ongoing trials of AZD3199 at the time of this writing.

Carmoterol, TA-2005

Carmoterol/TA-2005 was constructed based upon elements from both formoterol and procaterol with a p-methoxyphenyl group on the amine side chain and an 8-hydroxyl group on the carbostyril aromatic ring.[71,82] In several models of smooth muscle constriction, carmoterol/TA-2005 produced robust bronchodilation and smooth muscle relaxation with a prolonged duration of action.[83,84] Radioligand experiments showed carmoterol/TA-2005 binds the β_2 adrenergic receptor with very high affinity and specificity.[85] The high-affinity binding of carmoterol/TA-2005 appears to be due in large part to Tyr308 within the transmembrane 7 region of the β_2 adrenergic receptor.[86] Its onset of action in vitro is similar to formoterol and its duration of muscle relaxation activity is longer than salmeterol or formoterol.[87]

Phase II studies in individuals with COPD showed that carmoterol/TA-2005 was safe and well-tolerated with no apparent cardiovascular adverse events.[88] In a randomized, double-blind parallel group trial enrolling 124 participants with persistent asthma, carmoterol/TA-2005 was as effective as formoterol and significantly more effective than placebo in improving trough FEV_1 at the end of the eight-day treatment period.[89] Carmoterol/TA-2005 had a safety and tolerability profile similar to formoterol.[90] In 2010, clinical trials of Carmoterol/TA-2005 were stopped by Chiesi Famarceutici because it was not considered to have a competitive profile.[91]

GSK597901; GSK159802; GSK678007

Other ultralong acting β_2 agonist bronchodilators include GSK597901; GSK159802; GSK678007.[82] There is little information available for GSK597901 or GSK678007. One trial of GSK159802 is registered on Clinicaltrials.gov (NCT00364273). This study assessed the safety and tolerability of single inhaled doses of GSK159802 compared with salmeterol and placebo with no results posted at the time of this writing.

Drug Backbone Structure, β-Arrestins and Bivalent Agents

There is also a recent focus on restructuring the "backbone" of inhaled medications to increase receptor affinity and drug efficacy. This innovation has led to the creation of different 'classes' of medication but with the shared goal of achieving bronchodilation through airway smooth muscle relaxation. Additionally, newer β-arrestin biased β_2 adrenoceptor agonists are being developed. Finally, bivalent molecules that both possess both muscarinic receptor antagonist and β_2 agonist activities are being tested for COPD management.

Drug Backbone Restructuring

Enantiomers and drug scaffolding are a potential target for future LABA medications. Recently, the Medicinal Chemistry group at Shenyan Pharmaceutical University has modified existing ultralong acting β_2 agonists to create novel compounds with the potential for clinical applications. They utilized the indacaterol scaffold to create new β_2 agonists with a 5-(2-amino-1-hydroxyethyl)-8-hydroxyquinolin-2(1H)-one moiety.[92] Two of these novel molecules, 9g and (R)-18c, are potent and selective β_2 agonists with a rapid onset of action similar to isoprenaline and a duration of action equivalent to salmeterol in cell and isolated guinea pig trachea assays and were selected for further development. They have also combined the

head and tail groups of indacaterol with the core of trantinterol to produce a compound, 5a, and a series of analogs with modifications of the tail group.[60] One of these compounds, (S)-5j (8-hydroxy-5-(2-hydroxy-1-((4-hydroxyphenethyl)amino)ethyl)quinolin-2(1H)-one), had higher binding selectivity for the β_2 than β_1 adrenergic receptor, robust stimulation of cAMP through the β_2 receptor, and a maximal effect in the isolated guinea pig tracheal relaxation assay similar to isoprenaline.

Modifications of the 3- and 5-positions of the phenyl head group of the trantinterol scaffold have also produced a novel compound, 2f (2-amino-3-fluoro-5-(2-hydroxy-1-(isopropylamino)ethyl)benzonitrile) that stimulates cAMP production through the β_2 adrenoreceptor with an EC50 of 0.25 nM and exhibits β2 receptor selectivity.[93] This compound induced smooth muscle relaxation in the isolated guinea pig trachea model that was attenuated by ICI-118551, an antagonist of β_2-adrenergic receptor binding. The (S)-isomer was more active than the (R)-isomer.

Modification of the tail group of the olodoterol scaffold produced (R)-18c that is a potent β_2 agonist with an EC50 of 24 pM for the in vitro production of cAMP.[94] In the guinea pig tracheal assay, the smooth muscle cell relaxant effect was similar to olodoterol with a rapid onset of action and prolonged duration of effect. Clinical studies of these novel β_2 agonists will be needed to assess their safety, tolerability, and efficacy.

