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A Comparison of Mipomersen (Kynamro®) and Lomitapide (Juxtapid®): Medications for the Treatment of Homozygous Familial Hypercholesterolemia

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This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

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Objectives

After completion of this program, the reader should be able to:

1. Describe the clinical symptoms of homozygous familial hypercholesterolemia (HoFH).
2. Identify conventional and adjunct treatments used for HoFH before the development and FDA approval of mipomersen and lomitapide.
3. Identify the mechanism of action for both mipomersen and lomitapide.
4. Identify mipomersen and lomitapide's place in therapy in the treatment of HoFH.
5. Discuss the common adverse events and appropriate monitoring parameters associated with mipomersen and lomitapide therapy.

Abstract

Homozygous familial hypercholesterolemia (HoFH) is a rare disease that involves mutations in the genes coding for low density lipoprotein (LDL) receptors, preventing the uptake of LDL cholesterol from the serum and resulting in extremely high cholesterol levels.[1] Between December 2012, and January 2013, two orphan drugs were approved by the U.S. Food and Drug Administration (FDA) for the treatment of HoFH. Mipomersen (Kynamro®) is a subcutaneous injection that functions as an antisense oligonucleotide inhibitor and ultimately prevents the translation of mRNA coding for apolipoprotein B (apoB)-100 which binds to LDL and very low density lipoprotein (vLDL) cholesterol.[7] Lomitapide (Juxtapid®) is an oral drug that inhibits microsomal triglyceride protein (MTP), an enteric and hepatic protein that promotes the lipid transfer to apoB and allows a complex to form. Through the inhibition of MTP, vLDL cholesterol and chylomicrons are not formed. Each of these drugs, when combined with a low-fat diet and additional lipid-lowering therapy, which may include statins, resins and LDL-apheresis, can produce a clinically significant reduction in serum LDL cholesterol.[7,14] Before the approval of these two drugs, patients faced a greatly shortened lifespan, uncertain and nonspecific treatment options and serious complications secondary to HoFH.[1,3-5]

Introduction

As the world's leading cause of death, cardiovascular disease (CVD) is a fairly common diagnosis in patients, although it can manifest in different ways. There are many factors that contribute to CVD, including poor diet, lack of exercise, hypertension and dyslipidemia. In a select number of patients, poor cardiovascular outcomes can be attributed to genetic mutations. Homozygous familial hypercholesterolemia, also known as type II hyperlipoproteinemia, most frequently results from mutations in both alleles coding for LDL receptors. This mutation of the LDL receptors greatly reduces the amount of serum cholesterol absorbed by cells.[1] There are several mechanisms by which this occurs, including inability of the receptor to be transported to the cell surface, bind to LDL when at the surface or be internalized or released upon binding the LDL cholesterol.[2] It is estimated that HoFH affects approximately one in 1 million individuals,[3,4] although it is likely that this disease is grossly under diagnosed, given the number of diagnosed cases of CVD and the number of attributable factors.[4] Without proper lipid-lowering treatment, life expectancy is drastically reduced to before age 20[4] or the early 20s[3], with a 100 percent mortality rate by age 30.[5] The purpose of this paper is to review HoFH and to describe two emerging pharmacological treatment options.

Overview of Homozygous Familial Hypercholesterolemia

Homozygous familial hypercholesterolemia presents with several characteristic symptoms early in life: total serum cholesterol of greater than 600mg/dL[1] (up to 1,200mg/dL[5]), coronary artery disease, xanthomas (a yellow-orange, lipid-filled nodule) on the skin during childhood,[1,5] angina of effort (suffocating chest pain occurring during physical exertion),[3,5] aortic stenosis and myocardial infarction (MI).[5] In some patients, an MI is known to occur as young as 2 years old.[3] Interestingly, diabetes, hypertension and obesity are not often seen in patients with HoFH.[5] Patients who are most likely to develop HoFH are those who have parents that are diagnosed with or have a positive family history of heterozygous familial hypercholesterolemia. Clinically, it may be difficult to distinguish between severe heterozygous and normal-presenting HoFH; in homozygous familial hypercholesterolemia, the patient's fibroblasts or lymphocytes will show a reduction of LDL receptor activity of 20 percent or more.[1] Genetic testing will also provide a conclusive diagnosis and is useful in identifying silent cases, giving health care professionals a better understanding of the disease's clinical presentation and prognosis, as well as providing earlier diagnoses of familial hypercholesterolemia.[2]

Because HoFH is so rare, the best way to treat it has been with conventional methods used in treating "normal" or commonly occurring hyperlipidemia. Lifestyle changes, such

as eating a diet low in fat and cholesterol, increasing exercise, weight control, moderating alcohol intake and smoking cessation are often encouraged. There are several conventional drug options available to help treat the symptoms of HoFH. Statins and resins (such as cholestyramine; also known as bile acid sequestrants) can help to reduce serum levels of LDL cholesterol by increasing the activity of the LDL receptors; however, these drugs will not be effective in removing LDL cholesterol from the blood if the LDL receptor is absent or nonfunctional.[1] Bile acid resins can also cause undesirable gastrointestinal (GI) side effects and can deplete fat-soluble vitamins (vitamins A, D, E and K).[3] Fibrates, nicotinic acid (also known as niacin, a B vitamin that has shown to improve the overall lipid profile) and cholesterol absorption inhibitors like ezetimibe have also been used to improve the levels of serum LDL. The most promising nonpharmacological treatment for HoFH is LDL-apheresis. Somewhat similar to dialysis, this procedure works by passing the patient's blood through adsorption columns to remove LDL cholesterol and then returning the blood back to the patient. The components of the columns and the process itself may vary, but the goal is to remove as much LDL cholesterol as possible.[3] Treatment regimens that include a statin tend to prolong the effects of LDL-apheresis and slow the rebound rate of LDL cholesterol.[1] Although this process is effective, it is fairly expensive (costing approximately $2,500 per treatment[6]) and inconvenient for patients, who must be treated either weekly or every other week and often spend the entire day in the hospital.[3]

Mipomersen (Kynamro®)

Mipomersen is a Genzyme Corporation orphan drug that has just recently been approved by the FDA in January 2013. Mipomersen is formulated as a subcutaneous injection that is indicated as an additional therapy option to supplement other lipid-lowering medications and diet in adults with HoFH. The clinical ramifications of mipomersen include reductions in low density lipoprotein-cholesterol (LDL-C), apoB, total cholesterol (TC), and non-high density lipoprotein-cholesterol (non-HDL-C). These clinical results are attributed to mipomersen's antisense oligonucleotide inhibitor property that prevents translation of the mRNA strand that codes for apoB-100, the primary apolipoprotein in LDL and vLDL.[7]

In the FDA approval process, the efficacy of mipomersen was assessed primarily using one phase III clinical trial conducted by Raal et al.[8] The focus of this particular study is explained, as it was the only mipomersen phase III clinical trial specific to patients with HoFH. The other phase III clinical trials involved patients with a high risk for CVD, which included heterozygous familial hypercholesterolemia.[9] The Raal et al. study was a randomized, double-blind, placebo-controlled trial conducted in nine different lipid clinics in seven different countries for 26 weeks. The inclusion factors for patients were an age above 12 years and evidence that pointed to HoFH in the patient. This evidence included either genetic confirmation of HoFH, severe LDL-C concentrations from an early age or presence of heterozygous familial hypercholesterolemia in both parents of the patient. Additionally, the patients met the criteria of a consistent low-fat diet and maximum lipid-lowering medications that were continued throughout the trial. All but one patient were taking cholesterol-lowering medications. More specifically, 76 percent were taking a statin and an additional lipid-lowering medication.[8]

Out of patients screened, 51 patients met the inclusion criteria and were randomized in a 2:1 ratio in favor of the experimental group. Patients in the experimental group received 200 mg (160 mg if patient weighed <50 kg) mipomersen by subcutaneous injection once weekly.[8]

The primary outcome measure was to assess efficacy by the percent change of the LDL concentration from baseline. Secondary outcomes measured percent change from baseline for apoB, TC, and non-HDL-C concentrations. Of the 51 patients who entered the study, 45 completed the entire clinical trial. The patients who discontinued treatment did so because of adverse events, noncompliance or consent withdrawal. The results of the Raal et al. study yielded a mean percent change in LDL-C of -24.7 percent in the mipomersen group and -3.3 percent in the placebo group (p=0.0003). The results for the secondary outcomes included a mean percent change from baseline for apoB of -26.8 percent in the mipomersen group compared to -2.5 percent in the placebo group (p=0.0001), a TC change of -21.2 percent mipomersen compared to -2.0 percent placebo (p=0.0002), and a non-HDL-C change of -24.5 percent compared to -2.9 percent (p=.0002) for mipomersen and placebo, respectively.[8]

The safety assessment of mipomersen included the Raal et al. study in a review of four phase III clinical trials in the FDA summary review. The Raal et al. study was specific to HoFH, but the other phase III trials involved patients with a high risk for CVD, which included heterozygous familial hypercholesterolemia. Altogether, the trials included a total of 390 patients randomized in a 2:1 ratio in the mipomersen and placebo groups respectively for six months.[9]

Using the pooled data of the phase III trials, the main safety issues were hepatic steatosis (fatty liver), injection site reactions, elevated serum transaminases, flu-like symptoms, immune/antibody responses and proteinuria.[9] The Raal et al. study, specific to HoFH, reported hepatic steatosis, elevated transaminases, injection site reactions and flu-like symptoms, but also mentioned nausea and headache.[8]

In the Raal et al. study, hepatic steatosis was measured by magnetic resonance imaging (MRI) only when a patient's aminotransferase levels reached three times their upper limit of normal (ULN). Consequently, four patients had an MRI performed, which resulted in one case of an increase in hepatic fat. Because of the few hepatic fat assessments, there is a chance that other patients experienced undetected hepatic steatosis.[8] This possibility is affirmed by two other phase III clinical trials, conducted by Stein et al. and Thomas et al., in which the researchers conducted an MRI at baseline and week 28.[10,11] The pooled results for these two studies showed 62 percent of the mipomersen group versus 8 percent of the placebo group had hepatic fat increases of ≥ 5 per-

cent, the study's numerical definition of hepatic steatosis.[9] Despite higher amounts of MRIs utilized in these two phase III trials, not all the patients were tested. For instance, in the Stein et al. study, only 70 percent of patients had MRIs completed. The other 30 percent were not measured for hepatic steatosis because of technical difficulties, timing, metal implants or claustrophobia.[10] Almost the exact same statistics for MRIs conducted were found for the Thomas et al. study for the same reasons.[11]

When considering all the pooled data, the most common adverse events were injection site reactions, flu-like symptoms, nausea, headache and elevated alanine transaminase (ALT) and aspartate aminotransferase (AST). These adverse events were assessed by an incidence >10 percent and higher than placebo.[9]

In the Raal et al. study, the injection site reaction was determined to be the most common adverse reaction, which turned out to be three times more likely in the mipomersen group. This adverse event usually manifested itself through mild erythema, but was sometimes accompanied by local pain, tenderness and swelling. These effects caused two patients to withdraw themselves from the trial.[8] When all the phase III clinical trials of mipomersen were pooled together, 5 percent of patients were forced to discontinue therapy because of injection site reactions.[9]

Flu-like symptoms were observed in nearly the same percentage of patients in both groups in the Raal et al. study, but more events per patient were noted for the mipomersen group.[8] In contrast, the pooled data revealed symptoms in 30 percent of the mipomersen group and 16 percent in the placebo.[9]

A marked difference in ALT and AST elevations between groups was noted in the Raal et al. study. An ALT value ≥ three times the ULN was observed in 12 percent of the mipomersen group compared to zero in the placebo group. However, no other irregular values in liver tests were observed. Only one patient discontinued treatment due to elevated ALT.[8] Similar results were found in the pooled studies with 16 percent in the mipomersen versus 1 percent in the placebo.[9]

Antibody response was an adverse event not measured in the Raal et al. study, but observed in the other phase III trials and an open-label extension study. Compiled data showed mipomersen to be very immunogenic. The percentage of mipomersen patients who developed antibodies to mipomersen increased from 4 percent in week 13 to 33 percent in week 50 of treatment. Proteinuria was also observed in 0.8 percent of the placebo group and 2.3 percent of the mipomersen group. According to the FDA summary review, clinical significance of this adverse event has yet to be determined.[9]

Based upon the safety and efficacy studies noted earlier, mipomersen should be taken 200 mg subcutaneously once a week.[8,9] Patients should also be informed that each weekly dose is priced at $4,860.46[12] and that the most common side effect is injection site reactions.[8,9]

There are several factors that need to be considered before a patient undergoes mipomersen treatment. First, as stated previously, mipomersen is indicated specifically for adults with HoFH. Studies have yet to be conducted with a sufficient number of pediatric or geriatric patients to assess safety. Additionally, patients should undergo a full liver panel inclusive of ALT, AST, total bilirubin and alkaline phosphatase before starting mipomersen. Liver panels should be repeated every month for the first year of treatment. After the first year, tests should be conducted at a minimum of every three months.[7] Careful monitoring of liver panels is necessary due to the increases in aminotransferases in some mipomersen patients, as noted previously.[9] Consequently, contraindications exist with moderate to severe hepatic impairment and active liver disease. Furthermore, due to the risk of hepatotoxicity, the Risk Evaluation and Mitigation Strategy (REMS) program restricts those who can prescribe and dispense mipomersen. Thus, prescribing doctors and dispensing pharmacists must be certified in the REMS program.[7]

The REMS program includes a prescriber training module intended to provide education about appropriate and safe prescribing practices. Each pharmacy wishing to dispense the medication must also obtain certification and implement strategies to ensure that the prescriber is certified in the REMS program and that the patient has the necessary prescription authorization form.[20] The overarching goals of the REMS program are the education of prescribers to ensure safe medication utilization and the limitation of therapy to those with a confirmed diagnosis of HoFH.

Lomitapide (Juxtapid®)

Lomitapide (Juxtapid®), an oral alternative to mipomersen (Kynamro®), is Aegerion Pharmaceutical, Inc.'s FDA-approved orphan drug serving as an adjunct treatment for HoFH. Approved in December 2012, it is indicated exclusively as an oral lipid-lowering therapy in patients diagnosed with HoFH. When supplemented with a low-fat diet, LDL-apheresis, and other lipid-lowering therapies, lomitapide has demonstrated reduction in LDL-C, total cholesterol, apoB, and non-HDL-C.[13] Its mechanism entails the small-molecule inhibition of the microsomal triglyceride protein (MTP). This enteric and hepatic endoplasmic reticular protein is responsible for the transfer of lipids to apoB to form a complex. Microsomal triglyceride protein inhibition ultimately precludes the synthesis and secretion of vLDL cholesterol and chylomicrons, which require apoB for assembly and subsequent function.[13] Patients can expect a clinically significant reduction in serum LDL cholesterol when combining lomitapide therapy with both a low-fat diet and lipid-lowering therapy, as demonstrated by the clinical trials utilized for FDA approval in the subsequent discussion.

The phase II clinical trial conducted to assess the safety, tolerability and efficacy of the novel MTP inhibitor was published in the New England Journal of Medicine in 2007.[14] This interventional, open-label, single-group assessment of lomitapide treatment in patients with HoFH was sponsored by

Aegerion.[15] Owing to the low incidence of the disease, six patients (three men and three women, ranging 18 to 40 years of age) comprised the study group, which was conducted at a single medical facility.[14] A diet of less than 10 percent of daily caloric intake from fat was initiated for each patient, and any other lipid-lowering therapies were held during the course of the study. Investigators initiated dosing at 0.03 mg/kg/day for four weeks with a successive titration to 0.1 mg/kg/day, 0.3 mg/kg/day, and 1.0 mg/mg/day every four weeks over the course of the 16-week study period.[14]

Percent reduction in LDL cholesterol was chosen as the primary outcome, followed by a number of secondary considerations including the change from baseline in triglycerides, apoB, ALT, AST, total bilirubin, vitamins A, E and D, among others.[14] Statistical analysis was performed using paired t-tests or the Wilcoxon signed-rank test for continuous variables and the chi-squared test for percentages.[14] Clinically significant reductions ($p<0.001$) were seen in LDL cholesterol levels, as well as both apoB and triglycerides. After four weeks of the 0.03 mg/kg/day dose, LDL decreased 24.7 percent from a baseline of 614 mg/dL. An additional four weeks of therapy with a 1.0 mg/kg/day dose demonstrated a total reduction from baseline of 50.9 percent. Triglycerides saw a decrease of 34.1 percent from baseline after four weeks of 0.03 mg/kg/day, with a total reduction of 65.2 percent after an additional four weeks of therapy with 1.0 mg/kg/day. After a similar dosing regimen, apoB levels were diminished 55.6 percent from baseline.[14]

During the course of the study, patients experienced both an elevation in liver transaminases and accumulation of liver fat.[14] This hepatic lipid accumulation is hypothesized to be a direct result of the mechanism and initiates potential progression to fibrotic liver disease. Although additional long-term studies are indicated to further assess these implications, patients should be monitored for increases in aminotransferase levels and hepatic steatosis during therapy. This study further suggests that the adverse hepatic effects may impair the clinical utility of lomitapide.

The phase III clinical assessment of the safety and efficacy of lomitapide was verified by the FDA in January 2013.[16] It was also an interventional, open-label, intention to treat, single-group assessment conducted in 29 patients at 11 medical facilities. For six weeks prior to initiation of lomitapide therapy, patients entered a 'run-in' phase, during which current lipid-lowering therapies were stabilized and a low-fat diet (less than 20 percent) was initiated. Dosing was titrated from an initial oral dose of 5 mg/day for two weeks to an eventual 60 mg/day at four-week intervals.

Percentage reduction in LDL cholesterol was again pronounced as the primary outcome and was assessed through week 26 of therapy. Secondary outcomes were very similar to phase II and included percent change from baseline in total cholesterol, apoB, triglycerides, HDL, AST, ALT, and numerous others. In the 29 patients evaluated, a 40.1 ± 31.25 percent reduction was observed in LDL cholesterol levels. Reductions from baseline in total cholesterol, apoB, and triglycerides were 36.4 ± 28.2 percent, 39.4 ± 30.01 percent, and 29.0 ± 55.72 percent, respectively.[16] Both the primary and secondary outcomes lack statistical analysis due to the trial information not yet having reached publication.

Six of the 29 initial participants failed to complete the study, and four of these discontinuations are attributed to adverse events. Both serious and more common adverse events associated with lomitapide therapy have been observed from the first dose until 28 days post-treatment. Rare yet serious adverse events included cardiac disorders (angina pectoris: chest pain secondary to ischemic cardiac muscle, coronary artery atherosclerosis: plaque accumulation in the coronary artery and acute coronary syndrome: an emergent situation in which blood supply to heart muscle is interrupted), lower respiratory tract infections and menorrhagia.[16] More notable common adverse events, at least one of which affected 23 of the 29 participants, included gastrointestinal disorders, pain, fatigue, pyrexia, increased infection incidence and diverse pain complaints. Elevations in ALT, AST and transaminases are also under investigation for a potential patient safety risk.

After analysis of available lomitapide safety information, the primary concern during the course of therapy is the risk of hepatotoxicity. This is manifested through an increase in both AST and ALT ≥ three times the ULN. Hepatic fat increases were also noted, augmenting a patient's risk of developing steatohepatitis and cirrhosis.[17] Therapy should be discontinued if a patient experiences transaminase elevations concomitantly with clinical symptoms of liver injury. Elevations resolve within one to four weeks of stopping therapy in most patients.[18]

Lomitapide therapy is contraindicated in moderate to severe hepatic impairment, active liver disease, pregnancy and concurrent therapy with moderate or strong CYP3A4 inhibitors, such as clarithromycin, ritonavir and telithromycin.[19] A number of dose adjustments should also be considered where applicable. Dose-related myopathy has been noted with concomitant use of simvastatin (also suspected with lovastatin), and a reduction of the simvastatin dose by 50 percent is recommended upon lomitapide initiation.[19] A maximum daily dose of 40 mg is recommended in patients with end stage renal disease (ESRD) or mild hepatic impairment (Child Pugh A).[18]

The target population for lomitapide therapy includes those with a clinical or laboratory diagnosis of HoFH, excluding those with routine dyslipidemia. The study was a once daily oral therapy available in 5 mg, 10 mg and 20 mg capsules with an average cost per a 28 capsule bottle of $27,156. Therapy is initiated at 5 mg once daily and increased to a 10 mg daily dose after two weeks of patient tolerance. The dose may then be increased to 20 mg, 40 mg and a maximum of 60 mg at four-week intervals for peak therapeutic efficacy.[18] Each capsule should be swallowed whole with a glass of water two hours following the evening meal.

