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In this issue…

The University at Buffalo School of Pharmacy and Pharmaceutical Sciences (UB SPPS) Drug Information Newsletter is dedicated to providing timely information relevant to healthcare practitioners in New York. The newsletter supplies information on clinical practice guidelines, medication safety issues, new drug approvals/medications under development, medication shortages, and drug class reviews.

Xofluza™ (baloxavir)

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In October 2018, the United States (US) Food and Drug Administration (FDA) approved Xofluza™ (baloxavir marboxil) for the treatment of acute uncomplicated influenza in patients ≥12 years of age who have been symptomatic for no more than 48 hours.[1,2] Baloxavir is a single-dose oral medication with a novel mechanism of action, and is intended to treat influenza types A and B, including strains resistant to currently available antiviral agents.[3] This agent is the first new antiviral influenza treatment approved by the FDA in nearly 20 years.[1]

Infection with the influenza virus causes a contagious respiratory condition commonly known as the flu.[1,4] When treatment is initiated within 48 hours of symptoms, antiviral drugs can reduce symptoms and shorten the duration of illness.[1] According to the Centers for Disease Control and Prevention (CDC), influenza in the US has caused 140,000 – 710,000 hospitalizations and 12,000 – 56,000 deaths annually since 2010.[5] Given these statistics, it is important to have other treatment options available to reduce symptoms once a person has contracted the virus.[1,6]

Baloxavir was granted priority review by the FDA, allowing for expedited approval since it is expected to improve the effectiveness and safety of treating uncomplicated influenza.[1] There is increasing concern regarding the resistance of influenza viruses to currently available antivirals (i.e., M2 ion-channel inhibitors and neuraminidase inhibitors).[6-8] Baloxavir is a novel, cap-dependent endonuclease inhibitor which prevents viral replication by inhibiting the initiation of messenger ribonucleic acid (mRNA) synthesis.[1,6,9,10] This is notable since its mechanism of action is different than previously available antivirals. Baloxavir has also shown significant antiviral activity against avian influenza strains and has demonstrated synergistic antiviral activity with neuraminidase inhibitors (i.e., oseltamivir, zanamivir).[11-14] Due to its recent FDA-approval, treatment guidelines for influenza have not yet addressed its place in therapy.

Clinical Trials

The efficacy and safety of baloxavir were assessed in one phase 2 and two phase 3 trials.[6,11,15] Hayden et al conducted the phase 2 trial, as well as 1 of the phase 3 trials in otherwise healthy patients with uncomplicated influenza.[6] The phase 2 trial was a double-blind, placebo-controlled, dose-ranging, randomized trial of single doses of baloxavir (10 mg, 20 mg, or 40 mg) or placebo. The trial enrolled adults 20 to 64 years of age with acute uncomplicated influenza in Japan. The phase 3 trial (CAPSTONE-1), performed after the phase 2 trial, was a multicenter, double-blind, placebo- and oseltamivir-controlled, randomized trial that enrolled patients 12 to 64 years of age with influenza-like illness in Japan and the US. The objective of the phase 2 and phase 3 trials was to evaluate the efficacy and safety of baloxavir. Patients 20 to 64 years of age were randomly assigned to receive a 5-day regimen consisting of a single dose of baloxavir (40 mg for patients weighing <80 kg or 80 mg for those weighing ≥80 kg), oseltamivir 75 mg twice daily for 5 days, or matching placebo. Patients 12 to 19 years of age were randomly assigned to receive either baloxavir or placebo (for 1 day only).

In both studies, patients had a fever (axillary temperature ≥38ºC), at least 1 systemic symptom, and at least 1 respiratory symptom of at least moderate severity.[6] The onset of symptoms was no more than 48 hours prior to starting treatment. Unlike the phase 3 trial, the phase 2 trial also utilized a positive rapid antigen test as an entry criterion. Both clinical trials focused on uncomplicated participants with mild to moderate symptoms, who were otherwise healthy. Pregnant women, patients weighing <40 kg, and those with illness resulting in hospitalization were excluded from the trials. The primary efficacy endpoint for both trials was the time to alleviation of influenza symptoms, which was defined as the time from the start of the trial regimen to the time when all 7 influenza-related symptoms (cough, sore throat, headache, nasal congestion, feverishness/chills, muscle/joint pain and fatigue) were rated by the patient as absent or mild for at least 21.5 hours. Selected secondary endpoints included time to resolution of fever, time to return to usual health, use of antibiotics as a result of new complications, and the occurrence of adverse events.

For both trials, patients in the placebo and treatment groups had similar baseline characteristics.[6] Both had a diagnosis of influenza confirmed by a fever ≥38ºC (axillary) in the pre-dose examination or >4 hours after dosing of antipyretics if they were taken, at least 1 general systemic symptom associated with influenza with a severity of moderate or greater (headache, feverishness/chills, muscle/joint pain, fatigue), and at least 1 respiratory symptom associated with influenza with a severity of moderate or greater (cough, sore throat, nasal congestion).

