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Overview of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis

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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.

ACPE Universal Activity Number (UAN): 0048-0000-13-007-H01-P

Objectives

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

1. Discuss the impact of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).
2. Describe the three most commonly proposed immunological mechanisms underlying SJS and TEN.
3. List medications commonly implicated in causing SJS and TEN.
4. Discuss commonly used therapies for SJS and TEN and the controversy surrounding them.

Abstract

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are immunologic reactions that typically present due to drug hypersensitivity. These reactions present with serious mucocutaneous manifestations that can lead to significant morbidity and mortality. The pathogeneses of SJS and TEN have yet to be clearly elucidated, but three potential immunologic mechanisms have been defined in literature: granulysin, Fas-FasL, and perforin and granzyme B. Medications have been immunologically linked as the primary causative agents of SJS/TEN. Corticosteroids, intravenous immunoglobulin administration (IVIG) and cyclosporine have been employed as treatments; however, none have resulted in consistent positive outcomes. Pharmacists have a significant role in identifying and discontinuing the offending agent and recommending pharmacotherapy for treatment.

Overview

Drug hypersensitivity reactions are major clinical complications that can result in serious and life-threatening conditions. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severe immunologic reactions that clinically present with a widespread, cutaneous rash, target-like lesions and skin detachment.[1] Stevens-Johnson syndrome and toxic epidermal necrolysis are rare occurrences with only one to two cases per one million individuals reported annually.[2] The characteristic rash and lesions tend to localize in the facial region, upper trunk and extremities of afflicted individuals especially as the severity of the reaction progresses (Figure 1). However, as a practicing pharmacist, it is important to note that a majority of these cases are precipitated by a hypersensitivity reaction to certain medications. Therefore, SJS and TEN are typically classified as severe cutaneous adverse drug reactions (SCARs).[3] Common medications that elicit such a violent response from the body are discussed below.

Patients who develop SJS/TEN may present with a variety of symptoms. Initial symptoms, which often precede cutaneous involvement, can be non-specific and include fever, sore throat and stinging eyes.[2] While the level of epidermal skin detachment is utilized to determine the extent of the reaction, any of the mucous membranes in the body can be impacted.[3] All major organ systems containing mucosal membranes can be drastically impacted; gastrointestinal, ocular, nasal, respiratory and genital membranes may potentially inflame and scar.[4] In severe cases, the scarring of organs results in a complete, irreversible loss of function that can contribute to mortality.[4] It is also common for patients to experience secondary infections of the skin or other organs during the course of the syndrome.[5] Frequently, survivors of SJS/TEN will experience ophthalmologic sequelae based on the extent of ocular membrane damage incurred by the reaction.[1] These potential complications illustrate that SJS/TEN can result in both significant morbidity and mortality.

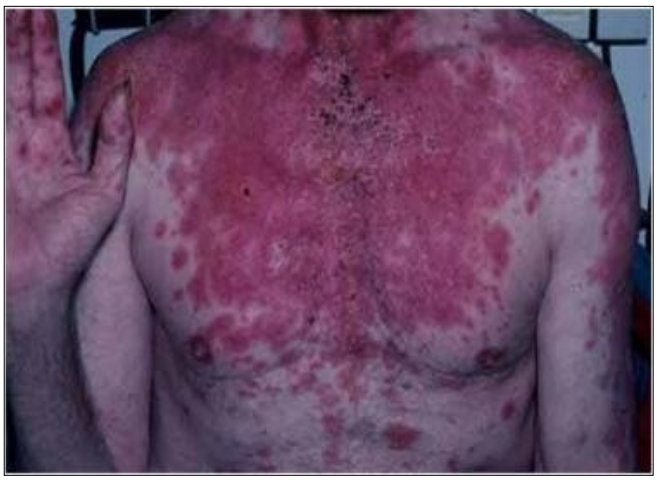
Stevens-Johnson syndrome and toxic epidermal necrolysis have similar pathophysiology and clinical presentation but are differentiated based on severity of disease.[6] Stevens-Johnson syndrome is classified as presenting with skin detachment that affects 10 percent or less of the body.[6] A patient will be diagnosed with TEN when 30 percent or more of the skin becomes detached. This separation of the epidermis from the underlying dermis is the direct result of immune-mediated keratinocyte apoptosis, and the extent of apoptosis determines the total percentage of skin impacted.[5] Overlap of SJS and TEN can result when 10 to 30 percent of the body is visibly impacted, making a distinct diagnosis difficult.[6] Stevens-Johnson syndrome/toxic epidermal necrolysis can be assessed with the SCORTEN (SCORe of Toxic Epidermal Necrolysis) system, a set of criteria utilized to predict mortality outcomes for diagnosed individuals.[7] Such criteria include patient age, serum bicarbonate levels, heart rate and the presentation of malignancies.[7]