Table 1. Clinical Comparison of Mipomersen and Lomitapide[7,12]

Basis of Comparison	Mipomersen (Kynamro®)	Lomitapide (Juxtapid®)
Cost	$4,860.46 per weekly dose	$27,156.00 per 28 capsules
Route and Frequency of Administration	subQ, Q week	oral, QD
Side Effects	Injection site reactions, flu-like symptoms, nausea, headache and elevated transaminases	GI upset, blood and lymphatic disorders, cardiac palpitations, chest pain, fatigue, pyrexia, headache, dizziness, weight loss and diverse musculoskeletal pain
Adverse Effects	Hepatotoxicity, hepatic steatosis, elevated ALT and AST, immunogenicity and proteinuria	Hepatotoxicity, cardiac disorders, lower respiratory tract infections and reproductive system disorders
Monitoring	Baseline: ALT, AST, total bilirubin and alkaline phosphatase Test liver transaminases levels monthly for the first year and subsequently every three months. Also test before dosage increases.	Baseline: ALT, AST, total bilirubin, alkaline phosphatase, and pregnancy testing Test liver transaminases levels monthly for the first year and subsequently every three months. Also test before dosage increases.
Contraindications	Moderate to severe hepatic impairment and active liver disease	Moderate to severe hepatic impairment, active liver disease, pregnancy and concurrent therapy with moderate or strong CYP3A4 inhibitors
Additional Considerations	Prescriber and pharmacy require REMS certification	Prescriber and pharmacy require REMS certification

Pharmacists need to be cognizant of both common and serious adverse events that may impact patients during the course of therapy. During the escalation of treatment doses in the safety and efficacy trial, 10.34 percent of patients experienced a serious adverse event that included cardiac disorders, lower respiratory tract infections and reproductive system disorders. More commonly, patients were at risk for a number of mild adverse effects. Gastrointestinal upset, blood and lymphatic disorders, cardiac palpitations, chest pain, fatigue, pyrexia, headache, dizziness, weight loss and diverse musculoskeletal pain are among the most notable.[16]

Additional counseling points may be appropriate for certain patient populations. Because lomitapide is formulated with lactose, diarrhea and intestinal malabsorption may be experienced in patients with hereditary galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption. It would be appropriate to suggest supplementation with fat-soluble vitamins to all patients due to decreased absorption.[18]

Upon initiation of therapy, baseline AST, ALT, total bilirubin, alkaline phosphatase and pregnancy testing in females of reproductive age should be recommended. Liver transaminases should subsequently be measured monthly during the first year, every three months thereafter and prior to any increase in dose.[18]

Due to the specificity of its indication, risk of hepatotoxicity and continuous monitoring associated with therapy, lomitapide may only be prescribed and dispensed by health care professionals and pharmacies that are certified in the REMS program.[20]

Conclusion

As an orphan disease, HoFH has long been treated using the standardized treatments indicated for hyperlipidemia, despite its greatly increased severity and treatment challenges. With the approval of mipomersen and lomitapide as more targeted and specialized treatments for HoFH, patients can experience greater convenience in taking an oral medication or administering a subcutaneous injection than they would experience with LDL-apheresis, an expensive and time-consuming procedure that has long been the best treatment option. These orphan drugs have been shown to improve serum cholesterol levels and may promote favorable clinical outcomes for patients with HoFH.

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Assessment Questions

1. Mild adverse events associated with administration of lomitapide include all of the following EXCEPT:
    A. Blood and lymphatic disorders
    B. Chest pain
    C. GI upset
    D. Hyperkalemia

2. Which of the following are appropriate baseline monitoring parameters for a patient initiating lomitapide therapy?
    A. AST/ALT
    B. Total bilirubin
    C. Pregnancy testing
    D. Two of the above
    E. All of the above

3. In which of the following patient populations is lomitapide therapy most appropriately indicated?
    A. Monotherapy in patients diagnosed with HoFH
    B. Lipid-lowering therapy in patients with hyperlipidemia unresponsive to statin therapy
    C. As an adjunct to low-fat diet and lipid-lowering therapy in patients with HoFH diagnosis
    D. Monotherapy in patients diagnosed with heterozygous familial hypercholesterolemia

4. Health care professionals and pharmacists must be enrolled in the Risk Evaluation and Mitigation Strategy (REMS) program for which of the following reasons?
    A. Risk of hepatotoxicity
    B. Specificity of indication
    C. Need for continuous monitoring
    D. All of the above

5. What is the most common side effect associated with mipomersen treatment?
    A. Flu-like symptoms
    B. Nausea
    C. Injection site reactions
    D. Headache

6. Baseline monitoring for mipomersen is the same as lomitapide EXCEPT for:
    A. ALT/AST
    B. Pregnancy testing
    C. Total bilirubin
    D. Alkaline phosphatase

7. What is the mechanism of action associated with mipomersen?
    A. Small-molecule inhibition of microsomal triglyceride protein (MTP)
    B. Antisense oligonucleotide inhibitor
    C. HMG-CoA reductase inhibitor
    D. NPC1L1 antagonist

8. After initiation of mipomersen or lomitapide treatment, how frequently should a patient have ALT/AST tests conducted?
    A. Every six months
    B. Every month for the first year, then discontinue tests
    C. Every month during the course of treatment
    D. Every month for the first year, then every three months

9. Which of the following are characteristic symptoms of HoFH?
    A. Xanthomas
    B. Total serum cholesterol of greater than 1,300 mg/dL
    C. Early-onset cardiovascular diseases, including coronary artery disease, angina of effort, aortic stenosis and myocardial infarction
    D. A and C only
    E. All of the above

10. Which of the following conventional treatments (nonspecific for HoFH) can be used in the treatment of HoFH?
    A. Lifestyle modifications including low-fat, low-cholesterol diet, weight control, moderation of alcohol intake and smoking cessation
    B. Pharmacological therapy including statins, resins (also known as bile acid sequestrants), fibrates, nicotinic acid (also known as niacin) and cholesterol absorption inhibitors
    C. LDL-apheresis
    D. A and B only
    E. All of the above

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Ohio Northern University
525 South Main Street
Ada, Ohio 45810

Ohio Northern University Continuing Education Registration & Evaluation Form
Raabe College of Pharmacy Continuing Education Evaluation Form

Program Title: **A Comparison of Mipomersen (Kynamro®) and Lomitapide (Juxtapid®): Medications for the Treatment of Homozygous Familial Hypercholesterolemia**
UAN: 0048-0000-14-031-H01-P CEUs: 0.1

All information must be printed CLEARLY to ensure accurate record keeping for attendance and the awarding of continuing education credit. Certificates will be distributed as a PDF document to a valid email address.

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Program Content:	**Strongly Disagree**				**Strongly Agree**
The program objectives were clear.	**1**	**2**	**3**	**4**	**5**
The program met the stated goals and objectives:					
Describe the clinical symptoms of homozygous familial hypercholesterolemia (HoFH).	**1**	**2**	**3**	**4**	**5**
Identify conventional and adjunct treatments used for HoFH before the development and FDA approval of mipomersen and lomitapide.	**1**	**2**	**3**	**4**	**5**
Identify the mechanism of action for both mipomersen and lomitapide.	**1**	**2**	**3**	**4**	**5**
Identify mipomersen and lomitapide's place in therapy in the treatment of HoFH.	**1**	**2**	**3**	**4**	**5**
Discuss the common adverse events and appropriate monitoring parameters associated with mipomersen and lomitapide therapy.	**1**	**2**	**3**	**4**	**5**
The program met your educational needs.	**1**	**2**	**3**	**4**	**5**
Content of the program was interesting.	**1**	**2**	**3**	**4**	**5**
Material presented was relevant to my practice.	**1**	**2**	**3**	**4**	**5**

Comments/Suggestions for future programs:

_____

_____

_____

Thank you!

Answers to Assessment Questions—Please Circle Your Answer

1. A B C D **4. A B C D** **7. A B C D** **10. A B C D E**

2. A B C D E **5. A B C D** **8. A B C D**

3. A B C D **6. A B C D** **9. A B C D E**

Any questions/comments regarding this continuing education program can be directed to Lauren Hamman, Advanced Administrative Assistant for the Office of Continuing Education (email: l-hamman@onu.edu, phone 419-772-2280).

Ohio Northern University is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program is eligible for credit until 02/25/2017.

Celiac Disease: Current and Investigational Therapies and the Role of the Pharmacist

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Erin Petersen, PharmD '11, BCPS, assistant professor of pharmacy practice

This knowledge-based activity is targeted for all pharmacists and is acceptable for 1.0 hour (0.1 CEU) of continuing education credit. This course requires completion of the program evaluation and at least a 70 percent grade on the program assessment questions.

ACPE Universal Activity Number (UAN): 0048-0000-14-032-H01-P

Objectives

After completion of this program, the reader should be able to:

1. Explain the etiology, patient presentation and diagnosis of Celiac disease.
2. Discuss the current therapy for Celiac disease, highlighting the gluten-free diet.
3. Identify investigational pharmacotherapeutic options for Celiac disease.
4. Define the pharmacist's role in patient education and counseling for Celiac disease.

Abstract

Celiac disease is a genetically-linked autoimmune disease which affects the gastrointestinal tract. It is an inflammatory reaction to ingested gluten-containing substances that produces the most frequent symptoms of abdominal pain, bloating and intermittent or chronic diarrhea. Diagnosis can be made by blood testing for specific IgA autoantibodies and a confirmation duodenal biopsy to look for the characteristic scalloping and villous atrophy that occurs in response to the inflammation. A gluten-free diet, until recently, was the only treatment available and continues to be the mainstay of treatment. Newer adjunct therapies to dietary management include larazotide acetate, peptidases, the use of parasite Necator americanus, a desensitizing vaccine, polymeric binders, cytokine antagonists, tissue transglutaminase inhibitors, probiotics and anti-inflammatory therapy. This review will outline the potential of each of these therapies and discuss the role of the pharmacist in assisting patients with Celiac disease.

Introduction

In recent years, Celiac disease has emerged in society as a common, genetically-linked condition affecting the gastrointestinal (GI) system. It is an autoimmune disease that leads to gastrointestinal side effects as a result of ingestion of gluten-containing substances. The disease has risen in prevalence as physician awareness and diagnosis of the condition has increased. Still, many patients live with the condition and deal with the symptoms while remaining undiagnosed. Celiac disease can negatively affect patient quality of life for a multitude of reasons. These include physical discomfort associated with the disease as well as the inconvenience of maintaining a gluten-free diet, which is currently the only treatment option.

Several new pharmacological therapies and drug targets are under investigation for relief of symptoms and may be viable options for use as adjunct therapy in Celiac disease patients. While none of these products are currently on the market, they have the potential to be realistic additions to therapeutic regimens in the future. Pharmacists have an important role in counseling patients about the disease and how to manage symptoms. They will be sought out as drug experts for the disease state, as well as excellent resources for information about gluten-free foods and medications. The number of patients with Celiac disease will only continue to increase, and it is important to be knowledgeable about the disease state and incorporate patient counseling and education into pharmacists' everyday practice.

Disease Overview

Celiac disease is an increasingly prominent disease state that is highly linked to genetic factors. Such genetic factors are linked to mutations on the human leukocyte antigen (HLA) Class II genes, specifically haplotypes HLA-DQ2 and HLA-DQ8, found on the 6p21 chromosome.[1] Genetic mutations are the most predominant factor in eliciting the immune-mediated response to gluten, as 4 to 12 percent of Celiac disease patients have a first degree relative also suffering from this disease state.[2] It is important to note, however, that 30 to 40 percent of Caucasians have these HLA mutations with only 2 to 5 percent of carriers presenting with Celiac disease signifying that genetic mutations are necessary for disease presentation but are not the sole cause of Celiac disease.[1]

While genetic predisposition is important to consider, other factors may also contribute to the development of Celiac disease. These include environmental factors, such as a past enteric infection or patients who are exposed to gluten prior to 4 months of age.[1] Furthermore, patients who suffer from other immune-mediated genetic disorders that affect the GI tract, such as Crohn's disease and ulcerative colitis, are more susceptible than other individuals to develop this disease state.[2]

Celiac disease is classified as an immune-mediated disorder, as its symptomatic presentation is due to gluten, which triggers immunological reactions.[3] These immunological reactions stimulate an autoimmune response by the cells of the GI tract, stimulating inflammatory mediators.[4] Inflammatory mediators present in Celiac disease may lead to the opening of tight junctions in the intestinal epithelium. Tight junctions

regulate fluid and molecule passage between intestinal epithelial cells to the lamina propria. Proteins known as zonula occludins also regulate the structure and function of the cellular cytoskeleton by linking tight junctions with the actin network. When the tight junctions are not functioning properly, gluten (or gliaden) peptides gain access across the intestinal epithelium and are then modified by the enzyme, tissue transglutaminase (tTG).[1, 5] T-cells will then present the modified gluten as an antigen via HLA-DQ2 and HLA-DQ8 proteins. Gluten presentation then initiates both humoral and cell-mediated immune responses, leading to a temporary and reversible remodeling of intestinal mucosa, including scalloping of the small intestine mucosa and villous atrophy leading to malabsorption and symptoms such as abdominal pain, bloating and diarrhea.[1]

Patient Presentation

Celiac disease is prevalent across ethnicities, ages and genders with increasing prevalence not only in the pediatric population but also the adult population. Symptoms present in 1 percent of the U.S. population but may be undiagnosed in up to 85 to 90 percent of cases.[1,2] Celiac disease classically presents with symptoms related to malabsorption of gluten, which can include but are not limited to abdominal pain, bloating and intermittent or chronic diarrhea.[1,3] Chronic diarrhea is due to changes in the gastrointestinal wall leading to malabsorption of gluten, and can cause dehydration, weight loss and muscle wasting. Further signs of Celiac disease include anemia, most commonly iron-deficiency, due to malabsorption. Vitamin D deficiency and Vitamin B_{12} deficiency can also be signs of Celiac disease.[1] Of those patients with Celiac disease, 15 to 25 percent present with the non-traditional symptom of dermatitis herpetiformis, a rash that occurs without the accompaniment of GI symptoms.[2] The inflammatory process associated with dermatitis herpetiformis results from IgA deposition and neutrophil accumulation, which leads to vesicle formation, producing a rash commonly found on the elbows, knees and buttocks, an important clinical observation for patients with suspected Celiac disease.[2]

Due to similar GI symptoms across various GI disorders, it is important to note that some patients who suffer from Celiac disease also have a secondary disorder including lactose intolerance or inflammatory bowel disease (IBD).[1] Those patients suffering from autoimmune diseases including type 1 diabetes mellitus and autoimmune thyroid disorder may be more likely to present with Celiac disease and should be tested regardless of symptom presentation.[1,3] Celiac disease patients may also be more likely to have other immune-mediated diseases that affect the GI tract, such as Crohn's disease or ulcerative colitis.[2] Patients who have been diagnosed with lactose intolerance or diarrhea-predominant IBD and have not showed improvement should consider being tested for Celiac disease. The diagnosis process is an important step for patients because, although death is not a common outcome of this disease state, patients with multiple disease states are at an increased risk for complications such as vitamin deficiencies, malnutrition, ulcerative jejunitis, T-cell lymphoma and an overall decrease in quality of life.[1]

Diagnosis

Diagnosis is vital for patients suffering from Celiac disease due to a fourfold increase in mortality in patients with an untreated disease state.[7] Patients who present with Celiac disease symptoms should be screened via a blood test or intestinal biopsy.[2] Furthermore, asymptomatic patients who have a first-degree or second-degree relative with confirmed Celiac disease, type 1 diabetes, autoimmune thyroid disorders, rheumatoid arthritis or GI associated autoimmune disorder should be tested for Celiac disease. The first step for suspected patients is testing a blood sample for specific IgA autoantibodies via immunofluorescence. For patients undergoing a blood sample, it is important to eat foods containing gluten prior to testing, otherwise the patient may receive a false negative result for Celiac disease.[1] Those patients suffering from Celiac disease will present with elevated IgA to tTG or epithelial membrane antigen (EMA).[2] Most likely, tTG IgA will be screened due to its cost efficiency and comparable accuracy to the EMA IgA test. Another method of testing is via an upper endoscopy with duodenal biopsies to look for scalloping of the folds or cracking of the small intestine as well as villous atrophy linked to inflammatory changes. Due to the biopsy expense, this step in diagnosis should be suggested after blood testing in order to confirm the disease state.[1]

Treatment

Treatment should be started once Celiac disease is suspected. Currently, a gluten-free diet is the only therapeutic option for patients with Celiac disease. Gluten can be found in wheat, barley and rye containing products. Due to cross-contamination in manufacturing, it is very difficult to completely avoid the irritating substances. Due to the difficulty finding specifically gluten-free foods, many Celiac disease patients are exposed to low levels of gluten on a regular basis. Also, many medications have inert ingredients that contain gluten, making total avoidance even more difficult. It is estimated that 30 to 50 percent of patients are not able to strictly adhere to the proper diet, and at any given time 50 percent of all Celiac disease patients have an active disease state.[4] A gluten-free diet will aid in the healing of intestinal mucosa.[1] Those patients who suffer from dermatitis herpetiformis can treat the rash with dapsone, which inhibits neutrophil recruitment and downstream inflammatory processes, if the rash does not resolve after committing to a gluten-free diet.[1,6] About 90 percent of patients will present with no symptoms after five years of a gluten-free diet, and almost all patients will experience some relief from symptoms immediately after beginning the diet.[8] Those patients who follow a strict gluten-free diet have a better, long-term quality of life due to greater and more consistent relief, as well as an overall enhanced state of health (i.e. mental health, pain, vitality, social function, physical function).[9] Overall, relief of Celiac disease symptoms is due to a decrease in IgA specific autoantibody production via removal of the antigen (gluten).[10] Patients continuing to suffer from symptoms can more rigorously utilize pharmacological agents to treat symptoms related to deficiencies in Vitamin B_{12}, Vitamin D and folic acid. Furthermore, nonsteroidal anti-inflammatory agents (NSAIDs) and anti-diarrheals can be used for symp-

tom management. If symptoms persist after symptom management and strict adherence to a gluten-free diet, it is recommended that the patient revisit his or her doctor to determine if the patient is suffering from an additional disorder.[11]

New Pharmacological Therapies

New pharmacological therapies are in development to treat Celiac disease as an adjunct to the gluten-free diet. These novel therapies are necessary to increase the quality of life in patients who are still exposed to gluten even with best efforts to avoid the offending agent.[4] Currently, many different methods of therapy have been investigated, including larazotide acetate, peptidases, the use of parasite Necator americanus, a desensitizing vaccine, polymeric binders, cytokine antagonists, tissue transglutaminase inhibitors, probiotics and anti-inflammatory therapy.[4,12,13]

Cellular exposure to gluten can be reduced by use of larazotide acetate, a therapy in development. Larazotide acetate (ALBA Therapeutics) acts on the cytoskeleton to prevent opening of tight junctions and reduce gluten transport into cells from the intestinal lumen.[4] It also promotes redistribution and reorganization of zonula occludins and other proteins that associate with actin in the cytoskeleton. ALBA Therapeutics conducted a study testing the effects of larazotide acetate on junction assembly in kidney and intestinal cells. This study was conducted in vitro and showed promising results through several mechanisms including promotion of tight junction assembly, actin reorganization for stronger assembly of tight junctions, GTPase regulation of the cytoskeleton and inhibition of tight junction disassembly.[5] Improved tight junctions will lessen intestinal cell exposure to gluten, which can reduce inflammatory reactions in the GI tract.