In the phase 2 trial, for the primary endpoint, patients who received baloxavir (n=100 for each dose) had significant reductions in time to alleviation of symptoms compared to patients who received placebo (n=100) (54.2 hours in the 10 mg group, 51.0 hours in the 20 mg group, and 49.5 hours in the 40 mg group vs. 77.7 hours in the placebo group; p=0.009, p=0.02, and p=0.005, respectively) and in time to resolution of fever (28.9 – 33.4 hours vs. 45.3 hours, respectively; p≤0.0001).[6] In the phase 3 trial (CAPSTONE-1), the time to alleviation of symptoms was significantly shorter in the baloxavir group compared with placebo (53.7 hours vs. 80.2 hours, respectively; p<0.001), but similar to the oseltamivir group (53.5 hours vs. 53.8 hours, respectively [p-value not reported]). The median time to resolution of fever was shorter with baloxavir vs. placebo (24.5 hours vs. 42 hours; p<0.001). Both the phase 2 and 3 studies reported similar rates of adverse events between

the baloxavir and placebo groups; however, adverse events were more common in the oseltamivir vs. baloxavir group (8.4% vs. 4.4%, respectively; p=0.009). Based on the results, the authors concluded that baloxavir was safe, non-inferior to oseltamivir, and superior to placebo for the primary endpoint (time to alleviation of influenza symptoms).

In addition to uncomplicated influenza, baloxavir was studied in high risk patients in another phase 3 trial.[11,15] CAPSTONE-2 was an international, randomized, double-blind, placebo- and oseltamivir-controlled study. The objective of the study was to assess the safety and efficacy of baloxavir in patients at high risk for complications from influenza. Given that the study has only been published in abstract form thus far, there is limited information regarding the details of the study. Inclusion criteria included age ≥12 years, fever, influenza symptoms with a duration ≤48 hours, and the presence of at least 1 high risk factor (based on CDC criteria). Patients were randomized in a 1:1:1 ratio to a single dose of baloxavir 40 mg or 80 mg (based on patient's weight), oseltamivir 75 mg twice daily for 5 days, or placebo. The primary endpoint was time to improvement of influenza symptoms. Secondary endpoints included detection of virus in serial nasopharyngeal swabs, use of prescription antibiotics, and complications related to influenza.

A total of 2184 patients were randomized to treatment.[11,15] Asthma or chronic lung disease (39.2%) and age ≥65 years (27.4%) were the most common risk factors for development of influenza. For the primary outcome, the time to alleviation of symptoms was significantly shorter in the baloxavir vs. placebo groups (73.2 hours vs. 102.3 hours, respectively; p<0.0001); for comparison of baloxavir to oseltamivir, the results were not statistically significant (73.2 hours vs. 81.0 hours, respectively; p=0.8347). When examining patients with influenza A/H3N2, the time to alleviation of symptoms was significantly shorter in the baloxavir vs. placebo groups (75.4 hours vs. 100.4 hours, respectively; p<0.0141) (results not reported for comparison to oseltamivir). For patients with influenza B, the time to alleviation of symptoms was significantly shorter when baloxavir was compared to placebo (74.6 hours vs. 100.6 hours, respectively; p<0.0138) or oseltamivir (74.6 hours vs. 101.6 hours, respectively; p<0.0251).

In terms of secondary endpoints, the time for viral shedding to stop was significantly shorter in baloxavir-treated patients (48 hours) compared to oseltamivir- and placebo-treated patients (96 hours) (p-value not reported).[11,15] The baloxavir group also had significantly less systemic antibiotic use and influenza-related complications (3.4% and 2.8%, respectively) than placebo (7.5% and 10.4%, respectively; p=0.0112 and p<0.0001). The occurrence of adverse or serious adverse events was similar across treatment groups. The authors concluded that baloxavir was superior to oseltamivir in reducing viral replication duration and in resolving influenza B illness, and compared to placebo, baloxavir was associated with a more rapid recovery and reduced risk of complications in high-risk patients with influenza. Baloxavir was also well-tolerated with similar rates of adverse events in each of the treatment groups.

Dosing

Baloxavir is dosed orally by weight.[2,9] Patients weighing at least 40 kg but <80 kg require a single 40 mg dose; patients weighing ≥80 kg require a single 80 mg dose. Baloxavir can be taken without regard to meals; however, co-administration of baloxavir with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids, or oral supplements (calcium, iron, magnesium or zinc) should be avoided.[2] Cation-containing products may decrease plasma concentrations of baloxavir leading to decreased efficacy. Unlike oseltamivir (Tamiflu®), which is taken twice daily for 5 days, baloxavir is administered as a single dose.[16] The simplified single oral dose may be an attractive option for patients who are unlikely to adhere to a 5-day course of therapy with oseltamivir. This could also be particularly useful in pandemics, where delivery of a single dose has both practical and logistical advantages.[1,9]

Warnings and Precautions

Baloxavir has a warning regarding the potential risk for secondary bacterial infections.[2] Bacterial infections may present with influenza-like symptoms, may be present in addition to influenza, or be a complication of influenza. Baloxavir has not been proven to prevent these complications or to have efficacy in treating any illness caused by pathogens other than the influenza virus.