Immunologic Mechanism

Although the pathogeneses of SJS and TEN are not fully understood, the processes are known to be due to an immune response. Re-challenging with the offending stimulus hastens the onset and provokes a more severe reaction; therefore re-challenging is not recommended. The majority of cells that

present in this immunological reaction are CD8+ Cytotoxic T-lymphocytes (CTL), CD3+ T Cells, CD56+ Natural Killer (NK) cells and Natural Killer T-lymphocytes (NKT).[3] The cytotoxic response of CD8+ T cells in the skin is induced by the recognition of the human leukocyte antigen (HLA) class I molecules that bind the drug or endogenous antigen promoting clonal expansion of the cytotoxic lymphocytes. These cells migrate to the skin and produce inflammatory mediators, such as granulysin, perforin and granzyme B. These mediators then promote apoptosis of keratinocytes which causes the separation of the epidermis from the dermis.[6] There have been recent findings that certain genotypes of the HLA-I molecules may be associated with this reaction.[5] The complete mechanism of this reaction has not been clearly defined in the literature, but there are currently three major theories proposed to explain the mechanism.

Figure 1. Male presenting with SJS along chest, hands and mucosal tissue around the mouth



http://missinglink.ucsf.edu/lm/DermatologyGlossary/stevens_johnson_syndrome.html This work is licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 2.5 License.

The first proposed mechanism is granulysin as a mediator of SJS and TEN. Granulysin is a cytolytic cationic protein stored in the granules of CTLs and NK cells that is cytotoxic for tumor cells, bacteria, fungi and parasites. In SJS and TEN granulysin is released and binds to the keratinocyte surface via its charge, promoting ion flux. Ion flux within the keratinocytes causes increased permeability of the mitochondrial membrane resulting in mitochondrial damage and cytochrome-c release, which in turn promotes apoptosis. Granulysin is a chemo-attractant and pro-inflammatory activator of T cells and monocytes, thus recruiting more cells to amplify this reaction.[3] In one study, granulysin was found to be a key molecule responsible for keratinocyte death with a direct correlation between amount of granulysin and severity of tissue destruction.[3] Granulysin levels in serum were suggested to have clinical significance by acting as a potential marker for predicting the prognosis, monitoring the progression and evaluating the therapeutic response for SJS/TEN.[5]

Activation of the apoptosis-inducing surface receptor Fas by its corresponding ligand (FasL) has also been suggested as a proposed mechanism of keratinocyte apoptosis. Fas is a death domain receptor expressed on the surface of a wide array of other cells including keratinocytes. FasL, which is prominently expressed by activated CTLs, binds and activates Fas to promote the trimerization of Fas receptors which then activate Fas-associated death domain protein (FADD). Fas-associated death domain protein causes the nucleation of inactive procaspase 8 allowing autoactivation of procaspase 8 molecules to active caspase 8. Caspase 8, in turn, activates the caspase cascade activating executioner caspases which cause the degradation of cytoskeletal proteins and DNA.[5] The IVIG treatment strategy to prevent further apoptosis of keratinocytes is based upon the Fas-FasL hypothesis.[6]

The perforin and granzyme B pathway is the last mechanism proposed to produce the keratinocyte apoptosis. Activated CTLs and NK cells produce perforin and secrete it into the keratinocyte membrane. Perforin is a transmembrane protein that binds and forms a pore through the cell membrane. Granzyme B is a protease released to enter the keratinocyte activating the caspase cascade resulting in apoptosis. It has been proposed that increasing levels of perforin, granzyme B, TNF-alpha and FasL have been observed to be related to disease severity of drug hypersensitivity (from mild maculopapular rashes to severe TEN).[5]

Although the exact immune mechanism is unknown, medications have been immunologically linked as the primary causative agents of this hypersensitivity reaction. Up to 77 to 95 percent of cases are directly associated with specific medication use and more than 100 drugs have been associated with SJS/TEN.[1] Table 1 illustrates some of the most common medications causing SJS and TEN. Other potential causative agents are *Mycoplasma pneumoniae,* viruses and one study implicated vaccines specifically for smallpox, anthrax and tetanus.[8,9]

Table 1. Summary of Commonly Implicated Medications of SJS and TEN.

Antibiotics	Cephalosporins, fluoroquinolones, macrolides, sulfamethoxazole and trimethoprim, penicillins
Anticonvulsants	Phenytoin, carbamazepine,*[5] valproic acid, Phenobarbital
NSAIDs	acetaminophen, ibuprofen, nimesulide, diclofenac
Gout	Allopurinol*[5]
Other	Thiazides, multivitamins, ranitidine

**data currently recommending genotype testing before use of this medication*

Treatment Strategies

Finding an ideal therapeutic treatment option for SJS/TEN patients has proven to be difficult. Due to the rarity of the disease, obtaining and producing a case-controlled clinical

trial with a large sample size of patients is a daunting task. However, based on limited clinical data, the outcome of SJS/TEN patients is largely dependent on three management measures: supportive care, withdrawal of the suspecting drug and active treatment.