Furthermore, in a randomized, placebo-controlled study by Kelly et al., the efficacy of larazotide acetate was assessed in patients receiving small amounts of gluten daily (2.7 g of gluten, equivalent to one slice of bread).[14] The primary endpoint of the study was a measure of intestinal permeability known as the lactulose-to-mannitol (LAMA) ratio. Patients with Celiac disease have an increased LAMA ratio. Results showed no statistical differences in LAMA ratio between placebo and treatment groups; however, the study acknowledged flaws in timing of LAMA assay and outpatient testing that may have affected results. Secondary endpoints included measures of serum anti-tTG IgA levels and showed the greatest increase in the placebo group from zero to six weeks, in which 30 percent of patients in the group seroconverted. Serum concentrations of the treatment group remained below levels that qualify a positive antibody test.[14] When compared to placebo, the treatment groups showed significantly lower anti-tTG IgA levels (1 mg dose $p=0.010$, 4 mg dose $p=0.005$, 8 mg dose $p=0.025$). There was also evidence to suggest that patients treated with larazotide acetate had fewer gastrointestinal side effects when compared to placebo. However, only the 1 mg daily dose of larazotide acetate reached statistically significant lower scores in patient-reported abdominal pain, indigestion and diarrhea versus placebo by the end of the treatment period ($p=0.017$).[14]

Another randomized, double-blinded, placebo-controlled study by Leffler et al. also had a primary endpoint of changes in LAMA ratio as well as measures of serum tTG antibodies. Results were similar to the Kelly et al. study, with the changes in LAMA ratio not reaching statistical significance. However, serum tTG did not reach statistically lower levels in this study. This study did show a significant difference in severity of gastrointestinal side effects between the patients receiving larazotide acetate with a gluten challenge versus the gluten challenge control group as evidenced by the Gastrointestinal Symptom Rating Scale ($p<0.05$).[15] Results from all three studies suggest that larazotide acetate has the benefit of inhibiting the opening of tight junctions in intestinal cells. Larazotide acetate may in the future have the possible therapeutic use as an adjunct to a gluten-free diet and relief of some symptoms of Celiac disease.[5,14,15]

Another novel drug therapy for the treatment of Celiac disease is the use of oral peptidases to hydrolyze gluten polypeptides. In this form, the gluten molecules can no longer stimulate damaging intestinal immune responses. Alvine Pharmaceuticals has developed ALV003, a combination of two gluten-sensitive peptidases. The company DSM has also developed a peptidase (AN-PEP), and a third is being tested by Stanford University. A phase I clinical trial showed that the use of ALV003 for pretreatment of gluten ingestion in Celiac disease patients caused a decrease in activation of immunological markers, as well as benefit in breaking down high gluten-containing foods.[4] However, this trial was underpowered and did not achieve statistically significant values for serology or symptom improvement. AN-PEP has showed less success in reaching significant endpoints in trials. However, AN-PEP is being considered as a food supplement as it is particularly active at degrading gluten in the stomach. One drawback of peptidase use is the susceptibility of these peptides to the acidic conditions of the stomach, and modification with polymer substitutes has been considered.[12] Use of oral peptidases has been one of the most investigated therapeutic options for the treatment of Celiac disease; however, its role in clinical practice has yet to be determined.

The use of the parasite Necator americanus is another investigational therapy for Celiac disease patients. Trials are underway to test whether or not this helminth infection can attenuate the autoimmune intestinal inflammation associated with Celiac disease.[16] The theory behind this therapy is derived from the hygiene hypothesis: the notion that increasing numbers of allergic and autoimmune disorders in developed countries may be associated with the decrease of infectious diseases present in society.[16,17] In a prospective, placebo-controlled, randomized, double-blind trial by Daveson et al., Necator americanus infection in Celiac disease patients was evaluated with primary endpoints of duodenal histology scores (for intestinal damage) and systemic interferon-gamma levels (for inflammation). Inoculation with the worm was instituted in patients who subsequently underwent a gluten challenge. A placebo group underwent the same gluten challenge without the worm for comparison. Results showed no statistical difference in duodenal histology scores or interferon-gamma levels between the infected and control

groups. This study in particular shows that helminth infection may not alleviate the need for a gluten-free diet in Celiac disease.[16] Limited studies using this therapy have been investigated at this time, and currently helminth infection therapy is not seen as a therapeutic option used in clinical practice.

Desensitization through the use of a Celiac disease-specific vaccination is also an investigational therapy. The biotechnology company ImmuSanT has developed a vaccine, Nexvax2®, which contains immunogenic gluten peptides from wheat, barley and rye. The vaccine was developed with the goal of restoring gluten-tolerance in Celiac disease patients through use as an immunotherapeutic and prophylactic agent.[12] A phase I study has evaluated the safety and efficacy of weekly intradermal injections of Nexvax2® compared to placebo by measuring immune T-cell response. The study's formally written publication has not yet been released. Thirty-four HLA-DQ2+ Celiac disease patients were randomized to four treatment groups (receiving 9 mcg, 30 mcg, 60 mcg and 90 mcg of Nexvax2® weekly for three weeks) and a placebo group (receiving saline injections on the same schedule). Results showed that the incidence of GI side effects was similar in the treatment and placebo groups. In the treatment group, immunological responses to Nexvax2® were similar to acute exposure to oral gluten (gluten ingestion) in the mobilization of gluten-specific T-cells.[18,19] Patients receiving the vaccine were found to have interferon-gamma-producing Nexvax2®-specific T-cells, which validates the bioactivity of the vaccine through immunological response. The hope is that through repeated vaccinations, a Celiac disease patient will develop tolerance to the immunogenic gluten peptides and be able to incorporate small amounts of gluten into his or her diet.[12] Thus far, data are extremely limited on the efficacy of such a therapy and more trials are needed. This may be a viable option in the future and an additional agent that could improve the quality of life of Celiac disease patients.

Many new therapeutic options for the treatment of Celiac disease are in very early stages of development. It may be some time before viable options are commercially available or before they become standards of practice for treatment. However, the amount of research and development into pharmacological therapies for Celiac disease is promising, and awareness and knowledge of these therapies are critical for pharmacists to be prepared for potential changes in Celiac disease state management in the future.

Pharmacists' Role

Pharmacists have a key role in improving the quality of life for patients suffering from Celiac disease and thus are best able to share important medication-nutrition and nutrition-disease state interactions with patients.[20] Resources for pa-

Table 1. Drug Excipients That are Safe or Require Further Investigation in Celiac Disease Patients[21,22]

Gluten-free Ingredients	Ingredients Needing Further Investigation (if source not specified)
Benzyl alcohol	
Cellulose	
Cornstarch	Caramel coloring
Croscarmellose sodium	Dextrate
Fructose	Dextrimaltose
Gelatin	Dextrin
Glycerin	Maltodextrin
Lactose	Modified starch
Mannitol	Potato
Polysorbates	Pregelatinized modified starch
Silicon dioxide	Pregelatinized starch
Sodium lauryl sulfate	Sodium starch glycolate
Stearates	Starch
Sucrose	Tapioca
Titanium dioxide	

Note: This chart is not an exhaustive list of gluten-free or gluten-containing ingredients used in medications. If there is ever a question about a specific medication ingredient, the drug manufacturer should be contacted for inquiry.

tient advising can be found through the National Foundation for Celiac Awareness (NFCA) at www.celiaccentral.org. Patient resources and brochures include information regarding what is Celiac disease, the choice to be gluten free, Celiac disease and women's health, and a Celiac disease symptoms checklist.[21] This information is free and available for pharmacists to provide to patients and will afford patients a better understanding of the disease.

Another important concern for pharmacists is the identification of gluten in various medications and over-the-counter products including vitamins, supplements and lip balms. These less obvious sources of gluten have been found to exacerbate patients' symptoms and should be monitored.[1] It is important for pharmacists to be aware of the excipients present in medications, especially because generic medications are not required to use the same excipients as the brand name medication. Likewise, not all generics are equal, and even two generics for the same medication may not contain the same excipients. Table 1 provides a list of excipients that are gluten-free and those ingredients that may need further investigation (if source not specified) to ensure safety. A drug manufacturer should be contacted if the pharmacist or patient is unsure of the excipient used, the source of the excipient or the possibility of cross contamination. As medication experts, pharmacists should know how to obtain this information for an inquiring patient.[22] Pharmacists and patients can find extensive lists of brand and generic prescription medications as well as over-the-counter medications that do not contain gluten at glutenfreedrugs.com. This website is kept up to date by a clinical pharmacist who continually updates the information for public access.[23]

Pharmacists are also an accessible resource for patients to approach about gluten-free food options and healthy living while on this restricted diet. It is important for pharmacists to counsel on the extra cost associated with preparing gluten-free foods and for patients to consider this in their budget. Equally important is directing patients to the aforementioned resources about Celiac disease for additional assistance. In order to help those patients on a gluten-free diet, labeling requirements have been added that mandate food labels to identify wheat and other common food allergens, as a result of a rising prevalence of patients suffering from Celiac disease and gluten intolerance. Additional requirements include regulations by the U.S. Food and Drug Administration (FDA) to control rules for the use of the term "gluten-free" on products. The FDA has standardized their definition of "gluten-free" such that foods containing this term or claiming to contain "no gluten," "free of gluten" and "without gluten" must contain less than 20 parts per million of gluten, an amount not seen to harm patients with Celiac disease.[24]

Conclusion

Celiac disease is gaining more and more recognition by health care professionals as the prevalence of the disease state increases. It is a genetically-linked disease whose diagnosis and treatment can lead to improved patient quality of life. While current practice only champions the gluten-free diet for treatment, newer investigational pharmacotherapy may emerge in the near future. Pharmacists will remain an important resource for patient education about Celiac disease. Pharmacists will be called upon to investigate medications and foods that may be appropriate or inappropriate in Celiac disease. Patient care is always a number one goal, and knowledge of this condition will allow pharmacists to be a primary resource for the treatment of Celiac disease.

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Assessment Questions

Etiology

1. Development of Celiac disease is genetically linked to which two haplotypes found on the mutated HLA Class II gene?
    A. HLA-DQ2
    B. HLA-DQ8
    C. HLA-DQ21
    D. Both A and B
    E. Both A and C

Patient Presentation

2. Symptoms of Celiac disease include all of the following EXCEPT:
    A. Abdominal pain
    B. Bloating
    C. Cyanosis
    D. Diarrhea
    E. Iron deficiency

Diagnosis

3. What counseling should be provided to a patient who is having a blood test for Celiac disease diagnosis?
    A. Eat gluten prior to the blood test
    B. Do not eat gluten prior to the blood test
    C. Fast for 12 hours prior to the blood test
    D. Exercise one hour prior to the blood test
    E. None of the above

Treatment

4. Relief of symptoms in Celiac disease patients is rooted in a decrease in which autoantibody?
    A. IgA
    B. IgD
    C. IgE
    D. IgG
    E. All of the above

5. After five years of following a gluten-free diet, about _____ of Celiac disease patients will be completely symptom free.
    A. 1%
    B. 10%
    C. 25%
    D. 50%
    E. 90%

6. Which of the following is NOT true about following a strict gluten-free diet?
    A. Following a gluten-free diet will improve patient quality of life.
    B. Patients who follow a gluten-free diet and no longer have symptoms do not need to visit their doctor for reevaluation.
    C. Patients who follow a gluten-free diet have a better health status.
    D. Patients who follow a gluten-free diet have a greater and more consistent relief of symptoms.

Investigational Therapy

7. Larazotide acetate is a novel therapeutic option for Celiac disease whose mechanism of action includes:
    A. Manipulation of the cytoskeleton to facilitate tight junction opening
    B. Actin reorganization for better assembly
    C. Inhibition of tight junction disassembly
    D. Both A and B
    E. Both B and C

8. Therapeutic use of gluten peptidases show the advantage of:
    A. Decrease in activation of immunologic markers
    B. Use as monotherapy for treatment of Celiac disease
    C. Gluten peptides are unsusceptible to acidic conditions in the stomach
    D. All of the above

9. The desensitization vaccine, Nexvax2®:
    A. Is currently on the market and available for patient use
    B. Targets three gluten peptides found in wheat, barley and rye
    C. Has an increased incidence of GI side effects compared to ingestion of gluten
    D. Recently completed phase III clinical trials

Pharmacists' Role

10. If a patient has a question about gluten in medications, a pharmacist should:
    A. Tell the patient to check the medication ingredients on their own.
    B. Explain that all medications are gluten-free and they should not worry.
    C. Contact the drug manufacturer about questionable ingredients or with concerns about cross-contamination.
    D. Assure patients that a small amount of gluten will not effect their condition.

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Ohio Northern University Continuing Education Registration & Evaluation Form
Raabe College of Pharmacy Continuing Education Evaluation Form

Program Title: **Celiac Disease: Current and Investigational Therapies and the Role of the Pharmacist**
UAN: 0048-0000-14-032-H01-P CEUs: 0.1

All information must be printed CLEARLY to ensure accurate record keeping for attendance and the awarding of continuing education credit. Certificates will be distributed as a PDF document to a valid email address.

Name:			
Address:			
City:	**State:**	**Zip:**	
Phone:	**Email:**		
Pharmacy License #:	**State:**	**ONU Alumni?**	**Y N**

Program Content:	**Strongly Disagree**				**Strongly Agree**
The program objectives were clear.	**1**	**2**	**3**	**4**	**5**
The program met the stated goals and objectives:					
Explain the etiology, patient presentation and diagnosis of Celiac disease.	**1**	**2**	**3**	**4**	**5**
Discuss the current therapy for Celiac disease, highlighting the gluten-free diet.	**1**	**2**	**3**	**4**	**5**
Identify investigational pharmacotherapeutic options for Celiac disease.	**1**	**2**	**3**	**4**	**5**
Define the pharmacist's role in patient education and counseling for Celiac disease.	**1**	**2**	**3**	**4**	**5**
The program met your educational needs.	**1**	**2**	**3**	**4**	**5**
Content of the program was interesting.	**1**	**2**	**3**	**4**	**5**
Material presented was relevant to my practice.	**1**	**2**	**3**	**4**	**5**

Comments/Suggestions for future programs:

_____

_____

_____

Thank you!

Answers to Assessment Questions—Please Circle Your Answer

1. A B C D E	**4. A B C D E**	**7. A B C D E**	**10. A B C D**
2. A B C D E	**5. A B C D E**	**8. A B C D**	
3. A B C D E	**6. A B C D**	**9. A B C D**	

Any questions/comments regarding this continuing education program can be directed to Lauren Hamman, Advanced Administrative Assistant for the Office of Continuing Education (email: l-hamman@onu.edu, phone 419-772-2280).

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Drugs of Abuse: A Review of Tramadol Abuse

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Abstract
Prescription drug abuse is the fastest growing drug problem in America. Among the different prescription drugs being abused, analgesics are the most commonly abused group of drugs. In the last few years, there is increasing evidence of abuse of tramadol, which is an atypical, centrally acting opioid analgesic. The increasing abuse of tramadol has prompted regulatory authorities to strengthen the product labeling of tramadol with respect to its abuse potential. Furthermore, several states have added tramadol to their controlled substances list. In this article, we will review the pharmacology of tramadol and some of the preclinical and clinical studies that support its abuse liability. In addition, we will focus on the risk factors that may predispose individuals to tramadol abuse and the consequences of tramadol abuse such as tramadol poisoning and tramadol dependence. Lastly, potential strategies with an emphasis on the role of the pharmacist and other health care professionals in controlling tramadol abuse will be discussed.

Introduction

Prescription drug abuse is defined as the use of a medication for purposes outside of its original intention.[1] Examples of misuse include abusing a medication without a prescription, using a medication in ways other than prescribed or intending to misuse the medicine for an "experience" or a "feeling."[1] Prescription drug abuse is the fastest growing problem in the United States with approximately 6,600 new abusers each day.[2] Importantly, the problem affects the country as a whole due to the large societal costs associated with it. The societal cost of prescription drug abuse, including costs to health care, the criminal justice system and lost workplace productivity, was estimated to be $55.7 billion in 2007.[2] Prescription drugs commonly abused include analgesics (pain relievers), tranquilizers, stimulants and sedatives.[1] Among these drugs, analgesics are the most commonly abused prescription drug category. In 2010, 12 million Americans 12 years of age and older reported using prescription analgesics for nonmedical uses for the first time.[2]

Included in this category of prescription analgesics is tramadol (Ultram®).[1] Tramadol, approved in the United States in 1995, is a nonscheduled analgesic indicated for the treatment of moderate to moderately-severe pain.[3] For several years after its approval, tramadol was advocated as a unique drug due to its supposed weak narcotic effects.[3] These weak narcotic effects were initially seen as an advantage, as it was thought the drug could be safely used to treat pain in patients with a history of narcotic abuse.[3] However, due to increased reports of overdose and suicides, product labeling of tramadol was revised in July 2010.[4] Revisions included warnings of an increased suicide risk for patients using tranquilizers or antidepressants and patients at risk for addiction.[4] The labeling changes also emphasized the risks of overdose and the abuse potential of the drug.[4]

Despite these warnings, tramadol continued to be widely prescribed. In 2012, 29.8 million prescriptions of tramadol were dispensed.[3] Importantly, there has been increasing evidence of tramadol overdose and abuse.[3] In 2011, poison control centers reported 12,424 cases of tramadol overdose, with 6,361 of these exposures leading to death.[3] In addition to overdose, the 2011 National Survey on Drug Use and Health reported that 2.6 million people ages 12 and older used tramadol for nonmedical uses in the past year, with the most commonly abused dosage form being oral.[3,5] In 2013, the Drug Enforcement Administration (DEA) challenged the previous classification of tramadol[3] and stated in its report that, "Dependence and abuse, including drug seeking behavior and taking illicit actions to obtain tramadol are not limited to those patients with prior history of opioid dependence."[3] Furthermore, several states, including Arkansas, Kentucky and, most recently, New York, have included tramadol on their controlled substances lists.[6,7] In this review, we will discuss the pharmacology of tramadol and the underlying neural mechanism which facilitates tramadol abuse. We will also explore the factors that increase the risk for tramadol abuse and poisoning, as well as the treatment of tramadol poisoning and withdrawal. Lastly, we will discuss strategies to prevent tramadol abuse.