Contraindications

Baloxavir is contraindicated in patients with a history of hypersensitivity to baloxavir or any of its components.[2]

Adverse Reactions

In clinical trials, adverse events with baloxavir occurred in at least 1% of adult and adolescent patients; the most common included diarrhea (3%), bronchitis (2.6%), nasopharyngitis (1%), headache (1%), and nausea (1%).[2]

Special Populations

Baloxavir is only approved for patients aged ≥12 years, whereas oseltamivir can be used in children as young as 2 weeks of age.[2,16] Oseltamivir is also approved for pregnant women.[17] Both baloxavir and oseltamivir are approved only for uncomplicated influenza.[1,2,16] It is not known if baloxavir is safe and effective in children <12 years of age or those weighing less than 88 pounds (40 kg).[1,6,9]

Drug Interactions

Baloxavir may inhibit viral replication of the intranasal live attenuated influenza vaccine, however co-administration has not been evaluated.[2] Concurrent use of baloxavir with polyvalent cation-containing laxatives, antacids and oral supplements (e.g., calcium, iron, magnesium or zinc) should be avoided, as cation-containing products may decrease plasma concentrations of baloxavir, thus decreasing baloxavir efficacy.

How Much Will It Cost?

According to Micromedex Redbook®, the wholesale acquisition cost (WAC) of baloxavir is $150.[18] Genentech is providing coupons to reduce the out-of-pocket cost of the drug.[9,19] The coupon could reduce a patient's copay to as little as $30, if health insurance covers the drug; or $90 without insurance.[19] Compared to baloxavir, the WAC of a package of oseltamivir is similar, ranging from $139 - $152 (depending on the dosage formulation and strength).

Is the Flu Shot Still Necessary?

There are several FDA-approved medications used to treat influenza once it occurs, however they are not a substitute for yearly vaccination which helps prevent the occurrence of influenza.[1,20] The seasonal vaccine is 1 of the most effective and safest ways to protect patients from the influenza virus. The CDC recommends that everyone ≥6 months of age receive a yearly influenza vaccination during the flu season.[21]

Summary

Baloxavir is an oral, single-dose treatment approved by the FDA for treatment of uncomplicated influenza in patients ≥12 years of age.[2] It provides an additional treatment option in light of increasing resistance to previously approved influenza treatments.[6,15] In clinical trials, baloxavir was shown to be non-inferior to

oseltamivir and superior to placebo for the treatment of uncomplicated influenza with a well-tolerated safety profile. Currently, baloxavir is not included in the most updated influenza treatment guidelines from the Infectious Diseases Society of America (IDSA).[22] The IDSA finalized the guidelines prior to FDA-approval of baloxavir in October 2018; therefore, it does not address use of baloxavir. Although the CDC recommends use of baloxavir in patients ≥12 years of age, it recommends against its use in pregnant or breastfeeding females, complicated influenza, and hospitalized patients due to lack of data in these groups.[23]

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Lowering Low-Density Lipoprotein Cholesterol: How Low is Too Low?

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Despite effective treatment modalities, elevated cholesterol remains a significant public health issue in the United States (US). Over a third of US adults have low-density lipoprotein (LDL) levels or health conditions that warrant treatment.[1] Total cholesterol epidemiology reveals a similar issue, with 95 million US adults aged 20 years or over having elevated levels.[2] Unfortunately, over 40% of those who are appropriate candidates for cholesterol treatment are not receiving it.[1] As a major risk factor for heart disease and stroke, elevated cholesterol is a major cause of death and disease burden in the US and worldwide.[3] In recent years, there has been debate concerning overall treatment goals for LDL levels. Specifically, the question has been posed: How low is too low?

The most recent cholesterol treatment guidelines from the American Heart Association and American College of Cardiology (AHA/ACC) only briefly mention the issue.[4] In the 2018 update to these guidelines, the recommendations for cholesterol treatment do not indicate a minimum LDL level. Most of the recommendations involve using a specific strength of statin therapy to achieve a certain percentage of LDL reduction. The strength of statin recommended (and thus the percentage in LDL reduction) is based on the perceived atherosclerotic cardiovascular disease (ASCVD) risk of the patient in question. The only treatment group for whom the AHA/ACC recommends a specific LDL level goal are patients with clinical ASCVD who are considered very high risk for another event; the recommended goal is <70 mg/dL. Even for this group, there is no specific mention of a minimum LDL level. Notably, the only comment on extremely low LDL levels comes within the recommendation for adding a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor to statin therapy in high risk ASCVD patients. In this setting, the guidelines state that clinical judgment on de-intensification of therapy should be used in circumstances where a patient has 2 consecutive LDL levels of <25 mg/dL. The rationale for this statement is that the long-term safety of extremely low LDL levels is currently unknown.

The cholesterol treatment guidelines from the European Society of Cardiology only briefly mention extremely low LDL levels, stating that there is currently no LDL level below which benefit ceases or harm occurs.[5] Notably, the most current (2018) dyslipidemia guidelines from the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) state that current evidence suggests there is no threshold below which LDL level lowering ceases to be effective.[6] Thus, these guidelines recommend an LDL treatment goal of <55 mg/dL for patients who are categorized as “extreme risk” for ASCVD. While this is the lowest recommendation for any group in any set of guidelines reviewed, the AACE/ACE guidelines still do not address LDL levels below that level.