First, SJS/TEN patients have an improved chance of survival depending upon how quickly they are transferred to a burn unit for supportive care. Aggressive skin care is available in this setting, including critical fluid resuscitation, electrolyte balance and enteral nutrition maintenance. Body temperature and other signs of infection and sepsis should be closely monitored. Due to the potential eye complications, early ophthalmologic evaluation of these patients is critical.[7] Visual acuity and scarring can be protected and prevented with application of short-term topical corticosteroids (fluorometholone ointment 0.1 percent, applied every one to two hours), use of amniotic membranes and coverage of the ocular surface with symblepharon rings.[7,10] Moreover, patients are often unable to eat or drink due to oral and esophageal mucosa involvement from the disease. Viscous lidocaine or other topical oral local anesthetics can be used before meals, making food intake more tolerable.[7,8] Finally, wound care and skin treatment are necessary. Wounds should be treated conservatively using nonadhesive dressings.[2] Avoid topical sulfa containing medications and skin debridement, as blistered skin favors re-epithelialization.[2]

Second, upon diagnosis of SJS/TEN, the causative drug(s) should be rapidly identified and withdrawn.[11] In concordance with identifying the risk drug within a patient's recent history, analysis of drug intake and development of symptoms is necessary. The most likely offending drug that should be suspected as a causative drug for SJS/TEN is one that has been newly administered in the past four weeks.[11] Refer to Table 1 for a summary of commonly implicated medications of SJS and TEN.

Lastly, initiating an active treatment is a recommended measure. However, there is no agreement as to which, if any, treatment shortens the course of the disease.[11] Current active modulating therapies for SJS/TEN include: corticosteroids, intravenous immunoglobulin administration (IVIG) and cyclosporine.

Systemic corticosteroids are the most widely used for the treatment of SJS/TEN. Yet, they are also the most controversial. High doses of systemic corticosteroids are administered with the intent to suppress the intensity of immune reaction, control the extension of the necrolytic process, decrease the injury area, reduce fever and discomfort, and prevent damage to internal organs in the early stages of SJS/TEN.[5] Doses of 1 mg to 2.5mg/kg/day for three days of oral methylprednisolone have been used.[8,11] However, the use of corticosteroids with their robust immunosuppressive actions also poses concern for increased risk of infection. Decreased host resistance, increased morbidity and complications (sepsis, leuk ia, gastrointestinal ulcerations) and prolonged recovery for skin healing are additional concerns; therefore, an antibacterial treatment is recommended. Bacterial and fungal cultures should be taken two to three times a week from skin and mucosal erosions.[11] A prophylactic antibacterial treatment (sodium penicillin, 10 million units twice daily) should be administered immediately and adjusted according to the culture and sensitivity results.[11] Stevens-Johnson syndrome/toxic epidermal necrolysis patients should be closely monitored for the aforementioned potential complications, and further controlled studies will be required to substantiate whether systemic corticosteroids are ultimately beneficial.

The theory behind IVIG therapy is that IVIG may be able to block immune mediators of SJS/TEN reactions.[5] Intravenous immunoglobin administration is a promising strategy for reducing disease progression, based on the Fas-FasL hypothesis: that blocking FasL binding to the Fas receptor will interfere with the apoptotic signal, preventing cell death.[6] Therapeutic doses have been set from 2 to 3.9g/kg, infused over a two-, four-, or five-day period.[12] Further randomized controlled studies are needed to support IVIG as a standard therapy option.

Cyclosporine, a powerful anti-inflammatory and immunosuppressive agent, has not been closely studied but has been shown to be beneficial in various case studies.[7] Cyclosporine affects cytotoxic T-lymphocyte mediated actions and inhibits the inflammation caused by FasL, NK-kB, and TNF-α.[5] In addition to nephrotoxicity and hepatotoxicity, other potential complications secondary to cyclosporine therapy, such as hypomagnesemia and reversible posterior leukoencephalopathy, should also be carefully monitored.[5]

Recent advances in pharmacogenomic studies suggest a possible prevention strategy for the future cases of SJS/TEN. Studies have found a strong genetic association between certain HLAs and specific drug-induced SJS/TEN.[5] Particular HLA alleles were recognized as being main genetic determi-

Table 2. Associations Between Drug Hypersensitivity Reactions and HLA Alleles.[5]