General Pharmacology

Tramadol is a centrally acting analgesic and is available as both oral immediate-release formulations (50 mg in either capsules, drops, tablets or soluble tablets) and sustained-release tablets. All formulations have a high bioavailability. The plasma protein binding of tramadol is approximately 20 percent.[8] Tramadol is metabolized mainly by hepatic cytochrome P450 isoenzymes 2D6 and 3A4.[8,9] Cytochrome P450 isoenzyme 2D6 (CYP2D6) is primarily responsible for the metabolism of tramadol to its active metabolite *O*-desmethyl-tramadol.[8,9,10-12] When CYP2D6 concentrations are low or O-demethylation is inhibited, isoenzymes 2B6 and 3A4 (CYP2B6 and CYP3A4) contribute to metabolism of tramadol into *N*-desmethyl-tramadol.[8,9,11] Tramadol is excreted via the kidneys and the elimination half-life is approximately six to eight hours.[8,9]

Structurally, tramadol is similar to codeine and morphine.[8,11] It is formulated as a racemic mixture of two enantiomers in its parent form: (+)-tramadol and (-)-tramadol, which play complementary and synergistic roles in mediating its analgesic effects.[8,11] (+)-Tramadol inhibits reuptake of serotonin and (-)-tramadol inhibits the reuptake of norepinephrine. In addition, (+)-tramadol and its active metabolite, (+)-*O*-desmethyl-tramadol, are mu opioid receptor agonists, which

further enhance the analgesic efficacy of tramadol.[8,11] Because of this dual mechanism of action, tramadol is classified as an atypical opioid analgesic. However, despite this dual mechanism of action, the analgesic potency of tramadol is only about 10 percent that of morphine, a potent mu opioid receptor agonist.[8]

The activation of mu opioid receptors by tramadol and its active metabolite *O*-desmethyl-tramadol play an important role in the abuse liability of tramadol.[8-11] In humans, activation of mu opioid receptors results in positive reinforcement and rewarding effects such as euphoria, relaxation and drowsiness. Relaxation and drowsiness can be reinforcing especially in individuals suffering from pain. These positive reinforcing effects thus provide the major motivation for continued use and subsequent abuse of tramadol. When comparing tramadol and its metabolite *O*-desmethyl-tramadol, the latter is a more potent agonist of the mu opioid receptor. Therefore, both the reinforcing and analgesic effects of tramadol are more dependent on its conversion to its active metabolite. Polymorphisms associated with the CYP450 enzyme CYP2D6 greatly influence the effects of tramadol. Based on the activity of CYP2D6, individuals can be classified as poor metabolizers, normal metabolizers and ultra-rapid metabolizers.[10,12] Poor metabolizers have reduced or absent activity of CYP2D6 and the analgesic efficacy of tramadol is decreased in these patients as compared to those who have normal CYP2D6 activity.[10,12] In contrast, ultra-rapid metabolizers of tramadol, who have increased activity of CYP2D6 and rapidly convert tramadol to its active metabolite, are at a higher risk of abusing tramadol. Consistent with this hypothesis, higher rates of tramadol abuse have been reported in individuals from Middle Eastern countries who are commonly ultra-rapid metabolizers of tramadol.[10,13]

Drug Abuse Potential: Evidence from Clinical and Preclinical Studies

Preclinically, the positive reinforcing effects of drugs can be assessed using the conditioned place preference (CPP) model.[14] Conditioned place preference is conducted using an apparatus that has two chambers, which are distinct with respect to their texture and/or color. The drug of interest is administered to the animal and the animal is placed in one of the chambers. This pairing of the drug to a particular chamber is done repeatedly over several days. This process is known as conditioning and allows the animals to associate the reinforcing effects of the drug (if any) with the specific environment. Along with this pairing of the drug to one of the chambers, the animal is also conditioned to a distinct chamber in the apparatus using a vehicle (control). On the test day, the animal is allowed to explore both the drug- and vehicle-associated chambers in a drug-free state. The time spent by the animal in the drug-associated compartment is compared to the time spent by the animal in the vehicle-associated compartment. If a drug is reinforcing, the animal will spend significantly more time in the drug-associated compartment compared to the vehicle-associated compartment.[14] Several preclinical studies showed that tramadol-administration induced CPP in rats.[15,16] Additionally, tramadol enhanced morphine-induced CPP. Importantly, pretreatment with mu receptor antagonist naloxone attenuated tramadol-induced CPP. Together these data suggest that tramadol has positive reinforcing effects, which are mediated by the mu opioid receptor. Furthermore, drugs with high abuse liability increase the activity of the mesolimbic dopaminergic neurons in the brain. These mesolimbic dopaminergic neurons originate in the ventral tegmental area in the midbrain and project to several limbic sites including the nucleus accumbens (NAcc). The increase in activity of these mesolimbic dopaminergic neurons is determined by measuring the increase in levels of the neurotransmitter dopamine in the NAcc using a procedure called in vivo microdialysis. Tramadol administration in rats increased NAcc dopamine levels.[15] In summary, these preclinical studies suggest that tramadol has positive reinforcing effects and support the abuse liability of tramadol.

Clinical Studies

A within-subject, randomized, double-blind, placebo-controlled study evaluated the reinforcing effects of different doses of tramadol (200 and 400 mg), oxycodone (20 and 40 mg) and codeine (100 and 200 mg) by allowing subjects to self-administer the different drugs and placebo. The highest self-administration was observed when subjects received the 400 mg tramadol compared to 200 mg of tramadol, placebo and both doses of oxycodone and codeine. The high rates of self-administration suggest that 400 mg of tramadol has strong reinforcing effects. In addition, the study also reported that 400 mg of tramadol increased mu opioid receptor agonist-like measures such as itchy skin and pupillary constriction. Lastly, the study reported that all drugs (except low doses of codeine) increased subjective measures of abuse liability such as "liking" or "high" for the drug. Taken together, these data suggested that tramadol has a high abuse potential.[17] Several other clinical studies also reported findings that support the abuse potential of tramadol.[8,11,13,15,17]

In contrast to the above studies, some clinical studies conducted immediately after the approval of tramadol reported that tramadol may not have abuse potential.[16] It is not entirely clear why these studies suggested that tramadol is not linked with the possibility of abuse. One possible reason could be that these studies were conducted in individuals with a history of opioid drug abuse, who generally develop tolerance to the reinforcing effects of weaker reinforcers. The relatively weak reinforcing effects of tramadol were, therefore, not detected in these subjects. Another possible reason could be that in most of these studies, tramadol was administered intramuscularly rather than orally. As described above, the active metabolite of tramadol is mainly responsible for its reinforcing effects. The conversion of tramadol to this specific active metabolite is maximal when it is administered orally, due to hepatic first pass effect via CYP isoenzymes. The results of the studies described above contributed to the misguided perception of low abuse potential of tramadol, and to its continued use and abuse.[1,4]

Tramadol Abuse and Overdose

One potentially fatal consequence of tramadol abuse is

tramadol overdose and poisoning. A review of 114 studies of tramadol-intoxicated subjects suggests that 80 percent of the patients poisoned themselves with the intent of suicide.[5] These data therefore suggest that physicians and pharmacists must be very careful in prescribing tramadol for patients with a history of suicidal ideation, previous suicide attempts or depression. Furthermore, patients suffering from depression are at an increased risk of tramadol poisoning. Clinical reports suggest that there is extensive comorbidity in patients suffering from depression and pain.[18] Patients with chronic pain have decreased serotonin and tryptophan concentrations in the hippocampus, which may predispose them to depression.[18] In addition, depressed patients may be more likely to develop chronic pain due to an alteration in the utilization of tryptophan.[18] It is logical to recognize that some patients on tramadol, who may also have chronic pain, may be diagnosed with, or be at an increased risk for, depression. Furthermore, taking tramadol concomitantly with a benzodiazepine (a class of drugs used to treat central nervous system (CNS) disorders, including depression) predisposes individuals to cardiopulmonary arrest.[5] The pharmacodynamic interaction of tramadol and a comorbid psychiatric disorder, like depression, along with the pharmacokinetic interactions between tramadol and depression medications may predispose individuals to tramadol poisoning. In addition to depression medications, risk of tramadol poisoning is increased following concomitant administration of tramadol with other CNS-depressant medications/substances including alcohol, tranquilizers, sedatives and muscle relaxants.[4,19] In summary, patient groups prone to tramadol-related poisonings and deaths include patients with a previous history of depression or suicidal ideation and attempts as well as a history of misuse of alcohol and other CNS-depressant medications.

Patients who have abused or intentionally overdosed on tramadol may present with adverse effects such as nausea, vomiting, central nervous system depression, tachycardia, seizures and apnea. Some patients may present with symptoms characteristic to serotonin syndrome, which include altered mental state, neuromuscular hyperactivity and autonomic dysfunction.[5,20,21] Management of tramadol poisoning involves treatment of symptoms of overdose as they arise and providing supportive care to ensure patient comfort and safety.[22] Naloxone, an opioid antagonist, is used as an antidote to treat tramadol poisoning.[23] However, a much larger dose of naloxone is required for tramadol poisoning in comparison to the dose needed to treat poisoning of other opioids.[23] However, the use of naloxone as an antidote to treat tramadol poisoning is controversial as an increased risk of seizures has been reported with its use.[23]

Tramadol Withdrawal and Treatment

Another major problem with tramadol abuse is tramadol dependence. In tramadol-dependent patients, withdrawal from tramadol results in symptoms such as abdominal cramps, anxiety, bone pain, diarrhea, goose flesh, insomnia, lacrimation, nausea, restlessness, rhinorrhea and sweating.[24] These withdrawal symptoms are similar to those seen in opioid dependent patients. Some patients report atypical withdrawal symptoms including severe anxiety, panic attacks, unusual CNS symptoms, sensory symptoms and hallucinations.[24] These latter symptoms are similar to those observed in patients who withdraw from selective serotonin reuptake inhibitors (SSRIs).[24] This parallel may be due to the ability of tramadol to block the reuptake of serotonin, similar to SSRIs.[24]

Treatment of tramadol withdrawal is patient specific. In most cases, a gradual reduction of the patient's tramadol dose, rather than stopping suddenly, yields the least withdrawal symptoms.[25] Unfortunately, there is no standardized protocol for reducing tramadol administration; patients should work with their doctor and pharmacist to set a schedule that works for them.[25] Tramadol withdrawal symptoms are generally managed through supportive care in a way that is most comforting to the patient.[25] Treatment of these symptoms is critical as the symptoms can lead to relapse among abstinent tramadol-dependent patients.[25]

In addition to treatment of the withdrawal symptoms, it is necessary to address any underlying factors that may have facilitated tramadol abuse. For example, if the patient continues to experience pain and needs an analgesic, switching to a nonopioid analgesic may be an option.[26] If that is not possible, another option would be the creation of a detailed monitoring strategy, in which both prescribers and pharmacists are deeply involved, in order to ensure that the therapeutic effects of tramadol outweigh negative consequences. This may include extensive laboratory testing of the cardiovascular, pulmonary and central nervous systems for objective data, as well as meeting with the patient to gain subjective data. Due to the possible link between tramadol abuse and depression, as discussed above, pharmacological treatment of depressive symptoms may help facilitate the reduction of tramadol abuse and prevent relapse in dependent patients. In addition to this pharmacological treatment, psychological support in the form of psychotherapy and support groups may help prevent relapse in abstinent tramadol-dependent patients.[26]

Prevention of Tramadol Abuse and Poisoning

Counseling and educating the patient is the first step to preventing tramadol abuse. Both prescribers and pharmacists have a duty to educate patients on tramadol toxicity, overdose and abuse potential, as well as a duty to formulate abuse prevention and treatment strategies individualized to each patient.

The use of multiple physicians and pharmacies by patients often makes it difficult for a health care professional to know every medication the patient is taking and the effects of each of these medications. One way to prevent toxic effects and fatalities in patients using tramadol, or any other opioid, is monitoring what drugs are being prescribed, dispensed and administered by one or more doctors using medication lists and patient profiles. Medication lists and patient profiles allow the pharmacist to identify potentially harmful and fatal drug interactions before they occur. For example, patient profiles increase pharmacists' ability to see if a patient taking

a CNS depressant prescribed by one doctor is prescribed tramadol by a different or the same doctor. Furthermore, it gives pharmacists an opportunity to discuss with prescribers possible alternatives to tramadol and/or other interacting medications. Thus, pharmacists have the unique ability to catch and rectify a problem before it occurs.

As stated previously, there is evidence of increased tramadol abuse in certain groups of patients, such as those with a previous or current history of emotional disturbances, depression, suicidal ideation, suicidal attempts, as well as previous or current use of tranquilizers, alcohol and other CNS-active drug abuse. Therefore, another useful approach to decrease tramadol abuse would be to screen such patients after careful review of their medical histories. In these patients, it may be necessary to either avoid prescribing tramadol or prescribe tramadol with careful and rigorous monitoring as described above. Additionally, ultra-rapid metabolizers of tramadol may be at greater risk for tramadol abuse compared to poor and normal metabolizers of tramadol. Thus, in the current era of personalized medicine, it may be possible to identify patients who may be at greater risk of tramadol abuse based on CYP2D6 polymorphisms. Although no such test currently exists, it is not inconceivable that such a test may be developed in the near future. The test may perhaps only require a simple cheek swab from a potential patient. Regardless of the challenges, it is critical for every health care professional to be alert to identify and prevent tramadol abuse among the different patient populations.

Regulatory mechanisms can also help in reducing and preventing tramadol abuse. The use of automated prescription reporting systems such as the Ohio Automated Rx Reporting System (OARRS) can also play an important role in controlling prescription drug abuse. The OARRS requires outpatient pharmacies to report every dispensed prescription of controlled substances, tramadol and carisoprodol. Because tramadol prescriptions have to be reported to OARRS, and because tramadol either is currently or is anticipated to be a controlled substance in many states, pharmacists have the ability to track patients' tramadol use, as well as the use of any other opioids that may increase tramadol abuse and poisoning. Additionally, OARRS provides pharmacists the opportunity to cut down on inappropriate opioid use and to work with prescribers and patients to find an alternate therapy. However, OARRS is not a perfect system. One major limitation is the system's dependence on the compliance of pharmacies. If pharmacies are not properly reporting each tramadol prescription within eight days of dispensing, as required by OARRS, the system cannot work to its full potential. Although OARRS generates a report identifying pharmacies which have "failed to report" in an eight-day period, it may not necessarily be a comprehensive list to identify all errant pharmacies. Furthermore, as with almost any rule, there are exceptions to reporting to OARRS. For example, inpatient pharmacies, including federal Veterans Affairs (VA) hospitals and nursing homes, as well as doctors who dispense out of their office, are not required to report to OARRS, making the system less reliable.[27, 28] While there are flaws in how tramadol use is monitored, important measures are being taken to rectify the deficiencies. The effort on part of some states (such as Arkansas, Kentucky and New York) to make tramadol a controlled substance is a welcome step and will help greatly in controlling the menace of tramadol drug abuse.

Conclusion

The abuse of prescription analgesics like tramadol is a growing problem in the United States. In fact, the number of tramadol poisoning cases over the last few years has increased despite improvements in label warnings. Tramadol abuse can be confronted through patient education, increased regulatory surveillance and identifying patient groups who may be predisposed to tramadol abuse/poisoning. In addition, increasing awareness among physicians and pharmacists regarding the high abuse potential of tramadol is warranted. This awareness, along with the resources described above (such as OARRS, medication lists and patient profiles), will allow pharmacists and prescribers to flag potential abuse before it occurs and step in with alternative therapies. As for patients who are already abusing tramadol or have experienced tramadol poisoning, management strategies for both toxicity and withdrawal symptoms are available in order to prevent further abuse and relapse.

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Emergency Contraception: A Comparison of Levonorgestrel and Ulipristal Acetate

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Abstract

Emergency contraceptives (EC) are a birth control method that is available to minimize unintended pregnancies that might result from unprotected intercourse. Several products are on the market and largely contain levonorgestrel as the active component, including Plan B One-Step®, Next Choice®, Next Choice One Dose™ and My Way®. These are labeled as effective up to 72 hours after intercourse and are available without a prescription. Another product, Ella™, contains ulipristal acetate and can be effective up to 120 hours after intercourse, but does require a prescription. Legislative issues have surrounded these products. At this point in time only Plan B One-Step® is available to anyone of any gender or age without a prescription. Ulipristal acetate has been shown to be more efficacious in reducing pregnancies than the levonorgestrel most likely due to its effects later in the ovulatory cycle. All of these products have similar side effects and none of them will terminate an existing pregnancy. Cost issues may influence an individual's choice to use these products. A pharmacist can aid in counseling on the appropriate selection of a product, timing of administration and methods for preventive birth control for the future.

Introduction

Emergency contraceptives (EC) are a birth control method that reduces the likelihood of pregnancy after unprotected intercourse. Emergency contraceptives are commonly called "the morning after pill" or "the day after pill" and come in a variety of different active ingredient and dosage options. In 2001, in the United States, about 50 percent of 6.7 million pregnancies were unintended, and one in 10 women aged 18 to 24 experienced an unintended pregnancy.[2] Unintended pregnancies are more common among unmarried, low-income, less educated and minority women. These rates have remained high in the past two decades, making EC an increasingly popular birth control option. Fifty-three percent of these unintended pregnancies used contraceptive methods that failed, which includes both a mechanical failure such as a condom slipping or breaking, as well as an oral contraceptive failure such as missing a dose. [2] Any of these failures encourage the use of an emergency contraceptive by women.[1]

Because of the high prevalence of these unintended pregnancies, EC options are relevant and need to be understood. Forty-nine percent of previous EC users attributed their use of an emergency contraceptive to the nonuse of any other form of birth control. Comparatively, only 39 percent attributed their use to worry that their regular method had not worked. One reason the percentages are so high for EC use is because women rely on health care professionals for information about contraceptives, however there is a lack of education about contraceptive methods that could reduce the usage of EC. In a study done by Kavanaugh et al., it was noted that among the 63 percent of women that received a Pap test or pelvic examination in the past year, only 4 percent reported that they were counseled about EC.[3] This lack of patient counseling in routine visits by female patients has resulted in an inadequacy of women's knowledge on how to obtain and safely and effectively use EC.

There are many different options for EC that can be purchased in a pharmacy. One of the most popular options is levonorgestrel (LNG)-based EC. These include Plan B One-Step®, Next Choice®, Next Choice One Dose™ and My Way®. Plan B is no longer marketed, but generic versions are still available. The U.S. Food and Drug Administration (FDA) approved its successor, Plan B One-Step®, in 2009. Plan B One-Step® is a single oral tablet that contains LNG 1.5 mg. Next Choice® is the generic form of Plan B, which consists of two oral tablets that contain LNG 0.75 mg each. Next Choice One Dose™ is the generic form of Plan B One-Step®, one oral tablet that contains LNG 1.5 mg. Similarly, My Way® is one oral tablet that contains LNG 1.5 mg. A different option is the non-LNG based Ella®. Ella® is the newest form of EC that is also an oral tablet, and it contains ulipristal acetate (UPA) 30 mg. Besides the difference in active ingredient, Ella® is currently available only as a prescription, while Plan B and Next Choice® can now be sold as over-the-counter (OTC) medications.

Female Ovulation Cycle

In order to understand how both LNG and UPA act in the body, familiarity with the female hormone cycle is required. Low progesterone and estrogen levels indicate the beginning of the ovulation cycle. The hypothalamus then begins to release gonadotropin-releasing hormone (GnRH), which stimulates the release of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary gland. Follicle stimulating hormone functions to promote several follicles in the ovary to grow and develop. These maturing follicles produce estrogen, which increases GnRH production, and in turn increases LH and FSH levels, inducing what is called the LH surge. Estrogen also stimulates the growth of the uterine lining. When LH and FSH levels reach their highest point, or the LH peak, LH stimulates the largest of the maturing follicles to leave the ovary and release its egg. As the egg travels down the fallopian tube, the follicle, or corpus luteum, produces progesterone and estrogen. Progesterone, in combination with limited estrogen levels, decreases the production of GnRH, LH, and FSH and stimulates the growth of the uterine lining. These two actions provide a good environment for a

fertilized egg to implant while preventing other follicles from being released from the ovary. If the egg is not fertilized within several days of ovulation, the corpus luteum will break down, causing a drop in progesterone and estrogen levels. This drop hinders the growth of the uterine lining, which will then break down and be removed during menstruation. Gonadotropin-releasing hormone levels then rise and the cycle begins again.[4]

Marketed Emergency Contraception

The most common options on the market for oral EC are Plan B One-Step® as well as its generic form, Next Choice One Dose™, both LNG products, and the relatively new product Ella®, UPA. In general, EC options attempt to slow the ovulation cycle in order to prevent an egg from being fertilized after unprotected intercourse.[5] It is thought that LNG can have some effects on the fusion of sperm to egg, and while this may be relevant for everyday LNG contraceptive use, the frequency and dose of LNG EC products do not have a sufficient impact on fusion. When used as an EC, studies have shown that LNG temporarily inhibits the release of LH, which prevents the follicle from releasing its egg. However, this LH prevention only works when the peak in LH levels is greater than one day away.[6] This means that "the ability of LNG to interfere with the ovulatory process decreases as ovulation nears."[5] Finally, while it is suggested that LNG could inhibit implantation of a fertilized egg on the endometrial lining, recent studies using dosing similar to EC do not support this mechanism of action.[7]

Ella®: A Prescription-Only Option for EC

Ella®, UPA, is an alternative emergency contraception medication and appears to work in a slightly different way than LNG. Ulipristal acetate is approved for use up to 120 hours after unprotected intercourse whereas LNG is only approved for 72 hours after unprotected intercourse.[2] Like LNG, UPA also delays the rupture of the follicle. However, unlike LNG, UPA has proven to be more effective at later stages in the ovulatory cycle.[6] In a randomized, placebo-controlled, double-blind, crossover study of 35 women, UPA delayed ovulation for at least five days in the majority of women, and in some cases inhibited ovulation for that cycle all together. These results were supported both when administered before LH levels had begun to rise and during the LH surge, but before the LH peak.[8] Because UPA is a selective progesterone receptor modulator (SPRM) it could have another role in emergency contraception. By acting as a partial agonist to the progesterone receptors of the endometrial lining and causing a perceived decrease in progesterone, UPA causes decreased thickness of the endometrium. The dominant mechanism of UPA depends on the time of the patient's menstrual cycle.[9] The difference in mechanism of action for LNG and UPA regarding the timing of the LH surge is important because "the immediate pre-ovulatory treatment window...carries a high probability of conception."[8] Consequently, choosing the correct emergency contraception option is vital. Levonorgestrel and UPA both delay LH from reaching its peak levels, but UPA seems to delay the peak closer to the time of expected ovulation compared to LNG.

