Transcript Details
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Why the Prevention of COPD Exacerbations Demands a Proactive Therapeutic Approach

Announcer:
Welcome to ReachMD. This medical industry feature, titled Why the Prevention of COPD Exacerbations Demands a Proactive Approach, is sponsored by AstraZeneca. This program is intended for health care providers.

Here's your host, Dr Jennifer Caudle.

Dr Caudle:
Chronic obstructive pulmonary disease, or COPD, can be devastating for patients. Consider that 50% of patients die within 3.6 years after their first hospitalization for a COPD exacerbation. Now if that seems like just another statistic, consider that 36% of men, and 47% of women, 45 years and older, will die within five years of their first myocardial infarction. Yet for some clinicians, the perceived consequences and need for appropriate prevention of heart attacks still outweighs those of COPD exacerbations. So, what can we do to address this? More on this and other related questions are coming up on today's program. Welcome to ReachMD. I'm your host, Dr Jennifer Caudle, and joining me to discuss COPD exacerbations and a treatment option for patients with COPD is Dr Antonio Anzueto, from the University of Texas Health and South Texas Veterans Health Care System. Dr Anzueto, welcome to the program.

Dr Anzueto:
Thank you. Thank you for having me here in the program.

Dr Caudle:
Absolutely. Dr Anzueto, to start, can you expand on the notion I just mentioned, about COPD exacerbations. Should we be taking them as seriously as heart attacks?

Dr Anzueto:
Absolutely. I will start with data statistics you described early. In a large cohort study of just over 73,000 patients, presenting with their first ever hospitalization for COPD, from 1990 to 2005 in Quebec, Canada, 50% of patients studied had died within 3.6 years of their first hospitalization for a COPD exacerbation. This data comes from a cohort study that evaluated severe COPD exacerbations, and their association with mortality in 73,106 patients with the first-ever severe COPD exacerbation requiring hospitalization in the Régie de l'assurance maladie du Québec (RAMQ) from the health insurance program of the province of Quebec, Canada. Severe exacerbations were defined as hospitalization with a primary discharge diagnosis of COPD. Now, for the context, the American Heart Association's 2019 heart disease and stroke statistics update reported that 36% of men and 47% of women, 45 years and older, will die within five years of their first myocardial infarction. This data comes from the heart disease and stroke statistics, the 2019 update which is created in conjunction with the American Heart Association, National Institutes of Health, and other government agencies, and includes the statistics related to heart disease, stroke and cardiovascular risk factors. So, we have to stop and think about that for a minute, because even though some of us may look at COPD exacerbations as being on a lower scale of severity than heart attacks, the data seems to suggest otherwise. And that should be a real eye-opener for creating more urgency around COPD and prevention of exacerbations. More important, COPD exacerbations impact the natural history of the disease, and result in hospitalizations and mortality.

Dr Caudle:
So, with that frame of mind, then, what would you say is important to remember about exacerbations?

Dr Anzueto:
I would say that even one exacerbation is too many, given that a single moderate or severe exacerbation can lead to a permanent

decline in lung function. This information comes from two studies: the UPLIFT trial and the COPDGene study. The UPLIFT trial was a four-year, randomized, double-blind, placebo-controlled, parallel group trial. A post hoc analysis of the UPLIFT trial was conducted to compare the rate of decline in lung function in patients with moderate to very severe COPD, before and after a single exacerbation. The analysis compared the rate of decline in lung function before and after a single moderate, requiring the use of antibiotics or systemic steroids, to severe, requiring hospitalization, exacerbations in patients who experienced only a single exacerbation during the trial.

COPDGene is a multi-centered, longitudinal, observational cohort study that has enrolled current and former smokers. This study obtains spirometry and detailed respiratory illness history at the time of enrollment, and captures exacerbations in longitudinal follow-up assessment. Exacerbations were defined as acute respiratory symptoms that required the use of either antibiotics or systemic steroids, or by the need for hospitalization. Both of these studies demonstrated this point: that even one moderate or severe exacerbation can lead to a permanent decline in lung function. A UK population based study of approximately 100,000 patients with COPD, compared those experiencing one moderate acute exacerbation of COPD with those who had none. That study found a 21% increased risk of a future hospitalization for severe COPD exacerbation, after just one moderate exacerbation. These data were acquired through a UK Clinical Practice Research Datalink, which investigated a natural history of COPD exacerbations over ten years of follow-up, in patients with COPD. Moderate exacerbations were defined as those managed outside hospital, and severe are those requiring hospitalization.