Causative Drug	HLA Allele(s)	Hypersensitivity Reaction(s)
Abacavir	B*57:01	Abacavir hypersensitivity
Allopurinol	B*58:01	SJS/TEN/DRESS
Carbamazepine	B*15:02	SJS/TEN
Carbamazepine	B*15:11	SJS/TEN
Carbamazepine	A*31:01	SJS/TEN/DRESS/MPE
Methazolamide	HLA-B*59:01	SJS/TEN
Nevirapine	DRB1*01:01	MPE/DRESS
Oxicam NSAIDs	A2, B12	TEN
Sulfonamide	A29, B12, DR7	TEN

nants of SJS/TEN in combination with specific causative drugs. For example, HLA-B*15:02 is strongly associated with carbamazepine (CBZ)-induced SJS/TEN.[5] Table 2 outlines further associations between drug hypersensitivity reactions and HLA alleles. Chung *et al*. suggested that the strong genetic association between HLAs and specific drug-induced SJS/TEN makes preventive screening tests prior to drug intake a possible practice to prevent SJS/TEN.[5]

Conclusion

Stevens-Johnson syndrome and toxic epidermal necrolysis are significant cutaneous reactions often caused by medications due to an immune response. Although there is a low incidence of SJS and TEN, these conditions have high rates of morbidity and mortality. Pharmacists may have a significant role in the prevention and treatment of SJS and TEN. Pharmacists can identify medications with potential to evoke this immunological reaction as well as recommend HLA testing for high risk drugs such as allopurinol and carbamazepine. Additionally, pharmacists are foremost in ability to perform medication review, an integral step in the treatment process. Pharmacists may also recommend pharmacotherapy, as there is a great deal of controversy surrounding treatment. Further studies need to be performed to help distinguish drug causes, the immunopathologic reaction and treatment options to prevent and successfully improve patient outcomes.

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Assessment Questions

Overview:

1. SJS/TEN presents clinically with:
   A. Myocardial infarction
   B. Cutaneous rash
   C. Excitability
   D. Abnormal hair loss

2. What percentage of epidermal detachment is associated exclusively with SJS?
   A. <10%
   B. >30%
   C. >55%
   D. 10-30%

3. The SCORTEN system:
   A. Aids in determining what agent elicited the immunologic response
   B. Does not include age as a criterion
   C. Assesses mortality outcomes
   D. Is a computer system that tracks all patients who currently have SJS/TEN

Immunology and Causative Drugs:

4. True or False: Re-challenging with the offending stimulus is not recommended due to a faster and more severe response to the causative agent.
   A. True
   B. False

5. Which immunological mediator is appropriately matched to its mechanism of keratinocyte death?
   A. Granulysin-Cation that creates ion flux resulting in damage of the mitochondrial membrane resulting in apoptosis
   B. Fas-FasL-death domain receptor trimerization which activates the caspase cascade resulting in apoptosis
   C. Perforin, granzyme B- released by keratinocytes to stimulate their own apoptosis
   D. All of the above
   E. Two of the above

6. Potential causative agents of SJS and TEN
   A. Allopurinol
   B. Acetaminophen
   C. Cephalosporins
   D. Phenytoin
   E. All of the above

7. Pharmacists can have a role in:
   A. Identifying and discontinuing offending agent
   B. Recommending treatment options
   C. Drug information regarding treatment options
   D. Recommending HLA testing for carbamazepine and allopurinol
   E. All of the above

Treatment:

8. The outcome of SJS/TEN patients is dependent on which management measure?
   A. Supportive care
   B. Withdrawal of the suspecting drug
   C. Active treatment
   D. All the above

9. Prophylactic measures should be taken when administering systemic corticosteroids as treatment of SJS/TEN due to the possible risk of:
   A. Seizures
   B. Fatigue
   C. Infection
   D. Diarrhea

10. IVIG therapy can be used as a treatment option for SJS/TEN because of its immunologic binding activity of which mediator?
    A. TNF-α
    B. FasL
    C. INF-γ
    D. Granzyme B

11. The HLA*B 15:02 allele was recognized as being main genetic determinant of SJS/TEN in combination with which specific causative drug?
    A. Carbamazepine
    B. Methazolamide
    C. Nevirapine
    D. Allopurinol

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UAN: 0048-0000-13-007-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:					
Discuss the impact of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).	**1**	**2**	**3**	**4**	**5**
Describe the three most commonly proposed immunological mechanisms underlying SJS and TEN.	**1**	**2**	**3**	**4**	**5**
List medications commonly implicated in causing SJS and TEN.	**1**	**2**	**3**	**4**	**5**
Discuss commonly used therapies for SJS and TEN and the controversy surrounding them.	**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:

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_____

Thank you!