β-Arrestin-Based β2 Adrenoceptor Agonists

The β_2 adrenergic receptor is a G protein-coupled receptor with complex signaling mechanisms that can be transduced by heterotrimeric G proteins and β-arrestins.[95] Originally, the β-arrestin adaptor proteins were found to have an inhibitory role in G protein-coupled receptor signaling.[96,97] Subsequent studies revealed β-arrestins could initiate endocytosis and kinase activation stimulating intracellular signaling pathways independent of G protein activation by G protein-coupled receptors.[97] Thus, biased ligands can target either G protein or β-arrestin signaling with diverse intracellular and biological effects. β-arrestin biased β_2 adrenoceptor agonists have the potential to be a new drug class for the treatment of COPD.

Woo and colleagues[93] synthesized β-arrestin compounds with a 5-(1-amino-2- hydroxyethyl)-8-hydroxyquinolin-2(1H)-1 core structure that stimulates cellular cAMP production in vitro and induces bronchodilation in a guinea pig trachea relaxation assay, with bronchodilatory effects less robust than isoproterenol. These β-arrestin biased β_2 adrenoceptor agonists have a potential role as new therapeutics in the management of COPD.

Combined Muscarinic and Beta Activity

In vitro studies demonstrate that muscarinic receptor antagonists synergistically increase bronchodilation by β2 receptor agonists.[98,99] This synergism may be mediated by increases in cAMP concentrations in smooth muscle and bronchial epithelial cells, a decrease in epithelial cell release of acetylcholine, and linkages between G proteins, large-conductance calcium activated potassium channels, and voltage-dependent calcium channels.[99] Hence, a unique approach to combination drug therapy for COPD is the creation of molecules with both muscarinic receptor antagonist and β_2 agonist activities.[100] Batefenterol (GSK961081) is a bivalent inhaled bronchodilator with both properties.[101] This molecule binds with high affinity to both muscarinic and β_2 adrenergic receptors with specificity for β_2 compared with β_1 or β_3. Batefenterol stimulates cAMP production in vitro and induces smooth muscle cell relaxation in the isolated guinea pig trachea assay. In an in vivo guinea pig model of bronchoconstriction, batefenterol provided dose-dependent bronchoprotection for up to 1 week.

A pharmacokinetic and pharmacodynamic study of 100, 400, and 800 mcg batefenterol once daily and 100, 200, and 400 mcg batefenterol twice daily in 47 patients with COPD measuring day 29 trough FEV_1 as the primary endpoint showed no significant difference between once daily and twice daily dosing.[102] The optimal dose appeared to be batefenterol 400 mcg. Blood levels of batenfenterol were well described with a two-compartment model and no clear relationships between batenfenterol levels and measured cardiac effects were observed.

In a randomized, double-blind, double dummy, crossover trial comparing 14 days of 400 mcg or 1200 mcg batefenterol once daily, 18 mcg tiotropium once daily and 50 mcg salmeterol twice daily, or placebo in 50 participants with COPD, showed that both doses of batefenterol stimulated a significant increase in FEV_1 that was similar to that induced by tiotropium/salmeterol but with a more rapid onset.[103] Adverse effects were similar in the treatment groups but tremor, dysgeusia, and dry mouth were only reported after batefenterol inhalation.

In a phase IIb dose-response study, individuals with COPD received 37.5, 75, 150, 300, or 600 mcg batefenterol, or 62.5 mcg umeclidinium and 25 mcg vilanterol, or placebo once daily for 42 days.[104] All batefenterol doses stimulated increases in FEV_1 measured as weighted mean FEV_1 over 0–6 h and trough FEV_1 at the end of the study. Batefenterol at doses of 150 mcg or greater had spirometric improvement comparable to umeclidinium/vilanterol. The most common adverse events in those participants receiving batefenterol were cough, nasopharyngitis, and dysgeusia.

A study to determine the bronchodilatory effects of batefenterol compared once daily 100, 400, or 800 mcg batefenterol, twice daily 100, 200, or 400 mcg batefenterol, or placebo in patients with COPD demonstrated significant improvement in trough FEV_1 on day 29 compared with placebo in all treatment groups.[105] The optimal dose appeared to be 400 mcg daily either as a single dose or 200 mcg twice daily. Glucose, potassium, heart rate, and blood pressure were not affected and no corrected QT elongation dose-response effect was observed.

In healthy volunteers receiving propranolol to induce β_2 blockade, 1200 mcg of batefenterol induced bronchodilation measured by specific airway conductance at 1 and 4 h but not 7 or more hours after dosing whereas 400 mcg batefenterol stimulated bronchodilation for only the first hour after dosing.[106] These results suggest that the bronchodilatory effect of the antimuscarinic agent dissipates faster than the β-agonist effect.