Recent Regulation Changes with Plan B

There has been a renewed focus on EC with recent changes in the regulation of EC, most specifically Plan B One-Step®. The FDA approved the active ingredient, LNG, in 1999 for use as an EC. In 2006, it became available as an OTC, but could only be sold to women who were 18 years or older. In 2009, the FDA expanded the availability of LNG so that it could be sold to men and also women who were 17 years or older. Levonorgestrel products were also available to women younger than 17, as long as they had a prescription for it.[2]

There was much controversy over legalizing OTC sales of EC, and the decision was a drawn out process with multiple court rulings and disagreements between government agencies and departments. The push for making EC available OTC began in December 2001, when Teva Women's Health filed an application for Plan B One-Step® to be sold OTC without a prescription or any age restrictions. On the day this was to take effect, Kathleen Sebelius, U.S. Health and Human Services Secretary, reversed the decision that required the FDA to remove restrictions on Plan B One-Step®; five days later, the FDA also denied a citizen's petition requesting Plan B One-Step® to be made available OTC. These two decisions left Plan-B One-Step® only available with the original restrictions, as a prescription. However, on April 5, 2013, Judge Korman, U.S. District Judge of New York, ordered the FDA to make all LNG-based contraceptives available OTC, and despite a proposal by the Obama administration to repeal the order, on April 30, 2013, the FDA partially complied with Judge Korman's order by making Plan B One-Step® available OTC but with restrictions that the buyer must be female and over the age of 15.[10,11] The debate was eventually settled and the final result was that starting on June 20, 2013, Plan B One-Step® could be sold to anyone as an OTC product, without a prescription, regardless of age or gender. This decision meant a wider patient base for EC and less regulation than was seen with any LNG product in the past. However, the changes to Plan B One-Step® availability do not apply to any other LNG-based contraceptives, including Plan B, Next Choice® and Next Choice One Dose™. These other LNG-based EC are only available behind the pharmacy counter, without a prescription, for anyone age 17 or older, and can be purchased with a prescription for those under 17. This is only in effect until Plan B One-Step®'s patent expires in three years. Then, the makers of Next Choice One Dose™ can file for an application to make it available OTC without age restrictions.

Comparing Levonorgestrel Products and Ella®

Ingredients and Mechanism of Action

Levonorgestrel

As stated previously, these products contain 1.5 mg LNG: Next Choice® with two tablets of 0.75 mg LNG each and Plan B One Step® and Next Choice One Dose™ with one tablet of 1.5 mg LNG. Levonorgestrel acts as an EC by primarily preventing ovulation, preventing fertilization by altering tubal transport of sperm or egg, and possibly inhibiting implantation by altering the endometrium.[6]

Ella®

Ella® contains 30 mg UPA and acts as a selective progesterone receptor modulator with antagonistic and partial agonist effects at the progesterone receptor, preventing progesterone from binding to its receptor. The primary action of Ella® is inhibiting ovulation by directly postponing follicular rupture.[6,9] Ella® potentially has a second mechanism in that it may cause endometrial changes to inhibit implantation.[6,9] Depending on the phase of the menstrual cycle in which the drug was administered, Ella® has other dose-dependent effects. A dose in the early luteal phase can decrease the thickness of the endometrium, delay endometrial maturation, and increase progesterone receptors. A dose in the mid-follicular phase causes inhibition of folliculogenesis and steroidogenesis, and a dose during the LH peak can delay follicular rupture considerably without interrupting luteinization.[9] All dose-dependent effects described above are specific to the menstrual phase in which the patient is currently in at the time of drug administration and all physiological effects are contributory to Ella®'s use in emergency contraception.

Availability

Levonorgestrel

Levonorgestrel products (Plan B One Step®, Next Choice®, and Next Choice One Dose™) are available to patients OTC at local drug stores. The LNG product Plan B that contained two 0.75 mg LNG tablets is no longer being manufactured or sold. As previously noted, Plan B One Step® is no longer sold behind the pharmacy counter with the requirement of verifying identification. Any patient of any age or gender can purchase Plan B One Step®. However, Next Choice® and Next Choice One Dose™ still require identification to validate a patient's age 17 or older for the purchase.

Ella

Unlike LNG, Ella® can only be dispensed to patients with a valid prescription. Prescriptions can be dispensed in two ways. First, most pharmacies have Ella® in stock and therefore the medication can be dispensed at the patient's preferred pharmacy. Second, patients can visit KwikMed at ellakwikmed.com or call 855-2ELLARX (855-235-5279) to fill their prescription. KwikMed is an online service staffed with licensed physicians to prescribe medications online or over the phone. Patients without a prescription can also visit this website or call the Ella-Rx line where they can complete an online consultation to determine if treatment with Ella® is appropriate. Clinics that aid young women with unplanned pregnancies, such as Planned Parenthood, may also carry Ella®.

Administration

Correct and timely administration of EC is crucial for ensuring maximum efficacy.

Levonorgestrel

Levonorgestrel products can be purchased in boxes containing either one or two tablets: Next Choice® contains two 0.75 mg LNG tablets; Plan B One Step® and Next Choice One Dose™ contain one 1.5 mg LNG tablet. Patients who chose the former option should take one tablet within 72 hours of unprotected intercourse, followed by the administration of the second tablet 12 hours later. The latter option is used by administering one tablet within 72 hours of unprotected intercourse or contraceptive failure. If vomiting occurs within one hour of taking LNG or within two hours of Plan B One Step®, the dose should be repeated. Patients should be aware that LNG is only effective within 72 hours of unprotected intercourse and immediate administration of the drug is encouraged for maximum efficacy.

Ella®

Ella® contains one 30 mg tablet of UPA, which can be taken within 120 hours (five days) of unprotected intercourse or suspected contraceptive failure. The dose is to be repeated if vomiting occurs within three hours of administration. Ella® can be taken with or without food and at any time during the menstrual cycle.

Efficacy of Levonorgestrel versus Ella®

In general, EC are most effective during the days directly prior to ovulation, considering intercourse during this time frame has the highest probability of pregnancy.[8] Ovulation must be prevented for at least five days, based upon the spermatozoa lifespan in the female genital tract of 120 hours.[8,9] In two double-blinded, randomized, multicenter studies, the widely used dose of LNG 1.5 mg reduced the expected pregnancy rate without emergency contraception of 8 percent to approximately 1 percent.[12] However, previous studies have agreed that LNG's ability to prevent ovulation decreases as ovulation nears. After the LH surge is triggered during the ovulatory process, LNG does not appear to prevent the follicle from rupturing.[8] Researchers saw an advantage of creating an EC that would be effective in delaying ovulation for five days, because LNG had no contraceptive effects in the presence of LH. In an analysis of pooled data from three randomized trials comparing EC efficacy, 48 cycles were treated with LNG, 34 cycles with UPA and 50 cycles with placebo. It was found that UPA "was effective in preventing follicle rupture in the five days following treatment, even when administered at the time of the LH surge (UPA 79%, LNG 14%, and placebo 10%)."[8] Moreover, women who took UPA were significantly less likely to become pregnant than those receiving LNG [Odds ratio (OR): 0.55, 95% Confident indicator (CI): 0.32-0.93].[8] As previously emphasized, timely administration of these EC is critical for their highest efficacy. Ulipristal acetate and LNG administered within 24 hours of unprotected intercourse or failed contraception showed lower pregnancy rates. Results showed a two-thirds lower risk for pregnancy in women who took UPA over LNG within the 24 hours (OR 0.35, 95% CI: 0.11-0.93).[8]

Side Effects, Warnings and Precautions, Contraindications

Levonorgestrel and UPA share very similar side effects, warnings, contraindications and drug interactions. For LNG, the most common side effects documented in more than 10 percent of women in clinical trials include: heavier menstrual bleeding (30.9%), nausea (13.7%), lower abdominal pain (13.3%), fatigue (13.3%), headache (10.3%), dizziness (9.6%) and breast tenderness (8.2%).[12] Side effects for UPA

seen in more than 5 percent of women in clinical trials include: headache (18%), abdominal pain (12%), nausea (12%), dysmenorrhea (9%), fatigue (6%) and dizziness (5%).[9] For both medications, there is a risk of ectopic pregnancy. One sign of ectopic pregnancy is lower abdominal pain after administration of EC, and patients who experience this symptom should seek medical attention immediately. Moreover, LNG and UPA do not terminate an existing pregnancy. Patients taking medications or herbal products that induce CYP3A4 may be hindering the efficacy of these EC. Finally, both medications are contraindicated in women with known or suspected pregnancy.

Cost

Unintended pregnancies in the United States are a prevalent public health issue and associated medical costs are about $5 billion since estimated in 2002.[2] A study conducted in 2012, used a decision analytic model to make comparisons of the use of LNG to UPA as EC for the prevention of unintended pregnancies. The study concluded that UPA would be a cost-effective option for preventing unintended pregnancies, indicating that "utilizing UPA instead of LNG would result in 37,589 fewer unintended pregnancies per 4,176,572 estimated U.S. annual EC uses (UPA failed to prevent 54,295 unintended pregnancies; LNG failed to prevent 91,884 unintended pregnancies) and a societal savings of $116.3 million annually."[2] However, from a more local standpoint, patients can purchase these products OTC, except for UPA. According to a 2013 survey conducted by the American Society for Emergency Contraception, the average price and price ranges for brand (Plan B One-Step®), generic (Next Choice®) and UPA widely vary (Table 1).[13] Ulipristal acetate's cost may vary depending on the patient's insurance, but it can be purchased via KwikMed service at ella-kwikmed.com with free shipping.[9] While these results displayed a wide range of prices, cost still remains a barrier for those seeking EC.

Patient Counseling

Patients having contraceptive failure or inconsistent contraceptive use should be counseled on correct and consistent forms of birth control to avoid unintended pregnancies. The combination of contraceptive failure with inconsistent or incorrect use is the cause of 48 percent of the 3.1 million unintended pregnancies.[14] Emergency contraceptives are not indicated for terminating existing pregnancies, therefore women with suspected pregnancies should not use these medications. When patients decide they would like to use EC, emphasize the importance of timely and correct administration. Levonorgestrel-based products are all effective within three days following unprotected intercourse or failed contraception, while Ella® is effective within five days. Taking these medications as soon as possible or "the morning after" is ideal for maximum efficacy. Patients should be counseled on potential side effects such as nausea and headache, and if patients are experiencing lower abdominal pain three to five weeks after taking EC, they should be instructed to seek medical attention immediately with the concern of ectopic pregnancy. Patients who miss menses for more than seven days after its expected date should contact their health care provider, as pregnancy may be a possibility. Continual users of EC should be urgently informed that these medications are not a regular form of birth control, nor do they pro-

Table 1. Emergency Contraceptive Product Comparison

	Plan-B One Step®	Next Choice®	Next Choice One Dose™	Ella®
Average Cost*	$48.65	$40.29	$41.63	Insurance Dependent or Available on Kwik Med: $40
Price Range*	$32-65	N/A	$26-62	N/A
Number of Tablets	1	2	1	1
Active Drug	LNG	LNG	LNG	UPA
Strength	1.5 mg	0.75 mg	1.5 mg	30 mg
Administration Timeline	Within 72 hours (3 days) of unprotected intercourse	First dose within 72 hours (3 days) of unprotected intercourse; Second dose 12 hours following first dose	Within 72 hours (3 days) of unprotected intercourse	Within 120 hours (5 days) of unprotected intercourse
Availability	OTC	OTC (must be ≥ 17 years old) Rx if < 17 years old	OTC (must be ≥ 17 years old) Rx if < 17 years old	Rx only
***Prices are averages from chain store pharmacies**				

tect against human immunodeficiency virus (HIV) infections or other sexually transmitted diseases. To ensure best practices from our patients and efficacious outcomes, it is critical that pharmacists ask relevant questions and provide information for the betterment of patients' health.

Conclusion

Emergency contraceptives are a quickly changing and currently underutilized aspect of public health. Unintended pregnancies are occurring at high rates, demonstrating that the need for education and information about EC in the population is not adequately being met by health care providers. With a more extensive understanding of how, when and why to use a particular EC product, patients can make their own decisions about their need for EC. With multiple options of EC on the market, including LNG and UPA, there are several important decisions to be made by the patient. As shown by recent regulation changes, the availability of LNG products are rapidly changing in regard to age and OTC status. Awareness of these changes is vital in aiding a patient in their final EC selection. These decisions also include cost comparison, side effect risk/benefit evaluations and determining which will be more effective in their specific situation. All of these decisions require health care providers, especially pharmacists, to understand the drugs' mechanisms to prevent pregnancy. Status and availability of EC products may be changing, but the role of the pharmacist is not. In light of new products entering the market, such as UPA, counseling and education is necessary now more than ever. Understanding the similarities and differences between two of the major EC options gives pharmacists a huge opportunity for education to greatly influence patient health.

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Evidence for the Potential Use of Polyphenols and their Derivatives in Moderating Allergic Immune Responses

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Abstract
Polyphenols are naturally occurring compounds that are found within numerous plant sources. They have a wide variety of structures and functions and have potential clinical uses in multiple disease states. Emerging studies involving polyphenols have demonstrated their antioxidative properties, as well as reduced risks of cardiovascular diseases and certain types of cancer. Due to these discoveries, there has been a marked increase in research related to the chemical properties of polyphenols and their potential uses in prevention of common acquired and inherited disease states. This article focuses on the effects that some polyphenolic compounds exert on immune function in regard to the induction and clinical manifestations of the allergic response and how supplementation with polyphenol-enriched apple extracts may alter the approach to treating atopic dermatitis and food allergies. Currently, due to the lack of large clinical trials detailing efficacy and safety data for these compounds when used to alter immune system responses to allergens, there are no strong recommendations for their use as prevention or acute treatment strategies for allergies.

Introduction

Researchers have been searching for natural products that are able to influence immune responses in regard to allergic disorders. Dietary polyphenols have been identified in multiple preclinical and a limited number of human trials as having the potential to alter the body's sensitivity to allergens and treat the allergic symptoms.[1,2] These compounds have been extensively researched in the past for many other conditions due to their anti-inflammatory and antioxidant properties, but the true connection to allergic disorders is still unclear. Polyphenols have shown benefits in studies focusing on animal models by having activity at the sensitization stage and during re-exposure to an allergen.

Most available therapies focus on treating allergy symptoms and not on the prevention or moderation of the allergic reaction. Current clinical recommendations for the treatment of symptoms associated with allergies include oral and topical antihistamines, corticosteroids, anticholinergics and mast cell stabilizers, which all focus on reducing the severity of the immune response and are relatively effective at doing so.[3,4] However, these medications should not be used long-term or in excessive doses due to an increased risk in associated adverse effects. For instance, long-term use of topical corticosteroids can cause side effects ranging from local skin atrophy to the development of Cushing's syndrome.[5] Also, although uncommon, overuse of antihistamines can result in adverse events as serious as QT prolongation and cardiac arrhythmias due to the drugs' inverse agonist activity at the Histamine 1 receptor (H1).[6] It is clear that there is a need for a therapeutic option that can effectively treat symptoms, as well as decrease the overall frequency of outbreaks by changing sensitivity to an allergen.

Allergic Immune Response

The exact mechanism of an immune response, while varied and specific for a particular allergen, generally revolves around the synthesis and resulting activity of inflammatory mediators, such as cytokines and interleukins that are produced by activated T helper (T_H) cells of the adaptive immune system.[7] These cells communicate with each other and with other cells of the immune system through the timed release of chemical mediators. These mediators' further activation of immune processes focuses on the isolation, destruction and removal of a "non-self" substance in order to avoid potentially adverse insults and to regulate normal internal homeostasis. T_H cells involved in this process are broken down and classified into two subcategories based upon cytokine production, through which subsequent immune cell types are activated and the specific protective outcome induced. T_H1 cells stimulate a nonspecific cellular immune response through the secretion of interferon gamma (IFN-γ) that activates innate immune system mediators including monocytes, tissue macrophages and natural killer (NK) cells. IFN-γ can also stimulate cytotoxic T-lymphocytes (T_C cells), as well as activate inducible nitric oxide synthase (iNOS) to produce nitric oxide (NO) free radicals in order to directly target bacteria and protozoa. T_H2 cells focus on stimulating the production of adaptive immune cells, B lymphocytes, basophils and eosinophils, in addition to up-regulating antigen-specific antibodies, which regulate humoral immunity.[7,8] Other cell types that are activated by this response include Immunoglobulin E (IgE), which stimulates mast cells to release histamine, serotonin and leukotrienes in order to cause bronchoconstriction. Optimal immune function relies on a dynamic balance between the two processes to effectively eradicate any foreign threat that is detected. Exaggerated allergic responses become problematic when there is an imbalance between T_H1 and T_H2 immunity, causing an overproduction of T_H2 pathway products.

An allergic disorder develops when the immune system detects a harmless allergen, considers it a threat and mounts local and systemic responses through T_H2 cell activity.[1] The immune response to the initial allergen exposure not only works to rid the body of the foreign contaminate through innate immune function, but will additionally sensitize the adaptive immune system to recognize the particular allergen more readily upon re-exposure.[9] This is accomplished through the production of antigen-specific IgE by plasma cells matured from activated B lymphocytes in response to the cytokines produced by T_H2 cells, most notably inter-

leukin 4 (IL-4).[9,10] Binding of these antigen-specific IgE molecules to the reintroduced allergen will cause symptoms of acute phase, as well as late phase immune reactions, due to the degranulation of mast cells. Inflammatory mediators released from these mast cells (histamine, interleukins and prostaglandins) can enhance vascular leakage while chemoattractants recruit basophils and eosinophils, as well as leukocytes in later stages, to the area of allergic reaction. Other cytokines cause upregulation of adhesion molecules for these leukocytes on vascular endothelial surfaces, which is critical for the progression to late phase reactions and chronic inflammation in future allergic reactions.[1,2,9,10]

In regard to specific types of allergic responses, food allergies can begin to develop during infancy after ingestion of an allergy-provoking food, but throughout life environmental factors can trigger respiratory allergies or skin allergies such as atopic dermatitis. Allergic reactions can also occur in part due to a genetic predisposition, called atopic syndrome (atopy).[11] This increased reactivity is characterized by the preferential production of IgE in response to allergens whose clinical manifestations may include atopic dermatitis, allergic contact urticaria, dyshidrotic eczema, allergic rhinitis, asthma, conjunctivitis, gastrointestinal allergies or any combination of the above.[11] An important diagnostic criteria of atopic syndrome is the production of allergen-specific IgE. Gene polymorphisms critical for the development of atopic syndrome are involved in the regulation of the T_H1/T_H2 ratio. Upon exposure to a specific allergen in a patient with atopy, the ratio skews toward a predominantly T_H2 cell response and the corresponding cytokine production. An overactivation of T_H2 lymphocytes against these presented antigens will cause a type I IgE-mediated allergy and hypersensitivity. More recently, alterations in genes for mast cell chymase (found only in dermal mast cells), and the α and β chains for the IgE receptor (representing a "gain of function" allele) have also been implicated in the preferential production of T_H2 cells and their respective cytokines.[11]

Polyphenol Chemistry

Polyphenols are naturally occurring and biologically active chemicals that are found in a variety of fruits (apples and grapes), plants (vegetables and legumes) and drinks (wine, cider, beer and tea) that are part of the human diet. They are considered nonnutrients because they are not required for normal body functions such as growth and development.[12] Polyphenolic compounds are byproducts of major metabolic pathways in plants and are extremely diverse in their chemical presentation. Currently, over 8,000 polyphenols have been identified, contributing significantly to the varied structures and bioactivity in plants and humans.[13] The highest concentrations of polyphenols are found in the parts of the plant source that are highly exposed to light, especially the leaves. Lower concentrations of polyphenols are found in portions of the plant that are underground, such as the tubers and roots.