Answers to Assessment Questions—Please Circle Your Answer

1. A B C D	**4. A B**	**7. A B C D E**	**10. A B C D**
2. A B C D	**5. A B C D E**	**8. A B C D**	**11. A B C D**
3. A B C D	**6. A B C D E**	**9. A B C D**	

Any questions/comments regarding this continuing education program can be directed to Lynn Bedford, Advanced Administrative Assistant for the Office of Continuing Education (email: l-bedford@onu.edu, phone 419-772-1871).

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Use of Pharmacogenomics in MTM Services

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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.

ACPE Universal Activity Number (UAN): 0048-0000-13-008-H04-P

Objectives

1. Describe why Medication Therapy Management (MTM) programs would be a vital place to implement pharmacogenomics.
2. Recognize how a patient's genetic makeup can lead to significant differences in pharmacokinetics and pharmacodynamics of certain drugs.
3. Utilize past and current studies of specific drugs and their pharmacogenomic properties to better assess patients' medication therapy and avoid preventable medication errors.
4. Educate other health care professionals on pharmacogenomics and seek to integrate its use into everyday practice.

Abstract

Incorporation of pharmacogenomic data into Medication Therapy Management (MTM) allows pharmacists to optimize treatment regimens for patients leading to better overall outcomes. Utilizing pharmacogenomics makes it easier for health care professionals to initiate medication regimens with reduced adverse reactions, improves outcomes due to specialized dosing and therapies and allows the treatment process to be as cost-effective as possible for the patient. Pharmacists have an opportunity to educate the rest of the health care team on issues such as: which ethnicities possess higher odds of carrying certain genetic variants, the most common or most relevant medications that can have variable effects and medications that have significant severe adverse effects or hypersensitivities related to specific genetic markers. Using specific examples where medications possess variable efficacy and safety, due to differences in genetics among the patient population, helps to explain why this is such an important topic. Medications discussed in the article include carvedilol (Coreg®), dabigatran (Pradaxa®), methadone (Dolophine®), clopidogrel (Plavix®), abacavir (Ziagen®), and carbamazepine (Tegretol®). These examples emphasize why pharmacogenomic education and testing is not only relevant, but extremely important, for patients taking certain drugs. Pharmacists are in a prime position to educate other health care professionals about new, clinically relevant, pharmacogenomic findings. With knowledge of pharmacogenomics, pharmacists have the opportunity to apply population and specific individual genetic data into everyday practice, and thus can improve the efficacy and safety while being more cost-efficient.

Introduction

Medication Therapy Management (MTM) includes the evaluation of a patient's complete medication regimen through a comprehensive medication therapy review, rather than focusing on one specific medication.[1] Pharmacogenomics (PGx) studies how the genetic make-up of an individual influences drug absorption, distribution, metabolism and excretion (i.e., pharmacokinetics) and how the individual responds to the drug (i.e., pharmacodynamics). This response is measured in terms of the drug's efficacy, and/or toxicity.[2] Using pharmacogenomics, health care professionals will be better able to select a patient's initial medication regimen leading to reduced adverse reactions, improved outcomes via specialized dosing and therapies and potentially improved cost-effectiveness. Integration of MTM services and pharmacogenomic data will allow pharmacists to optimize treatment regimens for patients leading to better overall outcomes. It is estimated that annually in the United States $177 billion is spent on hospital services associated with illness and death related to medication errors, including administration of drugs to patients with certain genetic constitutions that put them at risk for drug toxicity.[1] Being able to incorporate PGx information into practice will allow for a reduction in adverse effects and complications and, consequently, health care costs. Currently 17 of the top 200 drugs (8.5 percent) have information in their package labeling regarding pharmacogenomics, including the fifth most prescribed drug, clopidogrel (Plavix®), and the seventh most prescribed drug, atorvastatin (Lipitor®). In 2011, there were over 68.9 million prescriptions dispensed for these two medications alone.[3]

Research shows that many medications, or classes of medications, have significant interindividual pharmacokinetic and/or pharmacodynamic variability due in part to genetic variability. Genetic variability in many cases can be related to changes in efficacy and the risk of adverse events. Pharmacists have a unique opportunity to educate the rest of the health care team on issues such as: which ethnicities possess higher odds of being carriers of certain genetic variations, the most common or most relevant medications affected by genetics and medications for which significant severe adverse effects or hypersensitivities are possible and are influenced by genetics. Pharmacists, as drug experts, have an obligation to continuously bring forth new pharmacogenomic findings to clinical practice.