In addition to the guidelines, there are some published studies that attempt to address extremely low LDL levels. A recent meta-analysis by Sabatine et al., published just prior to the updated AHA/ACC cholesterol guidelines, provides insight into further lowering of LDL levels in patients who present with already-low levels.[7] This meta-analysis examined data from the Cholesterol Treatment Trialists Collaboration (CTTC) and other trials that included published data on the treatment of cholesterol levels in patients who started the study with low LDL levels (70 mg/dL or less). For studies to be included in the meta-analysis, they also needed to be randomized, double-blind, controlled cardiovascular outcome trials. The CTTC was included specifically for data on statin monotherapy, whereas other trials were examined for their data on the addition of a second LDL-lowering agent to a statin. Specifically, 3 additional studies of the following treatments were included in the meta-analysis: ezetimibe (cholesterol absorption blocker) plus a statin, evolocumab (PCSK9-inhibitor) plus a statin, and anacetrapib (a cholesteryl ester transfer protein inhibitor, development abandoned by Merck in 2017) plus a statin.

For the meta-analysis, the CTTC primary outcome of major vascular events, comprised of coronary heart death, myocardial infarction, ischemic stroke, or coronary revascularization, was used to calculate a risk ratio (RR) between treatment arms. In the CTTC, a reduction of cholesterol by 1 mmol/L (38.7 mg/dL) resulted in a statistically significant reduction in major vascular events (RR 0.78, 95% confidence interval (CI) 0.65-0.94) in the subgroup of patients who presented with low LDL at the beginning of the study (average starting LDL of 65.7 mg/dL in the subgroup). For the 3 studies examining a non-statin therapy added to a statin, the control arms examined patients with similarly low LDL levels at the outset: median 70 mg/dL in the ezetimibe trial, median 66 mg/dL in the evolocumab trial, and median 63 mg/dL in the anacetrapib trial. Analyses of these 3 studies also revealed a statistically significant reduction in major vascular events for every 1 mmol/L reduction in LDL-cholesterol (LDL-C) (RR 0.79, 95% CI 0.70-0.88) in the subset of patients who presented with already-low LDL levels. In terms of safety, the meta-analysis found no statistically significant increases in the incidences of any adverse events (myalgias/myopathy, aminotransferase elevation, new-onset diabetes, hemorrhagic stroke, or cancer) with the lowering of already-low LDL levels, either in the trials individually or when the trials were meta-analyzed. Despite the consistency of the results, the authors noted that the meta-analysis was somewhat limited by the small number of clinical trials (n=4) that were included. Nonetheless, the authors concluded that further lowering of LDL levels continued to provide benefit, with no offsetting adverse events. Based on their findings, they recommended a potential LDL treatment target as low as 20 mg/dL to further reduce cardiovascular risk.

In the same journal issue, an editorial was published that discusses the meta-analysis by Sabatine et al.[8] This editorial sheds further light on the topic by analyzing the meta-analysis in relation to other clinical trial data. Namely, the editorial notes the lack of any increase in adverse outcomes with further lowering of LDL-C levels in the studies that have been completed so far, including the CTTC trial, the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS), the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, the Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trial, and the Long-term Safety and Tolerability of Alirocumab in High Cardiovascular Risk Patients with Hypercholesterolemia Not Adequately Controlled with Their Lipid Modifying Therapy (ODYSSEY) trial. Despite the lack of increased adverse outcomes observed thus far, it is noted that more time may be needed to assess the potential for long-term effects. This editorial also did not discuss all of the pertinent research available; a post hoc analysis of the JUPITER trial data revealed statistically significant increases in type 2 diabetes, hematuria, and certain musculoskeletal, hepatobiliary, and psychiatric adverse effects.[9] These were identified in the group of subjects with LDL-C levels <30mg/dL. Furthermore, treating patients to extremely low LDL levels is still a relatively new concept that has arisen due to the low levels that can occur with a PCSK9 inhibitor. Thus, as more patients reach extremely low LDL levels over time, there will be a larger population to examine for possible new adverse reactions (or beneficial effects).

In the FOURIER trial, which examined the addition of evolocumab to statin therapy, the median duration of follow-up was 2.2 years.[10] Of note, this trial showed a lowering of LDL levels to a median of just 30 mg/dL in

the treatment group. In the ODYSSEY trial, which studied the use of alirocumab with statin therapy, the median duration of follow-up was 2.8 years.[11] In this trial, alirocumab was switched to placebo in patients who had LDL levels drop below 15 mg/dL. This was done solely due to the lack of historical data in the literature on patients with LDL levels that low; there were no increased adverse effects found in this group. Neither of these trials addressed the length of time extremely-low LDL levels were maintained in these patients. Without any clear indication in the current guidelines regarding discontinuation of PCSK9 inhibitor therapy, it can reasonably be assumed that most patients will remain on therapy far longer than 2-3 years. Thus, new adverse reactions may yet be seen. Still, in the meantime, the lack of current safety issues led the author of the editorial to recommend changes to the 2013 AHA/ACC guidelines. Specifically, the author called for more concrete targets or thresholds to provide guidance to physicians on the safety of very low LDL levels. With the new 2018 guidelines at least mentioning extremely-low LDL levels, it is apparent that these recent data and recommendations are starting to be incorporated.