Polyphenols have been considered deleterious to health due to their ability to bind to and precipitate proteins and other macromolecules, altering protein and macronutrient digestion and absorption from the gastrointestinal tract, as well as altering gut physiology (pH, colonic flora, biliary excretion, transit time, etc.).[14] Results of more recent studies have indicated that these interactions may also interfere with the bioavailability of polyphenols although the exact interaction remains undetermined. Renewal of interest in polyphenols, especially flavonoids, has been due to their proven antioxidant effects as free radical scavengers, Vitamin C and E regenerators and inhibitors of low density lipoprotein (LDL) oxidation. These properties have prompted research about other potential health benefits that these compounds may provide, including their potential use in altering immune response to allergic processes.[13] One of the most well-renowned types of polyphenols, the flavonoids, have displayed some medicinal applications in disease states including hypertension, allergies and hypercholesterolemia, and also as anti-inflammatory agents, anti-ulceratives, antibiotics and antidiarrheals.[13]

The overall structure of polyphenols is defined by the presence of one or more hydroxyl groups attached to aromatic rings.[1,12] Additional chemical and structural classifications of polyphenols divide this broad class of molecules into at least 10 subclasses depending on numerous factors including structural complexity, the presence of conjugated sugar groups, as well as other heteroatom linkages such as carboxylic acids, amines and phenols that alter the basic chemical structure.[13] The most basic classifications of polyphenols can be made into the following four groups: flavonoids, phenolic acids, stilbenes and lignans. Flavonoids and phenolic acids are the most abundant classes of polyphenols found in the human diet and can be further categorized based upon the location of hydroxyl groups. Flavonoids, with subclasses of flavones, isoflavones, flavanones, flavanols, flavonols and flavan-3-ols, are naturally abundant and are the basic building blocks of more complex polyphenols such as tannins which are highly hydrolyzed compounds capable of forming insoluble deposits with proteins.[13]

Polyphenols and Atopic Dermatitis

The possible anti-allergic effects of polyphenols have sparked studies looking at the potential benefits that supplementation could bring to patients suffering from skin allergies such as atopic dermatitis. Within the Atopy Outpatient Clinic of Kojima Hospital located in Tokyo, Japan, researchers examined the impact of apple extract supplementation on patients with atopic dermatitis.[15] Apple condensed tannins (ACT) were extracted from unripe apples and formulated into an oral dosage. Condensed tannins, also referred to as proanthocyanidin, are built from the flavan-3-ol class of polyphenols and have comparatively high molecular weights.[12] Previous studies in animal models had predicted that tannins are able to inhibit histamine release from mast cells and basophils, but this pilot study aimed to determine if ACTs are effective in human subjects as well.[15] Twenty-four patients between the ages of 8 and 18 years suffering from atopic dermatitis were selected for participation in the study, and then randomly divided into treatment or standard treatment control groups. Groups were determined to be comparable in regard to gender, age, peripheral eosinophil levels, and se-

rum IgE levels. Initially, both groups of patients began a standardized treatment using bufexamac ointment, half doses of alclometasone dipropionate ointment and hydroxyzine hydrochloride tablets (strengths and doses of medications not specified), which would be continued throughout the study period. Two weeks into the study, the treatment group added the ACT supplement to the regimen, dosed at 10 mg/kg divided into two daily doses. At the end of the ten-week study, the severity of the atopic dermatitis was assessed using a scoring system. The severity of each of the following was rated on a scale of zero to two: inflammation, cracking and hardening of the skin. Each location on the body, defined as trunk, arms, legs and face, counted as a separate score. Itching and sleep disturbances were also evaluated using a scale of zero to three. Total scores greater than 21 points were classified as severe. Starting and ending levels of serum IgE, peripheral eosinophils, glutamic oxaloacetic transaminase (GOT) and glutamic pyruvic transaminase (GPT) were also obtained from each patient. IgE and eosinophil counts were used to measure the change in the immune response with treatment; whereas, GOT and GPT values acted as nonspecific indicators of inflammation and tissue damage that are often elevated in dermatitis cases.

Patients receiving the ACT treatment showed a decrease in dermatitis scores overall (amount of decrease not specified), especially in the categories of itching and sleep disturbance.[15] Also in the treatment group, a statistically significant decrease was seen in peripheral eosinophil levels (525 versus 760/μL at baseline; $p<0.01$), but there was no significant difference in these levels within the control group (673 versus 784/μL at baseline). Neither group showed a significant difference in IgE, GOT and GPT levels. The study concluded that ACT supplementation may be effective at decreasing atopic dermatitis when used in combination with standard treatment with no significant side effects. This study was only performed to gather baseline data on the use of apple extract supplements in the treatment of atopic dermatitis. In summary, results were positive regarding the improvement in allergic symptoms, but additional studies using a larger patient population are needed to assess symptom management and the possibility of an ACT effect on the sensitization stage of allergic disorders.

Polyphenols and Food Allergies

The research regarding the anti-allergic effects of polyphenol research has extended beyond skin allergies to examine the potential impact on food allergies. Researchers in Switzerland studied the use of apple extracts for the reduction of food allergy symptoms in mice.[16] The apple extracts chosen for the trial had been enriched with polyphenols, mainly flavonols. To begin, all mice were sensitized to the allergen ovalbumin (OVA), the main protein found in egg, using weekly doses of 20 mg. As an adjuvant, 10 μg of Cholera toxin (CT) was also given to the mice to ensure sensitivity to the allergen would develop during the seven weeks under study. Previous studies have found CT to stimulate long-term immunological memory, particularly in the gut mucosa.[17] At the same time, mice were divided into four groups.[16] One group received the apple extract (1% weight-in-weight) in their food pellets during the sensitization process, and another group started the apple extract in the final week of the sensitization process which was used to detect secondary prevention. The study used two controls; the positive control group was not treated with the apple extract, and the negative control group was only sensitized to CT and not OVA. At the end of the seven weeks, the mice were given a challenge to the newly sensitized allergen using 100 mg OVA. Allergic reactions in the mice were observed for 30 minutes and scores were recorded based on the severity and frequency of symptoms including scratching, bristled fur, diarrhea, labored respiration and anaphylaxis. Blood, lymph node and intestine samples were then obtained from the animal subjects.

Results of the study were generally positive in concern to the benefits of polyphenol-enriched apple extracts. As expected, the negative control group did not experience any symptoms upon challenge to the antigen. Mice who received the apple extract during the final week of sensitization to test the secondary prevention hypothesis had significantly lower observation scores for symptoms. However, the mice ingesting the apple extract throughout the entire sensitization period did not experience fewer symptoms compared to the positive control group, which may show that polyphenols cannot prevent the development of an allergic response. Serum IgE levels were not found to vary in any of the mice regardless of apple extract treatment, but lower levels of cytokines were released from lymph nodes in the treated population of mice. A protease from intestinal mast cells, known to be involved in allergic responses to food allergens, was found in lower concentrations only in the secondary treatment group, which suggests an inhibition of the effector cell. Researchers tested the hypothesis that polyphenols may bind to proteins and lead to a diminished immune response. In vitro experiments showed that macro-complexes formed between the apple extract and OVA, resulting in decreased antibody reactivity. Contrary to expectation, in mice receiving the apple extract in their food pellets throughout the entire sensitization process, the apple extract provided no benefit as a primary prevention mechanism.

Conclusion

Although common in dietary sources, polyphenols are often used as a supplement and are available as an extract that has been formulated into an oral dosage. A variety of natural polyphenol products are available over the counter, and pharmacists must be knowledgeable about the current options and safety information for proper patient counseling. Supplements on the store shelf may be labeled as tablets or capsules containing polyphenols in general or may specify a particular category of polyphenols such as flavonoids. Polyphenol-containing compounds are marketed mainly for their antioxidant properties. It is expected that extracts from fruits or plants act as the main ingredients in these products. Some of the most common polyphenol products purchased by patients include green tea, grape, berry or apple extracts.

Because of the limited number of human trials that have been conducted, proper dosing of polyphenol supplements is still unknown. Bioavailability of oral preparations of these

compounds is relatively low and dependent on the size of the chemical structure, which varies greatly between the subclasses.[12] Dosing becomes a balance of finding a high enough dose to cause the intended effect, such as decreasing allergic symptoms, but not causing adverse reactions due to excessive intake. For instance, high concentrations of polyphenols have been found to cause decreased viability of liver cells, interruption of cell signaling cascades and auto-oxidation processes within cells.[12]

Additional research is still necessary to fully determine bioavailability, optimal dosing, and overall safety of polyphenolic compounds in human subjects. The ability of polyphenol supplementation to alter the body's sensitivity to allergens and to treat allergic symptoms is still under investigation. Although it seems certain these compounds exhibit chemical mechanisms that may justify their therapeutic use in allergic responses, adequate scientific trials in large patient populations are not yet available. As pharmacists, it is important to educate patients on the risks associated with taking excessive doses of polyphenol supplements. However, difficulties in designing dosing regimen strategies may arise due to limited research data on the levels necessary to achieve a clinically significant effect and also due to the large variety of polyphenolic compounds available for use. Despite the promising potential for the use of polyphenol-containing products in the moderation of allergic immune responses, polyphenol supplements should not be recommended as an effective option for allergy purposes until further research is conducted.

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Overview of Kalydeco® (Ivacaftor) for Treatment of Cystic Fibrosis

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Abstract

Cystic fibrosis (CF) is a genetic disease associated with specific gene mutations that presents with pulmonary inflammation and frequent lung infections, exocrine pancreatic insufficiency, altered sweat composition and declining lung function. Ivacaftor (Kalydeco®) was approved for treatment of cystic fibrosis in patients 6 years of age and older with a G551D mutation on the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Ivacaftor is a CFTR potentiator and does not work in patients with a mutation of the F508del. Efficacy has been demonstrated in several trials with a primary outcome of improved FEV_1, improvements in pulmonary exacerbations, patient-reported decrease in respiratory symptoms and weight gain. Side effects that have been reported include oropharyngeal pain, nasal congestion, abdominal pain, upper respiratory tract infection, rash and dizziness. The drug is metabolized via the CYP3A4 enzyme system and should be monitored for potential drug interactions accordingly. Information on long-term safety is not yet available, but clearly this drug represents an advance in the management of a debilitating disease.

Introduction

On Jan. 31, 2012, Kalydeco® (ivacaftor) received FDA approval for treatment of cystic fibrosis (CF) in patients 6 years of age and older with a G551D mutation on the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Cystic fibrosis is a genetic disease that causes chronic pulmonary inflammation, exocrine pancreatic insufficiency, altered sweat composition and declining lung function.[1,2] This disease affects approximately 30,000 people in the United States and 70,000 people worldwide.[3] Diagnosis typically occurs early in life, with approximately 70 percent of patients with CF diagnosed before 2 years of age.[3] A variety of CFTR mutations have been identified as causing CF.[2] Ivacaftor is a CFTR potentiator that has shown efficacy in clinical trials for use in patients with at least one G551D mutation on the CFTR gene.[4,5] However, clinical trials have shown that ivacaftor is not effective in patients with a homozygous F508del mutation.[6] Treatment options may vary between individual patients due to the variety of genetic mutations that may cause CF.[2]

Disease State Overview

Cystic fibrosis is an autosomal-recessive disease, requiring a patient to have two mutated genes for the CFTR protein in order to be affected by the disease. The CFTR protein is a transmembrane protein present on the apical surface of exocrine epithelial cells, including cells in the lungs, pancreas and sweat glands. This protein primarily acts as a chloride channel, but it is also involved in the regulation of other ion channels.[2] More than 1,000 DNA mutations have been identified as causing CF, with different populations having higher prevalence of specific mutations depending on race, ethnicity and geography.[2,7] The most common mutation is F508del, which is a deletion mutation resulting in improper folding of the CFTR protein leading to little or no CFTR protein on the cell surface.[6] Another mutation, called G551D, is a missense mutation that prevents the binding of adenosine triphosphate (ATP) to the CFTR protein, resulting in an inability to activate the CFTR protein.[2] As of 2012, approximately 87 percent of people with CF were known to have at least one copy of the F508del mutation, and approximately 4 percent of people with CF had at least one copy of the G551D mutation.[8] Because there are numerous genetic mutations that can cause CF, the disease can vary in severity, pathogenesis and treatment approach between individual patients.[2]

Symptoms of CF commonly include pulmonary inflammation, recurrent respiratory infections, airway obstruction, exocrine pancreatic insufficiency and altered sweat composition.[2,9] Defective CFTR proteins in the respiratory tract lead to reduced chloride transport into the lumen, thereby decreasing surface water content and mucociliary clearance. The heightened mucus retention leads to chronic respiratory infections and inflammation, resulting in lung obstruction and structural damage beginning in infancy, often before symptoms are present.[9] Pancreatic insufficiency is the decreased ability to digest nutrients in the gastrointestinal tract with pancreatic enzymes. This occurs due to obstruction of the pancreatic ducts and autoactivation of trypsin, a digestive enzyme inside the pancreas, resulting in structural damage to the pancreas.[10] Pancreatic insufficiency is present in many phenotypes of CF, with more than 90 percent of diagnosed CF patients beginning to exhibit low pancreatic function before 1 year of age.[11] Individuals affected by CF also typically have a higher concentration of chloride in their sweat compared to individuals without CF.[12]

Screening for CF among newborns is becoming increasingly common; however, diagnosis of CF can be difficult in some patients. Multiple factors can serve as screening tools for CF. A routine newborn screening (NBS) test in infants measures levels of immunoreactive trypsinogen (IRT), a pancreatic protein. A high concentration of IRT constitutes a positive NBS for CF. Family history or presence of CF symptoms can also be screening tools for this disease, as they identify patients who might be at risk for CF. A positive result in any of these screening tests indicates that a patient needs to undergo diagnostic testing.[12]

The current diagnostic standard for CF is a sweat chloride test. This involves collecting sweat from the patient after stimulation of sweating, followed by comparing the resulting chloride concentration to a standard. A chloride concentra-

tion above 60 mmol/L is diagnostic for CF. Concentrations between 40 mmol/L (or 30 mmol/L for patients under 6 months) and 60 mmol/L indicate the need for genotype analysis to assess CFTR gene mutation. A chloride concentration below this range indicates that CF is very unlikely in the patient. When the sweat test results in intermediate values, the presence of two CF-inducing mutations is considered diagnostic for CF. Genotype analysis is available but is not preferred due to inaccuracy and difficult interpretation.[12] Early diagnosis of CF is critical in order to begin treatment as soon as possible to delay progression of the disease.[9]

The aim of many current treatment options is to reduce pulmonary infections, exacerbations, inflammation and deterioration; compensate for pancreatic insufficiency by pancreatic enzyme replacement therapy (PERT); and maintain healthy nutrition and growth.[11] Definitive treatment guidelines that are applicable to all patients with CF are still needed; however, a majority of CF patients utilize a treatment regimen including inhaled antibiotics, hypertonic saline, airway clearance techniques and bronchodilators.[13] Inhaled antibiotics aim to treat respiratory tract infections in CF patients, which are commonly due to Pseudomonas aeruginosa.[11] Multiple antibiotic options are available, including inhaled tobramycin, inhaled aztreonam and azithromycin.[11,13] Pulmonary exacerbations can be lessened by inhaled hypertonic saline in patients over 6 years of age; however, this may not be effective in patients under 6 years of age.[9] Airway clearance therapy, such as percussion or postural drainage, is recommended for all patients.[11] Inhaled β_2-agonists for bronchodilation may be used to reduce exacerbations, but evidence supporting this therapeutic option is not strong.[13] Pancreatic insufficiency should be treated with PERT, even if evidence of malabsorption is lacking. Following CF diagnosis, growth and weight gain in infants should be promoted, as a higher body mass index at 2 years of age is linked to improved lung function in later childhood. Thus, proper nutrition and growth should be lifelong therapeutic goals.[11] Additional studies are needed to resolve questions of prioritizing the importance of therapeutic options and identifying appropriate therapy options for patients less than 6 years of age.[13] New treatment options continue to be explored in order to better manage CF disease state.

Pharmacist Information and Counseling Points

Indication: Ivacaftor, a CFTR potentiator, is a U.S. Food and Drug Administration (FDA)-approved treatment option for the management of CF in patients 6 years of age and older.[14,15] This particular CFTR potentiator is used specifically in patients who are found to have the G551D mutation on the CFTR gene.[14,15] It should be noted that ivacaftor is not effective in treatment of patients with a homozygous mutation of the F508del mutation.[15] Ivacaftor works to re-potentiate the nonfunctional CFTR transmembrane protein. By increasing the chance of the CFTR being open, the regular flux of chloride ions in epithelial cells is restored.[14,15] Due to this normalization of flow, salt and water concentrations will also be stabilized, leading to less viscous mucous secretions and improved respiratory function.[16]

Target Population: Ivacaftor is targeting patients with a G551D mutation of the CFTR protein.[14,17] Pharmacological treatment options for patients are limited to mucolytics, prophylactic antibiotics, bronchodilators and anti-inflammatory medications.[18] By using ivacaftor, patients may have enhanced therapy by targeting a more direct cause of symptoms instead of only providing symptomatic relief. Pediatric patients are prime targets for CF treatment, and due to the natural progression of the disease, the ability to start therapies in patients at an early age will be beneficial in reducing the degenerative effects and long-term complications of CF. Ivacaftor, being approved for children ages 6 years of age and older, has the potential to be at the forefront of CF pharmacotherapy.

Dosing: Kalydeco® is formulated as a "light blue capsule-shaped, film-coated tablet for oral administration."[14] After clinical studies, the most effective dose was established at 150 mg twice daily.[14] Adult dosing is also recommended for pediatric patients due to similar pharmacokinetics.[14] The adherence to a high-fat diet while using ivacaftor helps to increase medication absorption approximately twofold to fourfold.[17]

Side Effects: Adverse reactions observed in over 10 percent of patients are as follows: oropharyngeal pain, nasal congestion, abdominal pain, upper respiratory tract infection and rash.[15] Some patients have reported feeling dizzy after taking ivacaftor, so it is advised that patients refrain from operating heavy machinery until aware of how they are personally affected by the drug.[17]

Drug Interactions: Because ivacaftor is metabolized via the CYP3A4 enzyme, it is important to be aware of the potential effects of taking other medications which also interact with CYP3A4. A brief guide to drug interactions and dosing adjustments related to changes in medication exposure may be found in the manufacturer's treatment guide.[17]

Monitoring Parameters: There are several measurements that can be monitored to demonstrate the positive effects of ivacaftor. Such factors include an increase in forced expiratory volume (FEV), decreased respiratory exacerbations, decreased sweat chloride concentration, an increase in body weight and an overall decrease in CF-like symptoms. Increases in alanine aminotransferase (ALT) or aspartate amino transferase (AST) have been observed in ivacaftor patients. Alanine aminotransferase and AST levels should be assessed prior to treatment, then "every three months during the first year of treatment, and annually thereafter."[17] If elevations occur, it is recommended that the patients be monitored monthly if treatment benefit outweighs risk or until numbers return to normal; however, if ALT and/or AST levels are greater than five times the normal upper limit, the drug should be discontinued and therapy should be reevaluated.[19,17]

Patient Expectations: Patients can expect to see positive results after less than a month of taking ivacaftor. They should notice a decrease in sputum production, easier

breathing patterns and an increase in weight gain.[17] Because CF is a chronic disease, their medication regimen will also be chronic, and patients should be made aware that ivacaftor is not a "cure" for CF.