Carvedilol (Coreg®)

The importance of pharmacogenomics can be illustrated by examining specific medications for which genetic variability influences efficacy and/or the toxicity profile. Heart failure is a multi-symptom syndrome with an increasing prevalence.[4] The mortality rate with heart failure is significantly high, but the use of beta adrenergic receptor antagonists (beta blockers) has been able to lower mortality rates significantly.[4] There is evidence of significant interpatient variability in response to beta blockers, indicating "one size does not fit all." This often leads to a "trial and error" process for selecting the proper beta blocker for use in heart failure patients. Here, incorporation of pharmacogenomics into MTM helps in optimizing treatment to reduce mortality and minimize costs, while improving the quality of life. **Carvedilol (Coreg®)** is one of the most commonly prescribed beta blockers for heart failure treatment. Recent evidence indicates that certain genetic polymorphisms of the β_1 and β_2 adrenergic receptors results in reduced carvedilol efficacy.[5] Carvedilol exerts its effects by antagonizing β_2 adrenergic receptors while inducing down-regulation of the β_1 adrenergic receptors.[5] This down-regulation of β_1 receptors could possibly sensitize the remaining β_1 receptors to agonist stimulation.[5] In regards to carvedilol, a combination of two specific beta adrenergic receptor polymorphisms are responsible for decreased efficacy.[5] The Gln27 allele of the Gln27Glu polymorphism of the β_2 adrenergic receptor is linked to β_2 receptor down-regulation.[5] The Arg389-homozygous genotype of the β_1 adrenergic receptor is associated with enhanced β_1 agonist-stimulated intracellular activity.[5] Because carvedilol works mainly on β_2 receptors, some antagonizing activity is lost as a result of down-regulation. Carvedilol may also induce a state of β_1 receptor hypersensitivity to agonist stimulation alone. A retrospective cohort study showed the use of carvedilol in heart failure patients with this genetic constitution was linked to 2.3-fold increase in mortality.[5]

Dabigatran (Pradaxa®)

A common gene variant, found in 33 percent of Europeans, has been found to influence bleeding risk associated with the drug **dabigatran (Pradaxa®),** but to have no effect on its antithrombotic efficacy. A single-nucleotide polymorphism, which is a single nucleotide change in the gene DNA sequence (SNP; rs2244613; the rs number is a specific and consistent reference of a given SNP) of the CES1 gene, results in the decreased conversion of the prodrug to the active form. Variant alleles that patients possess are associated with drops in serum trough levels since the drug will not be fully converted to the active form. A decrease in converted prodrug relates to a 27 percent decrease in relative bleeding risk. When risk of major and minor bleeding was assessed, patients who possessed this SNP were significantly less likely to bleed than those who did not possess the rs2244613 SNP and patients who were also randomized to warfarin (Coumadin®) therapy.[6]

Methadone (Dolophine®)

Methadone (Dolophine®), a synthetic μ-opioid agonist, is currently a treatment option for opioid dependence.[7] Successful methadone maintenance treatment (MMT) blocks the effects of opioids, reduces drug cravings, prevents relapses, and prevents adverse reactions.[7] B-Arrestin (ARRB2), a component of many g-coupled protein receptors, is involved in μ-opioid and dopamine receptor signaling and seems to possess some genetic variations that are of clinical significance.[8] A retrospective cohort study of 278 individuals indicated that single nucleotide polymorphism(s) (SNPs; rs34230287, rs3786047, rs1045280, and rs2036657) in the ARRB2 gene are linked to treatment failure in homozygous individuals, excepting rs34230287.[8] The study found the risk of being a non-responder to MMT increases up to threefold when these SNPs are present.[8] Additionally, a twelvefold shorter duration since the last positive urine test is also seen in the homozygous population for the variant alleles of ARRB2.[8] Successful treatment of opioid dependence and overall quality of life could be significantly improved by knowing the patients' genetic constitution prior to initiation of methadone treatment.

Clopidogrel (Plavix®)

Clopidogrel (Plavix®), one of the most commonly prescribed anti-platelet drugs in the United States, is metabolized by a CYP-450 enzyme (CYP2C19), as are other drugs in the same pharmacologic class. Therefore, SNPs in the CYP2C19 gene can affect the conversion of the prodrug to its active form.[9] The CYP2C19 gene is highly polymorphic with more than 25 known variant alleles.[10] For instance, the CYP2C19*2 variant, found in approximately 15 percent of Caucasians and Africans and 29 to 35 percent of Asians, is an inherited autosomal co-dominant trait, which affects a patient's ability to metabolize clopidogrel.[10] Patients receiving clopidogrel as anti-platelet therapy, (especially those who have coronary artery stents), who carry a CYP2C19*2 allele are at higher risk of major adverse cardiovascular events. Heterozygotic individuals (*1/*2) are considered intermediate metabolizers," while homozygotic individuals (*2/*2) are considered "poor metabolizers." Regardless, data show that individuals carrying even one of the *2 loss-of-function alleles is at increased risk of major cardiovascular events.[10] Patients possessing two CYP2C19*17 alleles are characterized as ultrarapid metabolizers. This allele is expressed in 3 to 21 percent of patients taking clopidogrel and can significantly increase therapeutic levels of the active drug, which can enhance platelet inhibition.[10] Based on substantial data, in April of 2010, the Food and Drug Administration (FDA) issued a "black box" warning for clopidogrel indicating a link between CYP2C19 genotype and drug response that could possibly result in diminished drug effectiveness for patients who are poor metabolizers. While the warning does not state a requirement of genetic testing, it is highly recommended as the drug's effectiveness may be altered by a patient's genetic disposition.[11]