Robinson et al evaluated the safety of alirocumab in a pooled analysis of 14 randomized, controlled clinical trials of the PCSK9 inhibitor, alirocumab.[12] Notably, this pooled analysis is referenced in the 2018 AHA/ACC guidelines.[4] This analysis examined the trials of alirocumab for the incidence and safety implications of LDL-C levels falling below 25 mg/dL and 15 mg/dL.[12] Out of a total 5234 patients across the studies, 839 (25.1%) achieved an LDL-C less than 25 mg/dL and 314 patients (9.4%) achieved levels less than 15 mg/dL. The median duration of exposure to LDL levels less than 25 mg/dL was 43.3 weeks. Importantly, the pooled analysis stated that none of the included studies allowed dose decreases of alirocumab, regardless of LDL level. Discontinuation rates were also similar across the studies between patients who reached very low LDL levels and those who did not. The overall incidence of treatment-related adverse events was similar across LDL level groups (76.6% for LDL-C ≥25 mg/dL, 72.7% for LDL-C <25 mg/dL, 71.7% for LDL-C <15 mg/dL). In a propensity analysis of the risk of treatment-related adverse events, it was found that patients with LDL-C levels <25 mg/dL actually had significantly lower incidences of certain adverse events when compared to patients with LDL-C ≥25 mg/dL, including neurological events (hazard ratio (HR) 0.53, 95% CI 0.30-0.93) and musculoskeletal events (HR 0.75, 95% CI 0.59-0.97). The differences in incidences of neurocognitive effects, diabetes-related effects, and hepatic effects were not statistically significantly different between groups. The only adverse event that was found to be significantly higher in the group with LDL-C <25 mg/dL was cataracts (HR 3.4, 95% CI 1.58-7.35). The authors did note some limitations to their analysis, including the possibility of confounding variables that predispose patients to lower LDL levels, which may not be controlled by randomization. Furthermore, the authors noted the relatively short durations of treatment that were utilized in the trials. Despite these and other limitations, however, the authors concluded that low levels of LDL-C are generally well tolerated, and that increased cataract incidence may be due to confounding variables.

Current cholesterol treatment guidelines by the ACC/AHA and AACE/ACE assert that low LDL-C values are ideal, especially for primary and secondary prevention of ASCVD.[4,6] With the recent advent of the PCSK9 inhibitors, it is becoming more common for patients to achieve extremely low LDL levels. The 2018 ACC/AHA guidelines recommend the addition of PCSK9 inhibitor therapy for high-risk ASCVD patients who cannot reach their cholesterol goals with the combination of a statin and ezetimibe. Thus, over time, the proportion of the population using a PCSK9 inhibitor will likely increase. Current guidelines do not address a minimum value for LDL-C, and current literature is limited. More research is needed in order to determine possible long-term effects. This additional research should focus on extending the length of time that patients are exposed to very low LDL-C levels in order to build upon what is already known. Investigators should also look into the possibility that the type of drug that causes the very low LDL levels (i.e., statins versus PCSK9 inhibitors) may have an impact on whether or not there are any adverse effects.

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Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors – Safety Update

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Background

Sodium-glucose cotransporter-2 (SGLT2) inhibitors are medications approved by the Food and Drug Administration (FDA) as adjuncts to diet and exercise to improve glucose control in patients with type 2 diabetes mellitus.[1-5] Currently, the American Diabetes Association (ADA), the American Association of Clinical Endocrinologists (AACE), and the American College of Endocrinology (ACE) include SGLT2 inhibitors as an option in place of or in addition to metformin for initial treatment of type 2 diabetes, based on patient-specific factors.[6,7] Medications in this class include canagliflozin (Invokana®), dapagliflozin (Farxiga®), empagliflozin (Jardiance®), and ertugliflozin (Steglatro®).[2-5] By inhibiting SGLT2, located in the proximal renal tubule, these agents decrease reabsorption of glucose, resulting in lower plasma glucose levels and lower glycosylated hemoglobin (A1c) levels.[8]

On August 29, 2018, the FDA posted a safety alert for prescribers that “cases of a rare but serious infection of the genitals and area around the genitals” have been reported with the SGLT2 inhibitors class of medications.[1] This infection is called necrotizing fasciitis of the perineum; it is also referred to as “Fournier’s gangrene.” Since then, a warning has been added to the labels of all SGLT2 inhibitors as well as to the patient Medication Guides.[2-5]

Fournier's gangrene is rare, but those with diabetes and long term alcohol abuse have an increased risk.[9] The condition is more likely to affect men, but it can also be seen in women and children. Fournier's gangrene is concerning because it can develop suddenly and can result in organ failure and death.

Safety Update

The FDA stated there have been 12 cases of Fournier's gangrene in patients taking an SGLT2 inhibitor reported via the FDA Adverse Event Reporting System (FAERS) or published between March 2013 and May 2018.[10] Among the patients, 7 were male and 5 were female. The infection typically occurred after patients were on the medication for several months, and all cases required hospitalization and surgery. One patient died as a result of Fournier's gangrene; some patients needed multiple surgical procedures; and some had complications. The FDA stated that "only six cases of Fournier's gangrene (all in men) were identified in review of other antidiabetic drug classes over a period of more than 30 years."