To assess the effect of adding short-acting β-agonists or muscarinic antagonists to batefenterol, 44 patients with moderate COPD received single inhalations of 400 or 1200 mcg batefenterol followed by multiple doses of salbutamol, ipratropium, or placebo for 24 h.[107] Both salbutamol and ipratropium had additional bronchodilating effects measured by an increase in FEV1 at 12 and 24 h after batefenterol administration, an effect not seen at 1 h after dosing. Mild increases in heart rate were noted after salbutamol with both batefenterol doses and four participants experienced declines in serum potassium levels after receiving 1200 mcg batefenterol and either salbutamol or placebo.

As of November 1, 2020, there were no ongoing or new trials of batefenterol registered at ClinicalTrials.gov (clinicaltrials.gov accessed November 1, 2020).

Conclusion

COPD affects over 250 million people worldwide[108] and 30 million people in the US.[109] As a leading cause of morbidity and mortality, COPD generates a significant and increasing medical, economic, and social burden.[110,111] COPD is increasingly being recognized as a heterogeneous disorder with a multitude of unique and overlapping phenotypes and endotypes that can be differentiated by clinical, radiographic, physiologic, cellular, or biochemical features.[112–114] Historically, clinical presentation was used to divide COPD into "blue bloaters" (chronic bronchitis) or "pink puffers" (those with emphysema). The number of prior COPD exacerbations can be used to create categories of frequent exacerbators and infrequent exacerbators.[115–117] The severity of airflow limitation is used to separate individuals with no, mild, moderate, severe, and very severe obstruction based upon spirometric measurement of the FEV1 and FEV1:FVC ratio. Serum or sputum eosinophil counts may be used to classify and hierarchize patients with COPD based upon their response to inhaled corticosteroids.[118] Plasma fibrinogen concentration is an FDA qualified biomarker for all-cause COPD mortality and COPD exacerbations.[119] One of the major goals of determining these COPD traits is to develop individualized precision medicine treatment strategies that will provide both prognostic and therapeutic guidance for the management of each person with COPD.[9]

These traits can be used to prognosticate the clinical course of individuals with COPD. Prior exacerbations predict those who are at increased risk of future exacerbations.[117] Elevated plasma fibrinogen levels correlate with increased COPD exacerbation frequency and with mortality.[120] A systemic review of over 400 prognostic models in individuals with COPD showed that the most commonly used predictors were age, FEV1, body mass index, and smoking history.[121] However, a detailed analysis of these models revealed methodological vulnerabilities and a lack of external validation. Most recently, machine learning algorithms have been used to predict the prognosis of patients hospitalized with COPD exacerbations utilizing 28 variables including vital signs, medical history, comorbidities, and inflammatory markers.[122] The C5.0 decision tree classifier analysis was 80.3% accurate with a 0.6991-to-0.8827 95% confidence interval in prognosticating deterioration or death in patients hospitalized with COPD exacerbations.

Other markers can be used to predict response to therapy and may be used to develop individualized therapeutic strategies based upon treatable traits. Elevated blood eosinophil counts predict the clinical response to inhaled corticosteroid treatment in individuals with COPD.[118] This relationship

appears to start at a level of 100 eosinophils/μl and the clinical response becomes more robust as the eosinophil count increases.[123,124] Although only a small proportion of individuals with COPD have alpha-1-antitrypsin deficiency, recognition of the genetic mutations that cause reduced functional alpha-1-antitrypsin within the lung and increased risk of emphysema leads to specific therapy with alpha-1-antitrypsin replacement.[125,126]

The current mainstays of COPD maintenance therapy consist of three classes of inhaled medications: β-agonists, muscarinic antagonists, and corticosteroids. Bronchodilators started as short-acting medications such as albuterol and ipratropium with durations of effect lasting from 2 to 6 h. Next, long-acting medications with effects lasting up to 12 h were discovered and, most recently, ultralong acting drugs that only require daily dosing have been developed and clinically tested. Although these medications have different durations of effect, within each class, they act through the same receptors and similar intracellular mechanisms. The benefit of less frequent dosing is believed to improve patient adherence and, consequently, clinical outcomes.[127]

Many of these medications were originally approved for clinical use as monotherapy, were then used and clinically tested with simultaneous use through separate devices, and subsequently joined in combined dual and triple single modality treatments. Vilanterol is the first to be approved only in combination. Although there are many other ULABA's in various stages of development, clinical testing of these medications is either proceeding slowly or on hold. Instead, existing approved medications are being combined in various permutations to develop new dual or triple therapies that are being tested for clinical use and efficacy. Increasingly these clinical trials are using clinical traits to define study populations and to begin to develop trait-specific therapies.

At this time, we are not aware of any treatable traits that portend clinical response to β-agonists or muscarinic antagonists. As mono- or dual-therapy these medications are the basis of maintenance COPD medication management and may be combined together with ICS as triple therapy. Until there are fundamental breakthroughs in the pathogenesis of COPD and new developments in lung airway biology leading to the development of novel therapeutic drug classes, β-agonists and muscarinic antagonists will remain the foundational medications for maintenance COPD management.

Disclosure

The authors report no conflicts of interest in this work.

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