How to Improve Compliance: While chronic medication regimens may seem overwhelming, it is important to stress the benefits of high adherence. In assessing the willingness of pediatric patients to follow their CF therapy, roughly half have been estimated to be noncompliant.[20] One benefit to using ivacaftor is the ability to see results in a relatively short period of time after initiation of therapy compared to long-term methods such as airway clearance techniques.[21] Seeing quick results will help patients to continue therapy, as "no perceived benefit" has been identified as one of the barriers to effective treatment.[22] Furthermore, parental involvement is a highly important aspect in pediatric care. In fact, parents may even be seen as part of the health care team due to their role in facilitating and assisting their child in following CF treatment protocol.[22] Therefore, counseling the primary caregiver will be just as important as counseling the pediatric patient. This being said, pharmacists should be able to recognize their own role in this education process. A single case study designed by McClellan, Cohen, and Moffett intending to increase pediatric compliance to CF therapy, attempted the use of a "time out" technique when children resisted compliance.[23] Time out may be generalized to the strategy of, "removing the child from reinforcers and reinforcing environments upon noncompliance with demands," and was shown to decrease behavioral conflicts with CF therapy. One given example of time out would be placing a child in a chair facing the wall for several minutes without permission to talk to others.[23] While this method of intervention may seem rudimentary, it demonstrates how reinforcing and encouraging children to adhere to CF therapy can be quite practical.

Cost: As of Nov. 6, 2013, the average wholesale price of 60 (150 mg) tablets (one month's supply) of ivacaftor is $30,723.60.[15] Therefore, the high cost of this medication may be a barrier in effective treatment for some patients.

Literature Review

Several clinical trials have been conducted that support the approval of ivacaftor for the treatment of CF containing the G551D mutation, while also possessing a manageable side effect profile. The first is a phase III clinical trial concluding that the utilization of ivacaftor led to a statistically significant increase in pulmonary function in patients over the age of 12 as defined by forced expiratory volume in one second (FEV_1).[4] The next study is a phase III clinical trial concluding a similar increase in pulmonary function as defined by FEV_1 in pediatric subjects between the ages of 6 and 11.[5] The third study is a phase II clinical trial assessing the safety and function of ivacaftor in CF that is homozygous for the F508del mutation concluding that ivacaftor, while reasonably safe, is not effective in this subpopulation.[6] The final study is a phase II clinical trial that provides a look into the safety profile of ivacaftor in patients with CF containing the G551D mutation, and suggests that the drug is safe for this subpopulation.[24] These four clinical trials are key to understanding the therapeutic benefit of ivacaftor in patients with CF containing the G551D mutation.

Ramsey et al. conducted the main efficacy trial supporting the use of ivacaftor for improved lung function in patients with CF containing the G551D mutation. The study was a 48-week, phase III clinical trial. Eligible patients for this trial included those aged 12 years or older who had a previous diagnosis of CF, possessed the G551D mutation on at least one CFTR allele, and had an FEV_1 between 40 and 90 percent of the predicted value given age, sex and height. No specific exclusion criteria were provided. The primary endpoint for the trial was the absolute change in FEV_1 from baseline at week 24. Secondary endpoints included change in FEV_1 from baseline at week 48, the time to pulmonary exacerbation, patient reported respiratory symptoms, weight change and CFTR function (via sweat chloride test).[4]

In the study, 161 patients were randomly assigned to one of two treatment groups: ivacaftor 150 mg twice daily (n=83) or placebo (n=78). The randomization was stratified for both age (<18 years or ≥18 years) and baseline pulmonary function (<70 percent or ≥70 percent predicted FEV_1 level). The stratification process was successful; lending equally distributed demographics across the two treatment groups. Power calculations had concluded that 160 patients would provide 80 percent power to detect a change of 4.5 percent in the predicted FEV_1. All patients received their medications twice daily for a full 48 weeks and were allowed to remain on all other medications with an FDA-approved indication for CF, such as dornase alfa and inhaled antibiotics. Primary outcome was assessed for all patients at week 24 and secondary outcomes were assessed for all patients at day 15, week 24, and week 48.[4]

At week 24, patients in the ivacaftor group witnessed a 10.4 percent increase in FEV_1 compared to a 0.2 percent decrease in the placebo group ($p<0.001$). The effect on FEV_1 was noted to be statistically significant at day 15, and was retained throughout all 48 weeks of treatment. This change in FEV_1 was analyzed over subgroups defined by baseline FEV_1, age and sex; there was no apparent difference in the efficacy of ivacaftor with respect to change in FEV_1 across any of these different subgroups. In addition to change in baseline FEV_1, other outcomes such as pulmonary exacerbations ($p=0.001$), patient reported respiratory symptoms ($p<0.001$), weight gain ($p<0.001$) and CFTR function ($p<0.001$) were all improved in the ivacaftor treatment group.[4]

Overall, patients in the placebo group experienced more adverse events than patients in the ivacaftor group, likely due to the decreased level of pulmonary exacerbation in patients treated with ivacaftor. Forty-two percent of subjects in the placebo group experienced a serious adverse event while only 24 percent of subjects in the ivacaftor group experienced such an event. However, two patients in the ivacaftor group experienced hypoglycemia while no patients in the placebo group experienced this adverse event. The study

yielded no adverse events that were concluded to have arisen as a result of ivacaftor treatment. All patients who were initiated on either of the treatment drugs completed the trial with the exception of one subject, a member of the placebo group who dropped out of the study following a severe pulmonary exacerbation. Ultimately, ivacaftor was not associated with any significant adverse events not seen in the placebo group.[4]

Limitations of this trial include restrictive inclusion criteria and limited documentation on use of other CF medications. The inclusion criteria only allowed patients who were between 40 and 90 percent of predicted FEV_1 levels.[4] This prevents the most critical of patients from enrolling in the study, limiting the external validity of the trial. It must also be noted that the trial utilized ivacaftor only as add-on therapy to an established CF treatment regimen. The protocol did require that patients be on their current medication regimen for a full year prior to trial initiation, but it is unclear what effect the impact that those drugs may or may not have on the efficacy value of ivacaftor.[4]

The second main efficacy trial, by Davies et al., is a 48-week phase III study conducted in children aged 6 to 11. Eligible patients for this trial included children aged 6 to 11 with a confirmed diagnosis of CF containing the G551D mutation. Additionally, subjects were required to have a predicted FEV_1 between 40 and 105 percent given their age, sex and height. The primary endpoint for the study was absolute change in FEV_1 from baseline at week 24. Secondary endpoints included change in FEV_1 from baseline at week 48, weight change, CFTR function (via sweat chloride tests), patient and parent reported respiratory symptoms, and safety.[5]

In the study, 52 patients were randomly assigned to one of two treatment arms: placebo (n=26) or ivacaftor 150 mg twice daily (n=26). There was no randomization stratification or power calculation. All patients received their treatment medication twice daily for a full 48 weeks and were allowed to remain on all medications that possessed an FDA-approved indication for CF. Endpoints were assessed at follow-up meetings every eight weeks (weeks 8, 16, 24, 32, 40, and 48) in addition to day 15.[5]

With regard to change in baseline FEV_1 at week 24, the ivacaftor group witnessed an increase of 12.6 percent compared to an increase of 0.1 percent in the placebo group ($p<0.001$). This statistically significant effect was noted at day 15 and was maintained throughout the course of the clinical trial to the week-48 endpoint. Other secondary outcomes that showed improvement in the ivacaftor treatment group compared to the placebo group included weight gain ($p<0.001$), patient and parent reported respiratory symptoms ($p=0.109$; $p=0.033$) and CFTR function ($p<0.001$).[5]

The total incidence of adverse events was similar between the two treatment groups. The ivacaftor group experienced the following side effects more often than the placebo group: oropharyngeal pain, headache, nasopharyngitis, upper respiratory tract infection, otitis media, diarrhea and increased blood eosinophil count. Serious adverse events such as pulmonary exacerbation and productive cough were witnessed infrequently with no difference between treatment groups. These results mimic those seen in the adult clinical trials and suggest that ivacaftor is well-tolerated in the pediatric population aged 6 and above.[5]

The main limitation of this trial is a clear lack of power. This inadequacy is quite common in pediatric clinical trials due to a multitude of factors including, but not limited to, the low incidence of CF and parental concern over experimental treatments. Even so, the lack of power must be considered when trying to determine the external validity of the trial.

The third efficacy trial, conducted by Flume et al., is a 16-week (followed by a 96-week open-label extension period) phase II study. Eligible patients for this trial included clinically stable subjects over the age of 12 who had been diagnosed with CF containing two F508del alleles (homozygous). Additionally, subjects were required to have a predicted FEV_1 above 40 percent given their age, sex and height. Subjects remained on their pre-study medication regimens throughout the study with the exception of hypertonic saline and known inducers/inhibitors of CYP3A4. The primary endpoints for the study were (1) absolute change in FEV_1 from baseline at week 16 and (2) safety as evaluated by adverse events, lab values, vital signs and physical examinations.[6]

In the study, 140 patients were randomly assigned in a 1:4 ratio to one of two treatment arms: placebo (n=28) or ivacaftor 150 mg twice daily (n=112). There was no randomization stratification or formal power calculation. All patients received their treatment medication twice daily for a full 48 weeks and were allowed to remain on all medications that possessed an FDA-approved indication for CF. Endpoints were assessed at follow-up meetings every eight weeks (8, 16) in addition to day 15. Any patient who experienced a greater than 10 percent increase in FEV_1 at any time point during the 16-week treatment period qualified to enroll in the 96-week open-label extension.[6]

With regard to change in baseline FEV_1 at week 16, the ivacaftor group witnessed an increase of 1.7 percent compared to placebo, which was not statistically significant ($p=0.15$). Twenty-eight members of the ivacaftor group (25%) and six members of the placebo group (21.4%) qualified for the open-label extension period as a result of their increased FEV_1. The difference in FEV_1 was not statistically significant in these patients at the conclusion of the open-label extension ($p=0.46$).[6]

The overall safety profile was similar in both treatment arms. However; cough, nausea, rash and contact dermatitis occurred more often in the ivacaftor group; none of these events was considered severe. On the other hand, pulmonary exacerbation occurred more often in the placebo group. Few members of the ivacaftor group experienced life-threatening events including fatigue, depression and suicidal ideation (n=1; 0.9%) as well as severe events including nasal congestion, epistaxis, diarrhea, rash, headache, and arthritis (n=10;

8.9%). Three subjects (2.7%) in the ivacaftor group discontinued the study drug due to adverse events.[6]

This study allows for the conclusion that ivacaftor is not effective in patients homozygous for the F508del mutation. The study does, however, provide additional information regarding the safety of ivacaftor in patients with diagnosed CF. The adverse event profile witnessed in this study supports the conclusion that ivacaftor is well-tolerated in patients over the age of 12 diagnosed with CF.

The final trial, conducted by Accurso et al., is a phase II study designed to assess the safety and adverse event profile of ivacaftor in patients who have CF containing the G551D mutation. Eligible patients for this trial included patients over the age of 18 who had been diagnosed with CF and possessed a G551D mutation on at least one CFTR allele; patients also had to have an FEV_1 of 40 percent or more of the estimated level for age, sex and height. No specific exclusion criteria were reported. The primary endpoint for the study was to assess the safety and adverse event profile of ivacaftor. Secondary endpoints included markers of CFTR function (nasal potential difference and sweat chloride concentration), pulmonary performance (FEV_1) and quality of life (Cystic Fibrosis Questionnaire-revised; CFQ-R).[24]

This trial was designed as a two-part study. In part one, 20 subjects were placed into one of five treatment groups: placebo (n=4), ivacaftor 25/75 mg (n=4), ivacaftor 75/25 mg (n=4), ivacaftor 75/150 mg (n=4), and ivacaftor 150/75 mg (n=4), where the first strength indicates the dose received prior to a 14-day washout period and the second strength indicates the dose received after the washout period. Subjects were given their initial treatment dose twice daily for 14 days; a 14-day washout period followed; subjects were then given their second treatment dose twice daily for an additional 14 days. Primary and secondary endpoints were assessed for all patients at the end of each 14-day treatment period. In part two, 19 subjects (different from the participants in part one) were placed into one of three treatment groups: placebo (n=4), ivacaftor 150 mg (n=8), ivacaftor 250 mg (n=7). Subjects were given their treatment doses twice daily for a continuous 28 days after which primary and secondary endpoints were assessed.[24]

The primary outcome for both part one and part two of this clinical trial yielded relatively few side effects associated with the use of ivacaftor at any dosage strength. There were 22 reported instances of drug-associated moderate or severe adverse events. Some of the more prominent adverse events that were reported included elevated blood glucose, body aches, glycosuria and nausea. Secondary efficacy outcomes yielded no statistical significance over placebo.[24] However, the low enrollment of the study combined with a lack of power make the lack of statistical efficacy over placebo a moot point.

These four trials outline the safety and efficacy data that is currently available for the use of ivacaftor in humans. However, it must also be noted that all four of these clinical trials were both funded and designed by the manufacturer of ivacaftor, Vertex Pharmaceuticals™, but given the infancy of the compound, orphan nature of the drug in question and the fact that these were the clinical trials involved in the FDA approval process for the medication; this manufacturer-driven study process is an economic necessity. Furthermore, the transparency with which the authors addressed their potential conflicts of interest limits any potential concern for bias. An additional point to consider is that given the genetic nature of CF, pulmonary function can begin to decrease well before age 6, meaning that these undeveloped patients are in a prime position to alter the course of their disease. It would be beneficial to see a clinical trial in patients younger than age 6, in order to determine if ivacaftor can maintain its thus-far impressive clinical impact on a younger set of patients. Currently, Vertex Pharmaceuticals™ is recruiting for a phase III clinical trial to assess the safety and efficacy of ivacaftor in patients aged 2 to 5.[25]

Ultimately, while the G551D mutation impacts less than 10 percent of all patients with a CF diagnosis, the success for ivacaftor with regard to improvement of clinical indicators in this subpopulation is a definitive step forward. In particular, consistent double-digit improvement of FEV_1 suggests a significant boost in lung function when compared to other commonly used CF therapies.[4] Unfortunately, it remains to be seen what long-term impact ivacaftor may have on life-expectancy and long-term quality of life in patients with CF.

Conclusion

Kalydeco® (ivacaftor) has been approved for the treatment and management of CF in pediatric patients as of Jan. 31, 2012. This medication is approved for patients 6 years of age and older, who have a G551D mutation on the CFTR gene.[14,15] Ivacaftor's novelty comes from its genetic specificity for the aforementioned CF mutation.[14,15] Because a majority of CF patients are diagnosed before they reach the age of 2, it is important to have medication therapy protocols approved and at the ready for children.[3] Short-term effects have shown promise with increasing FEV_1 values; however, information on long-term use is uncertain. Overall, introduction of ivacaftor into medication regimens is a positive step for the treatment of pediatric patients living with cystic fibrosis.

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The Safety of Artificial Sweeteners and their Use in Pharmaceuticals

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Abstract

Artificial sweeteners are sugar substitutes that add sweetness to foods and beverages without the extra calories found in sugar. These additives are used to help patients with diabetes avoid hyperglycemia and assist people in losing weight or avoiding weight gain by providing a replacement to higher calorie sugar-sweetened foods. Artificial sweeteners can be found in many sugar-free beverages, candies and gum, as well as pharmaceutical products. Although artificial sweeteners are often recommended over the sugar-sweetened alternatives in weight loss and diabetes prevention, the use of such products are not without risk. Studies have been conducted to assess artificial sweeteners involvement in contributing to cancer, genotoxicity and diabetes. To provide optimal health care to patients, it is imperative to know the implications involved with these risks. Pharmaceutical products formulated for oral and peroral administration have been sweetened by both artificial and natural sweeteners, and the utilization of artificial sweeteners has been deemed more beneficial than its natural counterpart. As health care professionals, it is our job to counsel patients on the benefits of artificial sweeteners over natural sweeteners along with the importance of using artificial sweeteners in moderation.

Introduction and Background Information on Artificial Sweeteners

Currently there are five artificial sweeteners approved by the U.S. Food and Drug Administration (FDA) including sucralose, aspartame, saccharin, stevia and acesulfame potassium (acesulfame). These compounds are regulated by the FDA as food additives and were evaluated for safety before being made available for public consumption (Table 1).[1] Artificial sweeteners are currently the gold standard as additives in food and beverages consumed by those with type II diabetes mellitus and those who either want to lose weight or avoid weight gain.[2] Artificial sweeteners help diabetics avoid hyperglycemia and maintain a more consistent blood sugar level. Artificial sweeteners add little to no calories to achieve the equivalent sucrose sweetness within their food and beverage formulations, which makes artificial sweeteners a viable choice for those limiting their daily caloric intake.[1] By limiting both sugar intake and overall calories consumed, the risk of developing diabetes and obesity decreases.[3]

However, artificial sweetener consumption has been linked to an increased cancer incidence, with both genotoxic and carcinogenic properties in studies conducted in lab rats. Subsequently, when more stringent safety studies were performed, an increase in cancer incidence was not observed in human subjects. However, long-term studies have not been conducted to assess the overall effect artificial sweeteners have in humans after consumption over a lifetime.[4]

Toxicity Testing

A study done in 2002, at the Center of Advanced Study, Cell and Chromosome Research, Department of Botany at the University of Calcutta, in conjunction with the Department of Internal Medicine at the University of Kentucky, studied the genotoxicity of the artificial sweeteners aspartame, acesulfame and saccharin. Genotoxicity was evaluated according to how much damage was sustained to the DNA when exposed to external factors. The study population included mice that were fed increasing dosages of one sweetener, and their bone marrow tissue was analyzed for genotoxicity. From the test performed in this study it was concluded that each of the three sweeteners induced DNA damage in the mouse bone marrow cell. This study concluded that it is impossible to assess the long-term effects of artificial sweetener use, but use should be limited based on the genotoxic effects found within the study.[6]

A bioassay evaluation of aspartame carcinogenicity in Sprague-Dawley rats was conducted by the Cesare Maltoni-Cancer Research Center of the European Ramazzini Foundation. Aspartame was added to the rat's normal feed at the concentrations of 100,000; 50,000; 10,000; 2,000; 400; 80 and from the control group 0 ppm. These concentrations were calibrated to parallel the human consumption of 5,000; 2,500; 500; 100; 20; 4 or 0 mg/kg, respectively, each day. Aspartame was added to the feed when the rats were 8 weeks old until natural death, upon which an extensive autopsy was conducted. Both the male and female population showed a significant increase in the incidence of malignant tumors with ($p \leq 0.05$) for males and ($p \leq 0.01$) as compared to controls. The study concluded that with aspartame consumption, the risk of malignant tumor development increased within the rat subjects. These findings show more research is necessary to adequately assess aspartame carcinogenicity with long-term consumption in the human population.[7]

Sucrose versus Artificial Sweeteners

A prospective cohort study examined the association of artificially and sugar-sweetened beverages in the development of type II diabetes.[8] The study included 51,529 men ages 40 to 75 years who were recruited to form a Health Professionals Follow-Up Study. The study consisted of questionnaires mailed every other year to assess health status and lifestyle factors. After excluding the men who did not respond to the survey and those with type II diabetes, cardiovascular disease and cancer, a 131-item semiquantitative food frequency

Table 1. Overview of FDA Approved Artificial Sweeteners [1,2,3,5]

Artificial Sweetener	Brand Name	Sweetness Compared to Sugar	Physical Characteristics	Food Additive
Sucralose	Splenda	600x	Heat-Stable	Diet Foods, Sugar-Free Beverages, Gum, Gelatin; can be used in baking
Aspartame	NutraSweet and Equal	220x	Combination of two amino acids	Sugar-Free Beverages
Saccharin	Sweet N'Low, Sweet Twin, NectaSweet	300x		Diet Foods and Beverages
Stevia	Truvia, Sun Crystals, Pure Via	200-300x	Dietary Supplement/ Extracted from Stevia rebaudiana plant	Diet Foods and Beverages
Acesulfame	Sunett, Sweet One	200x	Heat-Stable	Mostly in Carbonated Beverages; Baking

questionnaire was sent out to 40,389 qualified men every four years to assess the consumption of sugar-sweetened and artificially sweetened beverages. Artificially sweetened beverages included caffeinated, caffeine-free, and noncarbonated low-calorie colas. Sugar-sweetened beverages included caffeinated and caffeine-free colas; other carbonated sugar-sweetened beverages, and noncarbonated sugar-sweetened beverages (fruit punch, lemonade and other fruit drinks). Groups were divided into those that consumed sugar-sweetened beverages versus artificially sweetened beverages and then further divided into frequency of consumption.