Implications in Pharmacy Practice

The FDA's safety alert should be considered along with the benefits and other risks of SGLT2 inhibitors when prescribing and in patients who are currently using these medications. Patients should be counseled on the reported risk of Fournier's gangrene and instructed to immediately report symptoms: "any symptoms of tenderness, redness, or swelling of the genitals or the area from the genitals back to the rectum, and have a fever above 100.4 F or a general feeling of being unwell."[10] If it is thought that a patient may have Fournier's gangrene, practitioners should stop the SGLT2 inhibitor, initiate broad-spectrum antibiotics, and consider surgical debridement as necessary. An alternative anti-hyperglycemic medication should be added, and blood glucose levels should be monitored closely.

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Clinical Update on the Global Initiative for Chronic Obstructive Lung Disease (GOLD): the 2019 Report on a Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease

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Background

As defined by the Centers for Disease Control and Prevention (CDC), chronic obstructive pulmonary disease (COPD) is a lung disease characterized by coughing, shortness of breath, wheezing and excessive phlegm, which can lead to a limited quality of life.[1] COPD is both a preventable and treatable disease state. The CDC reports that a staggering 16 million Americans are diagnosed with COPD. However, many more have COPD but are not diagnosed or receiving treatment. Smoking is the most common cause of COPD but pollution and respiratory infections can also put someone at risk to develop this potentially debilitating disease. Mortality secondary to COPD continues to be an issue in the United States (US).[2] COPD was the fourth leading cause of death in the US in 2017. Since 1999, COPD mortality rates have significantly declined for men in the US but not for women.[3] COPD exacerbations can lead to hospitalization, which not only leads to a decreased quality of life but can also have economic consequences on the healthcare system.[4]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) program began in 1998 with the purpose of developing evidence-based recommendations for the management of COPD.[5] The GOLD Report is intended to guide healthcare providers to focus on both short- and long-term implications of COPD. Throughout the years, the GOLD Science Committee has continued to update their recommendations on a regular basis based on new published research. The last major revision of the GOLD Report was published in 2017. The 2019 report is the most recent update and includes the addition of key research publications from January 2017 to July 2018. There are changes and additions to several sections of the report but this review focuses on revised algorithms for initiation and follow-up management of pharmacologic treatment for COPD.

Pharmacologic Therapy for Stable COPD

Medications are used in the treatment of stable COPD to reduce symptoms, decrease exacerbation risk, and improve exercise tolerance and health status.[5] Medication classes used for maintenance therapy in COPD include short-acting beta$_2$ agonists (SABAs), long-acting beta$_2$ agonists (LABAs), short-acting muscarinic antagonists (SAMAs), long-acting muscarinic antagonists (LAMAs), SABA/SAMA combination medications, LABA/LAMA combination medications, combination LABA with an inhaled corticosteroid (ICS), combination LABA/LAMA/ICS medications, methylxanthines, mucolytic agents and phosphodiesterase-4 (PDE-4) inhibitors. See Table 1 for currently available medications within each class. Most of these medication classes are provided in formulations for inhalation and the patient must be able to use proper technique to effectively use the medication. Before modifying therapy, providers should ensure the patient is using proper technique. Choosing a class depends on patient preference, response, and availability of the medication, taking into consideration which medications within a class are covered by insurance. Of note, new generic formulations of Advair Diskus® and AirDuo RespiClick®, both LABA/ICS (fluticasone/salmeterol) inhaler products, are now available.

Table 1. COPD maintenance medications by class.[5]

Class	Medications				
SABA	Fenoterol	Levalbuterol	Salbutamol (albuterol)	Terbutaline	
LABA	Arformoterol	Formoterol	Indacaterol	Olodaterol	Salmeterol

Class	Medications				
SAMA	Ipratropium bromide	Oxitropium bromide			
LAMA	Aclidinium bromide	Glycopyrronium bromide	Tiotropium	Umeclidinium	
SABA/SAMA	Fenoterol/ ipratropium	Salbutamol/ ipratropium			
LABA/LAMA	Formoterol/ aclidinium	Formoterol/ glycopyrronium	Indacaterol/ glycopyrronium	Vilanterol/ umeclidinium	Olodaterol/ tiotropium
LABA/ICS	Formoterol/ beclomethasone	Formoterol/ budesonide	Formoterol/ mometasone	Salmeterol/ fluticasone	Vilanterol/ fluticasone furoate
LABA/LAMA/ICS	Fluticasone/ umeclidinium/ vilanterol	Beclomethasone/ formoterol/ glycopyrronium			
Methylxanthines	Aminophylline	Theophylline (SR)			
Mucolytics	Erdosteine				
PDE-4 Inhibitors	Roflumilast				

ICS=inhaled corticosteroid; LABA=long-acting beta$_2$ agonist; LAMA=long-acting muscarinic antagonist; PDE-4=phosphodiesterase-4; SABA=short-acting beta$_2$ agonist; SAMA=short-acting muscarinic antagonist; SR=sustained-release

When choosing a bronchodilator, inhaled therapy is preferred over oral, and LABAs and LAMAs are preferred over SABAs and SAMAs.[5] SABAs and SAMAs are only preferred over LABAs and LAMAs when a patient experiences occasional dyspnea and when a patient is already on long-acting therapy and requires immediate relief in addition to their maintenance therapy. Either a single or dual long-acting bronchodilator may be initiated for COPD; if a single agent is started and the patient continues to experience dyspnea regularly, the patient should initiate dual therapy. Theophylline, a methylxanthine, is only recommended when long-term treatment bronchodilators are not available.