Dr Caudle:
So, let's carry those considerations into our existing treatment strategies, Dr Anzueto. We know that COPD treatment currently uses a stepwise approach. But based on what you've been sharing, is a different approach needed?

Dr Anzueto:
Yes. I'm glad you brought this up, because this is really important. You recall the UPLIFT and COPDGene studies, I mentioned earlier. In patients with COPD, exacerbations of any severity, are associated with lung function decline with the greatest effect observed in patients with less severe disease. These are the patients who have the largest decline in lung function. This condition can also impact patients' quality of life. And expanding on what I mentioned before, the occurrence of a single moderate or severe exacerbation may almost double the rate of lung function decline. And yet, COPD treatment continues to be stepwise, despite the occurrence of exacerbations, with triple therapy – with inhaled corticosteroids, or ICS, long-acting muscarinic antagonists, or LAMA, and long-acting beta-2 agonists, or LABA therapy – being used late in disease progression. So this speaks to an ongoing treatment paradigm, where alternative approaches could be more appropriate to help prevent exacerbations.

Dr Caudle:
For those of you who are just tuning in, this is ReachMD, and I'm your host, Dr Jennifer Caudle, and here with me today, to review the burden of COPD exacerbations and the potential to prevent those exacerbations, is Dr Antonio Anzueto. So, Dr Anzueto, now that we've completed the review of the impact that COPD exacerbations can have, let's talk about the clinical data for Breztri Aerosphere, budesonide, glycopyrrolate, and formoterol fumarate, inhalation aerosol. What can you tell us about the supportive evidence for Breztri as a treatment option for COPD?

Dr Anzueto:
Breztri Aerosphere is approved for the maintenance treatment of COPD, and has been studied in patients with moderate to very severe COPD, with and without a history of moderate or severe exacerbations in the prior year. The clinical trial program from Breztri is very exciting because in one of these studies – KRONOS – the majority of patients – 74%, to be exact – did not have a history of moderate or severe exacerbations in the prior year. The data from KRONOS trial helped to characterize the effect of Breztri in a study where the majority of patients did not have history of moderate or severe exacerbations in the prior year.

Announcer:
We will now review Important Information for BREZTRI.

BREZTRI AEROSPHERE is indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease.

LIMITATIONS OF USE

Not indicated for the relief of acute bronchospasm or for the treatment of asthma.

SELECT SAFETY INFORMATION

BREZTRI is contraindicated in patients who have a hypersensitivity to budesonide, glycopyrrolate, formoterol fumarate, or product excipients.

BREZTRI is not indicated for treatment of asthma. Long-acting beta2-adrenergic agonist or (LABA) monotherapy for asthma is

associated with an increased risk of asthma-related death. These findings are considered a class effect of LABA monotherapy. When a LABA is used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone. Available data do not suggest an increased risk of death with use of LABA in patients with COPD.

Additional Important Safety Information will be provided at the end of this video.

Dr Anzueto:
Now, if we take a look at the clinical trial program for this treatment option, the U.S. Food and Drug Administration approved Breztri Aerosphere, based on the efficacy and safety data from two clinical trials, called ETHOS and KRONOS, which are respectively referred to as Study 1 and Study 2, in the prescribing information. ETHOS and KRONOS were both randomized, double-blind, multi-center, parallel-group studies. ETHOS was conducted over 52 weeks in a total of 8,588 patients, and KRONOS was conducted over 24 weeks in a total of 1,902 patients. Both studies were conducted in patients with moderate to very severe COPD. In addition to the difference in the study time, the trials also differed in enrollment criteria regarding exacerbations. Patients in ETHOS were required to have a history of one or more moderate or severe exacerbations in the prior year. Patients in KRONOS, by contrast, had no requirement for moderate or severe exacerbations in the prior year.

Dr Caudle:
And if we zero in on the ETHOS study, how were exacerbations defined, and what were the results regarding the rate of exacerbations?

Dr Anzueto:
Moderate exacerbations were defined as those leading to treatment with systemic corticosteroids and/or antibiotics, and severe exacerbations were defined as those resulting in hospitalization or death.