Abacavir (Ziagen®)

Abacavir (Ziagen®) is an effective antiretroviral agent used in Human Immunodeficiency Virus (HIV) therapy, but has risks of severe hypersensitivity linked to the HLA B*57:01 gene. In a 2007 study, 38 of 49 patients exposed to abacavir

demonstrated tolerance of the drug and were found not to possess the HLA B*57:01 gene.[12] This indicated both a lack of hypersensitivity reaction in patients not possessing HLA B*57:01, as well as provided data on the prevalence of this genetic biomarker in a random population. One year later, in a separate double-blind, prospective, randomized trial, 1,956 patients with HIV-1 who had no previous exposure to abacavir were studied to identify the effect of prospective HLA-B*57:01 screening on incidence of hypersensitivity reaction.[13] The patients were split into two groups, one of which was screened for HLA-B*57:01 while the other was not. Of those screened, only those patients who tested negative for the gene were given abacavir. In the second group, every patient was treated with abacavir without genetic screening. Results showed that none of the screened population had immunologically confirmed hypersensitivity reactions, compared to 2.7 percent in the second group. Researchers concluded that HLA-B*57:01 screening prior to initiation of abacavir therapy could reduce the risks of hypersensitivity reaction.[13] A more recent study showed that 46 percent of abacavir hypersensitive patients tested HLA-B*57:01 positive versus 10 percent of non-hypersensitive patients.[14] Today, there is an FDA "black box" warning on abacavir recommending pharmacogenomic testing prior to initiating this medication.[11] HLA-B*57:01 screening is now considered a standard of care in treating HIV-infected patients.

Carbamazepine (Tegretol®)

Carbamazepine (Tegretol®), a drug with indications for disease states such as seizure disorders, bipolar disorder, and trigeminal neuralgia, has a risk for hypersensitivity reactions that can range from benign to fatal. Recent studies have revealed important information about two of the fatal reactions—Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)—which have mortality rates reaching 30 percent.[15] Diagnosis of these conditions requires early recognition and prompt withdrawal of the causative agent (i.e. carbamazepine). More importantly, these reactions have shown strong links to the HLA-B*15:02 gene, which is most prevalent in Asian populations.[15] Ferrell et al. reviewed a study which began in Taiwan in 1996, in 44 of 73 reported cases of SJS/TEN caused by carbamazepine therapy, patients tested positive for the HLA-B*15:02 gene. All 44 patients were Han Chinese, so in 2006 researchers added 16 additional Chinese patients to the study and treated all 60 subjects with carbamazepine. Testing revealed that 59 of the 60 were HLA-B*15:02 positive.[15] Today, the FDA has included a guideline on the carbamazepine label strongly encouraging patients of Asian descent to be tested for the HLA-B*15:02 variant prior to therapy.[15]

Conclusion

The medications discussed above are a few key examples of why pharmacogenomic education and testing is not only relevant but extremely important for patients taking certain medications. Although pharmacogenomics has overcome many obstacles, challenges to implementation still exist. Pharmacists are in a prime position to educate other health care professionals about new, clinically relevant pharmacogenomic findings as well as to help integrate pharmacogenomics into standard health care practice. Pharmacists are key individuals in the implementation of this practice as they are the drug experts and are currently working to incorporate pharmacogenomics into their practices, including applications in MTM. Pharmacogenomics can be used to improve the efficacy, safety and cost-effectiveness of medication therapy. Most recommendations are based on data from reports of mechanism-based and population-based studies, such as: patients of Asian descent needing to be screened for HLA-B*15:02 before starting carbamazepine, all patients receiving HLA-B testing prior to initiating abacavir and to monitor patients on clopidogrel due to the potential for cardiovascular events especially in stent placement patients carrying the CYP2C19*2 variant. Once the health care system becomes more integrated, allowing a pharmacist to access and assess key regions of a patient's genome, personalizing a medicine plan for each patient will become possible. Because pharmacists are currently providing MTM services to many patients, incorporating pharmacogenomic information into MTM seems the logical next step to providing patients with the safest and most effective medication therapy. Being able to personalize medication regimens will not only reduce the number of adverse drug events, but also will reduce the amount of money spent annually to manage these events and, most importantly, will lead to better patient outcomes.