When choosing anti-inflammatory agents for COPD maintenance therapy, ICS and oral corticosteroid medications are not recommended for long-term monotherapy.[5] ICS can be used as long-term treatment in combination with LABA agents in patients who are treated with long-acting bronchodilators but continue to have exacerbations. A PDE-4 inhibitor, such as roflumilast, may be appropriate in a patient who continues to have exacerbations while treated with combination LABA/ICS or LABA/LAMA/ICS, or who has chronic bronchitis and severe or very severe airflow obstruction. Additionally, macrolide antibiotics, particularly azithromycin, should be considered in patients who are former smokers and continue to have exacerbations. Statins are not recommended to prevent exacerbations, but antioxidant mucolytics may be appropriate in select patients.

Initiation of Pharmacologic Treatment

The 2019 GOLD Report notes that the initiation of pharmacological agents in patients with newly diagnosed COPD lacks high-quality evidence.[5] When initiating pharmacological therapy, agents are chosen based on the ABCD Assessment, which takes into consideration the number of exacerbations, COPD Assessment Test (CAT) score, and the modified Medical Research Council dyspnea questionnaire (mMRC). A group A classification is the least severe (0-1 exacerbations, not leading to hospital admission; mMRC 0-1; CAT <10) and group D is the most severe (≥2 moderate exacerbations or ≥1 leading to hospitalization; mMRC ≥2; CAT ≥10). In addition to

these criteria, the revised algorithms for both initiation and modification of treatment in the 2019 report incorporate the use of peripheral blood eosinophil counts to guide the use of ICS medications in preventing exacerbations. The blood eosinophil count is a biomarker that may help determine which patients will benefit from ICS therapy. When blood eosinophil counts are low (<100 cells/µL), ICS have little to no effect on future exacerbations and should therefore not be used in these patients. As the eosinophil count increases, an ICS has a larger effect. At >300 cells/µL, COPD patients have the greatest probability of decreased exacerbations with ICS therapy.

Results of a study published in 2018 contributed to the evidence supporting the use of blood eosinophil count in the revised treatment algorithms.[6] Bafadhel et al aimed to determine which characteristics affect exacerbation rate and response to ICS in patients with COPD. The study was a post-hoc analysis of pooled data from 3 randomized, double-blind, double-dummy, parallel-group, multicenter trials of budesonide-formoterol in patients with COPD. The study population consisted of patients with COPD who were at least 40 years of age, current or former smokers, with airflow obstruction, a history of exacerbation, and documented blood eosinophil counts. Exclusion criteria included history of asthma or allergic rhinitis. The primary outcome was annual exacerbation rate adjusted for treatment, study allocation and exposure time. Negative binominal regression analysis was used for the primary analyses which compared budesonide-formoterol 160-4.5 µg to formoterol 4.5 µg. Exacerbations were defined as a worsening of COPD that resulted in treatment with an oral corticosteroid or a hospital admission. A total of 4,528 patients were included in the pooled analyses. A continuous spline modelling analysis demonstrated eosinophil count was directly related to exacerbation rate reduction with budesonide-formoterol compared to formoterol ($p_{interaction}$=0.015). A significant benefit was demonstrated at an eosinophil count of at least 100 cells/µL (rate ratio 0.75, 95% confidence interval [CI] 0.57–0.99) and up to over 340 cells/µL (rate ratio 0.50, 95% CI 0.38-0.66), suggesting a LABA/ICS treatment benefit in reducing future exacerbations.

Patients classified in group A should initially be treated with a bronchodilator, group B with a LABA or LAMA, group C with a LAMA, and group D with a LAMA or LAMA/LABA (if CAT >20) or LABA/ICS (if blood eosinophil count ≥300 cells/µL).[5] Once a patient is initiated on pharmacologic therapy, the patient should be monitored to determine if they are reaching their treatment goals. When monitoring a COPD patient, a review-assess-adjust management cycle should be followed: review symptoms of dyspnea and exacerbations; assess inhaler technique and adherence; adjust by escalating therapy, switching devices or medications, or de-escalating therapy.

Follow-Up Pharmacologic Treatment

The 2019 GOLD Report presents a new algorithm that is recommended when following up with patients to determine if their initial therapy is appropriate.[5] Throughout follow-up, management of symptoms and exacerbations continues, but treatment recommendations are not dependent on the ABCD classification at diagnosis. Recommendations are designed to help manage patients who are on maintenance therapy soon after therapy is initiated or years later. If initial therapy is adequately controlling symptoms, it should be continued along with follow-up. If therapy is not appropriate, determination should be made if the patient needs a treatment focused on dyspnea or exacerbations. There is a treatment algorithm for each. If a patient is experiencing both exacerbations and dyspnea, the exacerbations algorithm should be followed. The patient may need to escalate or de-escalate therapy based on the algorithm.