Over 52 weeks, Breztri demonstrated a statistically significant 24% reduction in the annual rate of moderate or severe exacerbations, versus LAMA/LABA therapy. The rate ratio was 0.76, and the P-value was less than 0.0001. Compared to ICS/LABA, there was a statistically significant 13% reduction. The rate ratio was 0.87, and the P-value was 0.0027. The model estimated annual rate of moderate or severe exacerbations was 1.08 for Breztri, 1.42 for LAMA/LABA, and 1.24 for ICS/LABA.

In addition, Breztri demonstrated a statistically significant, 20% reduction in severe exacerbations versus ICS/LABA. The rate ratio was 0.8 and the P-value was 0.02, which was based on the predefined, Type 1, error control plan. Breztri also reduced the rate of severe exacerbations versus LAMA/LABA therapy. However, this difference was not statistically significant. The rate ratio was 0.84, and a P-value of 0.09. The model estimated annual rate of severe exacerbation was 0.13 for Breztri, 0.15 for LAMA/LABA, and 0.16 for ICS/LABA.

Dr Caudle:
Okay. Thank you for that. Now switching over to the KRONOS study, Dr Anzueto, what can you tell us about those results?

Dr Anzueto:
In the KRONOS study, for the primary endpoints of forced expiratory volume in one second, area under the curve, from 0-4 hours, or FEV_1 AUC_{0-4}, and change from baseline in morning pre-dose trough FEV_1, Breztri demonstrated a significant improvement in FEV_1 AUC_{0-4} compared with ICS/LABA at week 24. The least square mean difference was 116 milliliters, and the P-value was less than 0.0001. And an improvement in mean change from baseline in morning pre-dose trough FEV_1, at week 24 compared with patients who received LAMA/LABA. The least square mean difference was 13 milliliters, and the P-value was 0.2375.

In addition, results from the secondary endpoint of the KRONOS study demonstrated a 52% reduction in the rate of moderate or severe exacerbations, compared with LAMA/LABA therapy. The rate ratio was 0.48 and the unadjusted P-value was less than 0.0001. Note this P-value is considered unadjusted due to nonsignificant results higher in the testing hierarchy. Breztri also reduced the rate of moderate or severe exacerbations compared with ICS/LABA, but these reductions were not significant. The rate ratio was 0.82 and the P-value was 0.2792. The model-estimated rate of moderate or severe COPD exacerbations per year ranged from 0.46 for Breztri, to 0.95 in the LAMA/LABA group. Now remember, this was the trial where 74% of the patients had no history of exacerbations in the prior year.

Dr Caudle:
Thanks for breaking down those findings for us, Dr Anzueto. Now that we've covered its efficacy, what can you tell us about the safety profile for Breztri?

Dr Anzueto:
In trials with more than 10,000 patients, Breztri had a sing - safety profile – let me start again.

Dr Anzueto:
In trials with more than 10,000 patients, Breztri had a safety profile comparable with LAMA/LABA and ICS/LABA. 2,783 patients with COPD received at least one dose of Breztri, 320/18/9.6 mcg. All adverse reactions for Breztri occurring at an incidence of 2% or greater in patients, and more common in Breztri compared with LAMA/LABA and ICS/LABA, in a 52-week trialwere upper respiratory tract infection – 5.7%, pneumonia – 4.6%, back pain – 3.1%, oral candidiasis – 3%, influenza – 2.9%, muscle spasms – 2.8%, urinary tract infection – 2.7%, cough – 2.7%, sinusitis – 2.6%, and diarrhea – 2.1%. In 24-week data from Study 2, adverse reactions that occurred in patients treated with BREZTRI 320/18/9.6 micrograms at an incidence of 2% or greater included dysphonia at 3.3% and muscle spasms also at 3.3% in addition to the adverse reactions that occur in ETHOS study.

Dr Caudle:
So Dr Anzueto, my last question for you today – uh, based on the data from the ETHOS and KRONOS studies that you've shared, what's your overall perspective on Breztri as a treatment choice for your patients?

Dr Anzueto:
Given this evidence, I plan to be more proactive in my treatment, in trying to prevent and protect against COPD exacerbations in my appropriate patients, thanks for these findings demonstrated by Breztri. Additionally, coming back to what we talked about before, I believe that a fundamental mentality shift, that even one COPD exacerbation is too many, can make a real positive impact on clinical practice. I'm excited about that development.

Dr Caudle:
Well, that brings us to the end of today's program, but before we close, I'd like to ask you to please stay tuned for additional important safety information, and I also want to thank my guest, Dr Antonio Anzueto, for helping us better understand the potential impact of COPD exacerbations and the clinical trial data for Breztri. Dr Anzueto, it was great speaking with you today.