A total of 2,680 incident cases of type II diabetes were noted over 20 years of follow-up.[8] Hazard ratios (HR) were determined using a Cox proportional hazard to determine the association of sugar-sweetened versus artificially sweetened beverages to type II diabetes. Statistical adjustments were made for smoking, physical activity, alcohol intake, multivitamin use, family history of diabetes, high triglycerides, high blood pressure, diuretic use, previous weight change, low-calorie diet and body mass index (BMI). After adjustments were made, consumption of sugar-sweetened beverages was associated significantly to the development of type II diabetes with an HR of 1.24, confidence interval (CI) of (1.09 to 1.40) and a p-value <0.01. Consumption of artificially sweetened beverages did not show a significant association with type II diabetes (HR 1.09 [CI 0.98-1.21]) and p-value of 0.13, after adjustments.

The major limitation to the study was weak external validity (lack of generalizability) caused by the study population being solely comprised of adult, white males.[8] Strengths included the measuring of beverage intake prior to type II diabetes development, similar socioeconomic status of the participants, beverage intake calculated as cumulative averages, a control present for several health and lifestyle factors and the large sample size. By measuring intake prior to the development of type II diabetes and adjusting for other health and lifestyle risk factors for type II diabetes, the study was able to limit many confounding variables that would likely have been a concern in determining the association of the two different sweeteners and type II diabetes. Although the study did not find significant statistical evidence for the association of artificial sweeteners to the development of type II diabetes, the study was limited to the effects of artificial sweeteners in adult, white males and cannot be properly generalized to include the general population. Therefore, the results were not conclusive in determining if artificial sweeteners have a reduced risk of type II diabetes when compared to natural sugars.

Pharmaceutical Application

Artificial sweeteners are extremely prevalent in the field of pharmaceutics. There is an abundance of oral medications that rely on this means of sweetening enhancement to produce a palatable dosage form for the patient. Dosage forms that rely on these sweetening enhancers include tablets, powders, solutions, suspensions, and medical products in these dosage forms range from prescription to nonprescription medications as well as herbals and vitamins.[9]

Sweeteners such as sucrose have been used in the past to overcome the bitterness and odor of a large amount of medications for patients. An example would be the commonly prescribed pain management medication morphine sulfate IR in oral solution.[10] Due to the chronic nature of this medication; sucrose in this solution can prove to be problematic. Two

issues predominate with this usage: dental caries and hyperglycemia in diabetic patients. Despite these issues, patient adherence to the medication still dictates the use of these sweeteners. Recently, artificial sweeteners have been a preferred alternative to classic sweeteners to alleviate the dental erosion and large intake of sugars. Studies such as Koning et al. and Nettleton et al. show conflicting data with the latter claiming that artificial sweeteners are related to the diagnosis of type II diabetes.[8,11] With inconclusive data health care providers, and specifically pharmacists, can play a large role in counseling patients and selecting safer medications that are artificially sweetened.

A population that is greatly influenced by sweeteners is pediatrics. In pharmacy, sweeteners are used extensively in regard to ease of administration of medication to children. Children are especially susceptible to dental caries and tooth erosion from an excess of sweetener in their diet as well as medications. As more pediatric medications come on the market, sweeteners will become a more problematic issue. Medications such as Chlor-Trimeton contain sucrose in the syrup formulation while other drugs such as Children's Tylenol elixir contains both aspartame and mannitol: a sugar and an artificial sweetener. Brief, short-term use has not proven to cause such adverse effects; however, long-term use of sucrose-sweetened medications has been associated with dental caries, teeth erosion, and diabetes.[12] Therefore, short-term use is a way in which artificial sweeteners can provide less adverse effects and be a better sweetener in pediatric medications.

Pharmacists can provide education to patients on artificial sweeteners through medication therapy management. Making the patient aware of sweetening agents, whether it is sucrose or an artificial sweetener, can improve the patient's conditions as well as his or her quality of life. It is important as pharmacists to explain how neither natural nor artificial sweeteners are healthy, yet artificial sweeteners are the preferred choice of the two.[1] This is especially imperative in patients who have conditions such as high blood pressure, obesity and diabetes.

Conclusion

Sweetening enhancers are heavily used throughout society whether it is through diet or pharmaceutical products. With diets high in sugars, prevalence of type II diabetes and obesity have reached record-breaking highs. Through extensive research, we have evaluated and compared the effects of using sugar sweeteners such as sucrose versus FDA-approved artificial sweeteners. Through the studies conducted, we can conclude that the adverse effects of sugar sweeteners are proven to be more detrimental than those of artificial sweeteners. Despite studies claiming that artificial sweeteners may have negative health effects, the data is inconclusive and the diagnoses of diabetes and obesity were attributed more toward sugar sweeteners than artificial sweeteners.

Pharmacists can play a major role in counseling recommendations in regard to sweetening medications for patients. Sweetening is a necessary aspect of pharmaceuticals in order to maintain patient adherence; therefore, the benefits of artificial sweeteners outweigh the risks. With artificial sweeteners, moderation is essential. Patients cannot avoid the intake of these sweeteners in their medications; however, dietary adjustments should be recommended to reduce the intake of artificial sweeteners. By educating patients, pharmacists can play a major role in helping patients to more safely consume products with artificial sweeteners.

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Whooping Cough: A Pharmacist's Role in an Emerging Endemic

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Abstract
Pertussis is an acute infectious disease caused by the organism Bordetella pertussis and characterized by a "whooping cough." Incidence of the disease had declined since the development of a vaccine, but is now increasing in reported cases. This increase has been attributed to both an increased awareness but also surmised to be related to a decrease in vaccinations. The pertussis vaccine is given in conjunction with tetanus and diphtheria vaccines to children before the age of 6 in five separate injections over the course of four to six years. A booster is now recommended for the older child and adults due to the declining protection of the vaccine over time. Pertussis is highly contagious and early treatment with a macrolide antibiotic is recommended to limit the severity and prevent transmission. It can be deadly in infants, which is why prevention via immunizations is so important. The pharmacist can assist with advising individuals of the importance of vaccination.

Introduction

Pertussis, also known as whooping cough, is an acute infectious disease caused by the organism Bordetella pertussis that has a history of being a common preventable yet fatal childhood disease. Since the development of the pertussis vaccine in the 1940s, the incidence rate has decreased by at least 75 percent among children. But recently, the number of reported cases of pertussis has increased. The Centers for Disease Control and Prevention (CDC) believes that this increase could be due to heightened awareness and improvement in clinicians' ability to diagnose pertussis, but they also believe that a large portion of the disease goes unreported or unrecognized.[1] According to the Council on Foreign Relations, since 2008 there have been 65,457 reported pertussis outbreaks around the world with an astonishing 56.4 percent of those cases happening in the United States.[2] Due to rapid spread of disease, these outbreaks usually occur in clusters. Over the years, these clusters of outbreaks experience peaks of incidence every three to five years and continue to follow this same pattern.[3] With the use of patient education on signs and treatment of pertussis as well as prevention and vaccination, this recent spike in incidence rate can be controlled.

Disease State

Bordetella pertussis is a gram-negative bacteria that produces many biologically active products, most notably the pertussis toxin (PT). Pertussis toxin modifies inhibitory G proteins rendering them unable to inhibit adenylyl cyclase, an enzyme that plays an essential role in transmitting signals to secondary messengers. Thus, PT forces other activated G proteins into continuous signaling, leading to various unwanted consequences such as immune suppression, which would promote bacterial colonization and potentially increase transmission of the disease.[4] Physiologically, Bordetella pertussis attaches to the cilia of respiratory epithelial cells and paralyzes them. This causes pulmonary secretions to be inadequately cleared and leads to inflammation in the respiratory tract.[1]

This very contagious disease is spread from person to person, most commonly by inhalation of droplets from a cough or a sneeze.[5] Symptoms usually start to occur within seven to 10 days of initial transmission. These symptoms start off as cold-like with a runny nose and mild cough along with a low-grade fever. This can develop into a severe cough or apnea, a pause in breathing pattern that is very common in infants. This severe cough can become so violent and rapid that all the air from the lungs is expelled and the patient is forced to inhale, which results in the characteristic "whooping" sound. These severe coughs can cause young children to vomit and become extremely lethargic.[6] Complications that occur in infants and children include pneumonia, convulsions, severe apnea, encephalopathy or even death. In teens and adults, complications can include weight loss, loss of bladder control, passing out or even rib fractures from severe coughing.[7] Infants develop the most severe complications of pertussis because their immune systems are not fully developed at birth and cannot offer full protection against the disease. Although receiving vaccines helps infants fight certain diseases, they are still vulnerable to disease until their immune system is fully developed. If left untreated, these complications can lead to hospitalization of young children and infants in which one to two out of 100 infants will die due to pertussis.[7] Diagnosis of pertussis involves evaluation of symptoms, a physical exam and a laboratory test of respiratory secretions. These secretions are taken from the back of the throat through the nose and are further evaluated for the presence of Bordetella pertussis.[8]

Prevention

The recommended form of prevention for pertussis is through immunizations.[9] Two vaccines providing pertussis protection are available; Pediatric Diphtheria, Tetanus, and acellular Pertussis vaccine (DTaP) and Adult Tetanus, diphtheria, and acellular pertussis vaccine (Tdap). The use of the upper-case letters in the abbreviations designate the doses of tetanus (T) and diphtheria (D) toxoids, and pertussis (P) vaccine are full-strength. Reduced doses of diphtheria and pertussis are represented by the lower-case "d" and "p" in the adult vaccination. The lowercase "a" in both vaccines represents "acellular" which means only part of the pertussis organism is present.[10] The DTaP is administered to children 6 years and younger in five separate doses usually occurring at ages 2 months, 4 months, 6 months, 15 to 18 months and 4 to 6 years. The Tdap is recommended for children ages 7 to 18

if they have not been fully vaccinated which means they have not received all five doses of DTaP. If they have not received either the DTaP or Tdap vaccines before, adults ages 19 and older should receive a dose of Tdap as soon as possible to protect themselves.[11]

Along with first time protection, Tdap is also employed as a booster available for older children and adults ages 11 to 64 years, and is especially recommended for patients when coming into contact with infants. Adults may receive Tdap instead of their next scheduled tetanus booster shot, which are usually administered every 10 years. This dose of Tdap can be given before the next 10-year mark.[11] Recent studies have shown that the immunity generated by these vaccines, especially DTaP, decreases over time. This waning immunity has led to numerous outbreaks affecting previously immunized individuals. One report studied a population of children between ages 4 and 12 and placed them into groups based on if they possessed pertussis. It was found that every year after receiving their fifth dose of the DTaP vaccine, the children had a 42 percent increased probability in obtaining pertussis.[12] This means the DTaP vaccine would only be 71 percent effective five years after administration when it was 95 percent effective initially.[13] The results of this study highlight the need for children to receive boosters of the Tdap vaccine in order to stop this waning immunity.

Special considerations about receiving the Tdap vaccine are made for pregnant women, health care professionals and the elderly. During each pregnancy, a woman should receive a dose of Tdap at 27 to 36 weeks to transfer pertussis antibodies to her baby and to protect herself. These antibodies provide the newborn with protection until they begin receiving DTaP vaccines after birth. If the mother has not received Tdap, it is recommended she receive the vaccine in the postpartum period, up to six weeks after birth. Adults 65 years or older should receive a single dose of the Tdap vaccine.[11] Health care personnel, such as pharmacists, who work in close contact with patients and have not previously been administered the Tdap vaccine should receive it to prevent spreading pertussis to their patients.

Of course, if a child or adult is moderately or severely ill or allergic to any ingredients, they should not receive either vaccine.[14] In general, the ingredients of purified DTaP/Tdap vaccines administered in the United States contain reduced pertussis toxin, trace amounts of mercury and an aluminum adjuvant.[15] The mechanism of action of these vaccines to prevent pertussis is not fully known, but an immune response is stimulated and protective antibodies are formed. Along with vaccines, prevention using post-exposure prophylaxis in at-risk individuals who have come in contact with a contaminated person can be avoided with the use of prophylactic antibiotics including azithromycin, clarithromycin and erythromycin.[16] These antibiotics are known as macrolides which have bacteriostatic activities.[17]

As the most accessible health care professionals, pharmacists are able to play a large role in the prevention of pertussis. In most states, pharmacists are able to administer the Tdap vaccine to patients ages 10 and older who have a prescription.[18] This places pharmacists at the center of pertussis prevention. Since retail pharmacists are in constant contact with patients, it proposes the chance to ask high-risk populations, pregnant women and elderly, if they have received their Tdap vaccines. Plus, by examining prescriptions and communicating with patients, pharmacists can recognize if someone is being treated for pertussis. This provides the pharmacist with an opportunity to counsel the patient about the danger of pertussis to infants and ways to minimize the spread of pertussis like good hand washing. Overall, pharmacists possess the ability to educate their communities about pertussis prevention while also administering the Tdap vaccine.

Acute Treatment

Even though multiple prevention techniques against pertussis exist, in 2012, the United States experienced 48,277 cases of pertussis reported to the CDC.[19] Although prophylactic antibiotics are used to prevent the development of pertussis in at-risk individuals, these antibiotics are mainly used to treat those already afflicted by the illness. Antibiotics including azithromycin, clarithromycin and erythromycin are commonly employed treatment medications. Because erythromycin and clarithromycin have a higher propensity to cause gastrointestinal irritation, azithromycin is the preferred antibiotic to be used in pertussis treatment. When used in patients 6 months and older, a 10 mg/kg single dose is given on day 1 and then a 5 mg/kg single dose is administered days 2 through 5. The second-line option is clarithromycin given as two divided doses of 15 mg/kg/day to patients over 1 month old for seven days. A doctor can also prescribe erythromycin for pertussis treatment which is typically given as four divided daily doses of 40 to 50 mg/kg/day administered for 14 days to patients over 1 month old. At least five days of treatment are required before the patient should leave isolation, and it is important for the patient to complete the drug schedule fully.[20] Since this disease is highly contagious, those with pertussis should stay isolated and avoid contact with other people, especially the unimmunized and infants. Early treatment is necessary to stop pertussis from spreading, and if the medications are administered before coughing fits begin, the severity can be decreased. These medications only reduce the person's infectivity and do not alter the disease's clinical course. Once the individual has been infected with pertussis for three weeks, the medications are not useful because the bacteria is now absent from the body.[8]

Along with antibiotics, simple adjustments can aid the treatment of pertussis and stop its spread. Those individuals suffering from pertussis should drink plenty of fluids to avoid dehydration. Plus, minimizing irritants such as smoke and dust along with using a cool mist vaporizer helps alleviate an ill person's cough. A key way to stop the spread of pertussis is as simple as good hand washing. Overall, the treatment options for pertussis stop the spread and decrease the severity of pertussis. More serious cases of pertussis may require hospitalization, especially in infants.[3] Since pharmacists are very accessible, counseling patients on these treatment points is convenient and beneficial to the community.

Special Populations

There are many special populations who are strongly advised to get the pertussis vaccine. The first population is infants and children, in which the highest incidence rate of pertussis occurs. Along with the vaccine, parents should be advised to keep their children away from anyone with cold symptoms or anyone coughing. The second population is caregivers of infants, who should get the vaccine and practice good hygiene in order to prevent them from spreading pertussis to children. Caregivers can collectively include parents, babysitters and other adults who have close contact frequently with young children. Another population that is recommended to get the vaccine is pregnant women or anyone around a pregnant woman or newborn. This is also a prevention measure taken to protect the child from contracting pertussis soon after birth. A more general population is anyone above preteen age who has not had a booster vaccine. This is solely for prevention of any future pertussis infection and to ensure that the individual has the maximum protection available. This is especially stressed in the elderly population in which immune systems are not as strong. Finally, international travelers should be especially cautious about hygiene and being up to date on the vaccine. Traveling to other countries that have outbreaks of pertussis can put a traveler at great risk to contract that disease, and it also heightens the risk that the traveler will bring the disease back to their country and cause an outbreak there.[9]

Disease Epidemiology

Even with vaccinations available to protect a majority of the population, pertussis is still considered as endemic within the United States.[3] Since 2003, pertussis has been on the rise in the Midwest and California.[21] Reported cases of pertussis across the country jumped to 48,277 cases in 2012, from 18,719 cases in 2011. A general increase in reporting is to blame for a portion of the jump, but the doubling in reported cases is troubling given that pertussis is easily preventable. While most cases of pertussis can be treated with little to no lasting sequelae, cases in infants can be especially severe, with high mortality rates.[22] The importance of herd immunity has emerged over the years while the number of reported pertussis cases continues to climb.

In 2010, the United States saw its largest pertussis outbreak since 1947, in a Californian community. With 9,120 reported cases and 10 deaths, this outbreak was one of the first to be studied in relation to vaccination rates. Atwell et al. studied the rate of pertussis spread among clusters of nonmedical exemptions (NME) in kindergartners. Californian parents obtained NMEs if vaccines were seen to be against their religious or philosophical beliefs. Using the Californian Department of Health's reported pertussis data and Kulldorff spatial scans, Atwell et al. found statistically significant higher rates of pertussis among communities with higher rates of NMEs. This study provides health care professionals with a strong correlation between vaccinations and pertussis prevention.[21]

In describing the importance of vaccinations to the prevention of pertussis to patients, a term commonly used is "herd immunity." Herd or community immunity is defined by the National Institute of Allergy and Infectious Disease as immunizing a critical portion of the population against a disease, thereby preventing an outbreak and protecting a smaller portion of the population which may not be able to receive vaccinations due to health or other rationale.[23] Childhood diseases such as polio and measles are essentially unheard of in first world countries due to the high vaccination rates among the children able to receive vaccinations. This high vaccination rate and immunity protects patients who may not be able to receive vaccinations due to disease states that may leave them immunocompromised or resistant to vaccination. As the number of people opting out of vaccinations grows, the herd immunity of communities within the United States weakens. This is especially troubling due to the disease's severe threat to infants. By informing patients of this concept while promoting vaccinations, high-risk populations can be easily protected until they are able to receive the vaccination themselves.

Conclusion

Pharmacists are one of the most readily available health care professionals and can therefore play an important role in counseling patients on the pertussis vaccination. When counseling patients about important vaccinations, pharmacists may run into patients hesitant to vaccinate due to many different reasons. The most common reasons include a belief that the vaccine-prevented disease no longer poses any risk, a doubt in the safety of the vaccine or a belief that the vaccine may overload a child's immune system or be linked to autism (which has been proven to be incorrect in multiple peer-reviewed studies). Conservative forms of Islam, Judaism and Christianity have reasons against vaccinations, often because of the production or contents of the vaccine. When counseling parents who are vaccine-hesitant, Dr. John Harrington outlines eight points that health care professionals should keep in mind. First, health care professionals should begin having vaccination conversations early (such as an infant's first pediatrician visit), and pharmacists can distribute vaccine information sheets often to promote questions and conversations. While counseling, it is important to take the time to listen to all questions without patronizing the patient. Health care professionals should never offend the patient or become offended by earnest questions. Acknowledging possible peer-reviewed risks, using clear, patient-friendly language, and respecting a patient's authority in decision-making allows for open conversations with patients about vaccinations. Pharmacists can also explain the reduction of pain for children receiving vaccinations through the use of sucrose or swaddling.[24] Community pharmacists can play a role in many of these steps by being available for patients with questions. Taking extra time to explain vaccinations or distribute educational material to the patient who has become a new parent, will add on to the information many parents will be receiving from their child's pediatrician. By educating vaccine-hesitant patient populations, pharmacists can help increase pertussis vaccination rates and help reverse the outbreak trend.

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