There are several options for changing a patient's maintenance therapy when experiencing dyspnea.[5] If a patient is experiencing uncontrolled dyspnea while on a LABA or LAMA, use of a combination LABA/LAMA is recommended. If dyspnea does not improve, the patient may de-escalate to monotherapy or switch device and/or medication. If a patient is experiencing dyspnea while using combination LABA/ICS, a LAMA may be added to current therapy or the patient may be switched to a LABA/LAMA if the initiation of the ICS was inappropriate to begin with, the patient does not respond to the ICS, or if there are significant side effects. Throughout management of dyspnea it is important to verify proper inhaler technique and adherence.

Maintenance therapy can also be adjusted when a patient is experiencing exacerbations.[5] If a patient is treated with a LABA or LAMA and continues to experience exacerbations, their therapy may be escalated to a LABA/LAMA or a LABA/ICS. If the patient has a history of asthma or symptoms suggestive of asthma, a LABA/ICS is preferred. Using the blood eosinophil biomarker can help in identifying patients who would benefit from ICS therapy. Patients with a blood eosinophil count of at least 300 cells/µL, and 1 exacerbation yearly may be initiated on the LABA/ICS combination. Patients with a blood eosinophil count of at least 100 cells/µL, and at least 2 moderate exacerbations or 1 severe hospitalized exacerbation yearly may also be initiated on a LABA/ICS combination.

Two options are recommended for patients on a LABA/LAMA combination who continue to have exacerbations.[5] Patients can be escalated to a LABA/LAMA/ICS combination medication if they have a blood eosinophil count of at least 100 cells/µL. If the blood eosinophil count is less than 100 cells/µL, roflumilast or azithromycin may be added. Patients who are on LABA/ICS and continue to have exacerbations may have a LAMA added to their treatment or switch to a LABA/LAMA if they are not responding to the ICS or are having significant side effects due to the ICS. Lastly, if a patient is on LABA/LAMA/ICS combination therapy and continues to experience exacerbations, roflumilast or a macrolide can be added, or the ICS can be discontinued. Roflumilast can be added for patients with a predicted forced expiratory volume in one second (FEV_1) <50% and chronic bronchitis. Azithromycin is the macrolide with the most evidence, especially in smokers.

The recommendation for escalation to triple therapy for patients currently receiving inadequate treatment with a LABA/LAMA or LABA/ICS is supported by results of another recent study published in 2018. Lipson et al evaluated the benefits of using triple LABA/LAMA/ICS therapy compared to LABA/ICS or LABA/LAMA therapy in patients with COPD.[7] The study was a phase 3, randomized, double-blind, parallel-group, multicenter trial that included patients who were at least 40 years of age, had a CAT score of at least 10, an FEV_1 <50% and a history of at least 1 moderate-to-severe exacerbation, or an FEV_1 of 50-80% and at least 2 moderate exacerbations or 1 severe exacerbation in the previous year. The primary objective was to evaluate the effects of 52 weeks of once-daily triple therapy with fluticasone furoate 100 µg (an ICS), umeclidinium 62.5 µg (a LAMA), and vilanterol 25 µg (a LABA) compared to dual therapy with either fluticasone furoate-vilanterol 100-25 µg (LABA/ICS) or umeclidinium-vilanterol 62.5-25 µg (LABA/LAMA) on the rate of moderate-to-severe COPD exacerbations. The primary outcome was annual exacerbation rate during treatment. A total of 10,355 patients were included in the intention-to-treat analysis which determined that there was a significant decrease in moderate-to-severe COPD exacerbations in the LABA/LAMA/ICS treatment group compared to the LABA/ICS group (rate ratio with triple therapy, 0.85; 95% CI, 0.80 to 0.90; P<0.001) and the LABA/LAMA group (rate ratio with triple therapy, 0.75; 95% CI, 0.70 to 0.81; P<0.001). Patients who were treated with LABA/LAMA/ICS had a severe exacerbation rate of 0.13 compared to 0.15 in the LABA/ICS group (rate ratio with triple therapy, 0.87; 95% CI, 0.76 to 1.01; P=0.06) and 0.19 in the LABA/LAMA group (rate ratio with triple therapy, 0.66; 95% CI, 0.56 to 0.78; P<0.001), indicating a significantly lower rate of severe exacerbations with triple therapy compared to LABA/LAMA but not LABA/ICS.

Summary

The 2019 GOLD guidelines include new updates on initial treatment of COPD as well as maintenance treatment upon follow-up.[5] Initial pharmacologic treatment should be based on the GOLD ABCD assessment tool. Follow-up of maintenance therapy should be reflective of the new treatment algorithm which focuses on whether a patient is experiencing dyspnea, exacerbations, or a combination of both. The use of blood eosinophil count as a biomarker to determine the appropriateness of ICS use in COPD patients is a new update that allows healthcare providers to make decisions that will potentially benefit the COPD patient without adding unnecessary therapy that can lead to decreased adherence or additional side effects. Despite our understanding of COPD disease progression and availability of a range of treatment options, COPD exacerbations continue to be an issue. Therefore, regular updates to the GOLD guidelines will continue to be essential in order to better manage this disease and improve patient outcomes.

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