Dr Anzueto:
Thank you for having me.

Dr Caudle:
Well, it was a pleasure. I'm Dr Jennifer Caudle, and now please take a moment to listen to the important safety information for Breztri.

Announcer:
IMPORTANT SAFETY INFORMATION

BREZTRI should not be initiated in patients with acutely deteriorating COPD, which may be a life-threatening condition

BREZTRI is NOT a rescue inhaler. Do NOT use to relieve acute symptoms; treat with an inhaled short-acting beta2-agonist

BREZTRI should not be used more often than recommended; at higher doses than recommended; or in combination with LABA-containing medicines, due to risk of overdose. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs

Oropharyngeal candidiasis has occurred in patients treated with orally inhaled drug products containing budesonide. Advise patients to rinse their mouths with water without swallowing after inhalation

Lower respiratory tract infections, including pneumonia, have been reported following ICS. Physicians should remain vigilant for the possible development of pneumonia in patients with COPD as the clinical features of pneumonia and exacerbations frequently overlap

Due to possible immunosuppression, potential worsening of infections could occur. Use with caution. A more serious or fatal course of chickenpox or measles can occur in susceptible patients

Particular care is needed for patients transferred from systemic corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients during and after transfer. Taper patients slowly from systemic corticosteroids if transferring to BREZTRI

Hypercorticism and adrenal suppression may occur with regular or very high dosage in susceptible individuals. If such changes occur, consider appropriate therapy

Caution should be exercised when considering the coadministration of BREZTRI with long-term ketoconazole and other known strong CYP3A4 Inhibitors. Adverse effects related to increased systemic exposure to budesonide may occur

If paradoxical bronchospasm occurs, discontinue BREZTRI immediately and institute alternative therapy

Anaphylaxis and other hypersensitivity reactions (eg, angioedema, urticaria or rash) have been reported. Discontinue and consider

alternative therapy

Use caution in patients with cardiovascular disorders, especially coronary insufficiency, as formoterol fumarate can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles

Decreases in bone mineral density have been observed with long-term administration of ICS. Assess initially and periodically thereafter in patients at high risk for decreased bone mineral content

Glaucoma and cataracts may occur with long-term use of ICS. Worsening of narrow-angle glaucoma may occur, so use with caution. Consider referral to an ophthalmologist in patients who develop ocular symptoms or use BREZTRI long term. Instruct patients to contact a healthcare provider immediately if symptoms occur

Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction. Instruct patients to contact a healthcare provider immediately if symptoms occur

Use caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis or unusually responsive to sympathomimetic amines

Be alert to hypokalemia or hyperglycemia

Most common adverse reactions in a 52-week trial (incidence ≥ 2%) were upper respiratory tract infection (5.7%), pneumonia (4.6%), back pain (3.1%), oral candidiasis (3.0%), influenza (2.9%), muscle spasms (2.8%), urinary tract infection (2.7%), cough (2.7%), sinusitis (2.6%), and diarrhea (2.1%). In a 24-week trial, adverse reactions (incidence ≥ 2%) were dysphonia (3.3%) and muscle spasms (3.3%)

BREZTRI should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors and tricyclic antidepressants, as these may potentiate the effect of formoterol fumarate on the cardiovascular system

BREZTRI should be administered with caution to patients being treated with:

- Strong cytochrome P450 3A4 inhibitors (may cause systemic corticosteroid effects)
- Adrenergic drugs (may potentiate effects of formoterol fumarate)
- Xanthine derivatives, steroids, or non-potassium sparing diuretics (may potentiate hypokalemia and/or ECG changes)
- Beta-blockers (may block bronchodilatory effects of beta-agonists and produce severe bronchospasm)
- Anticholinergic-containing drugs (may interact additively). Avoid use with BREZTRI

Use BREZTRI with caution in patients with hepatic impairment, as budesonide and formoterol fumarate systemic exposure may increase. Patients with severe hepatic disease should be closely monitored

For full Prescribing Information, including Patient Information, please go to www.breztrihcp.com.

Announcer:
This program was sponsored by AstraZeneca. If you missed any part of this discussion, and to learn more from other programs focusing on COPD exacerbations, visit ReachMD.com. This is ReachMD. Be part of the knowledge.