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Assessment Questions

1. It is estimated that _____ is spent on hospital services annually in the United States associated with illness and death related to medication errors.

    A. $53 million
    B. $177 billion
    C. $98 billion
    D. $105 million

2. In terms of Pradaxa®, about one in three _____ possess a gene variant that has been found to _____.

    A. Europeans; influence pain suppression.
    B. African-Americans; influence bleeding risk.
    C. Hispanics; influence seizure threshold.
    D. Europeans; influence bleeding risk.

3. Patients taking Plavix® as antiplatelet therapy who carry a CYP2C19*2 allele are at _____ risk of major adverse cardiovascular events.

    A. Higher
    B. Lower
    C. No
    D. Intermediate

4. Which of the following drugs has a "black box" warning indicating a link between a specific genotype and a diminished drug response?

    A. Abacavir (Ziagen®)
    B. Dabigatran (Pradaxa®)
    C. Clopidogrel (Plavix®)
    D. Methadone (Dolophine®)

5. In a recent study on abacavir, researchers concluded that HLA-B*57:01 _____ prior to initiation of therapy could _____ hypersensitivity reaction.

    A. screening; increase the risks of
    B. screening; reduce the risks of
    C. injection; reduce the risks of
    D. screening; have no effect on

6. These two potentially fatal reactions are associated with carbamazepine therapy:

    A. Stevens-Johnson syndrome (SJS) and profound neutropenia
    B. Gangrene and hemorrhage
    C. Hemorrhage and toxic epidermal necrolysis (TEN)
    D. Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

7. The HLA-B*15:02 gene, associated with carbamazepine hypersensitivity, is most prevalent in which population?

    A. Asian
    B. Caucasian
    C. African-American
    D. Hispanic

8. Heart-failure patients that possess the variant alleles associated with β2 adrenergic receptor down-regulation and enhanced β1 agonist-stimulated intracellular activity are at increased risk of _____.

    A. Carvedilol (Coreg®) toxicity
    B. Carvedilol (Coreg®) therapeutic failure
    C. Both of the above
    D. None of the above

9. Methadone maintenance treatment is currently used to treat what medical condition?

    A. Opioid dependence
    B. Mild pain
    C. Narcolepsy
    D. Chemotherapy-induced nausea and vomiting

10. Why are pharmacists in such a key position in regard to incorporation of pharmacogenetic data into MTM services?

    A. Pharmacists, as drug experts, have an obligation to continuously bring forth new pharmacogenetic findings to clinical practice.
    B. Pharmacists have a unique opportunity to educate the rest of the health care team on issues such as: which ethnicities possess higher frequencies of certain genetic variations; the most common or most relevant medications affected by genetics; and medications for which significant severe adverse effects or hypersensitivities are possible and are influenced by genetics.
    C. A and B
    D. None of the above

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UAN: 0048-0000-13-008-H04-P CEUs: 0.1

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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 why Medication Therapy Management (MTM) programs would be a vital place to implement pharmacogenomics.	**1**	**2**	**3**	**4**	**5**
Recognize how a patient's genetic makeup can lead to significant differences in pharmacokinetics and pharmacodynamics of certain drugs.	**1**	**2**	**3**	**4**	**5**
Utilize past and current studies of specific drugs and their pharmacogenomic properties to better assess patients' medication therapy and avoid preventable medication errors.	**1**	**2**	**3**	**4**	**5**
Educate other health care professionals on pharmacogenomics and seek to integrate its use into everyday practice.	**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**
2. A B C D	**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**	

Any questions/comments regarding this continuing education program can be directed to Lynn Bedford, Advanced Administrative Assistant for the Office of Continuing Education (email: l-bedford@onu.edu, phone 419-772-1871).

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Sildenafil as an Appropriate Monotherapy Option in the Treatment of Pulmonary Arterial Hypertension (PAH)

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Abstract

Pulmonary arterial hypertension (PAH) is a debilitating disease characterized by constriction in the diameter of the pulmonary arterial lumen.[1,2] This leads to increased pressure and stress on the right ventricle of the heart, which may lead to heart failure and death.[2,3] Currently there are only a few treatment options for patients with PAH. Sildenafil, a phosphodiesterase type 5 (PDE-5) inhibitor, can be used to treat PAH. Sildenafil inhibits the degradation of cyclic guanosine monophosphate (cGMP). Increased cGMP concentration results in pulmonary vasculature relaxation. Current clinical trials have indicated that sildenafil can significantly improve many of the symptoms of PAH. The trials have also shown that when used appropriately, sildenafil can be used with minimal side effects. It is important for pharmacists and other health care professionals to understand PAH as a disease state and its treatment options, such as sildenafil.

Introduction

Pulmonary arterial hypertension (PAH) is a debilitating disease that, if left untreated, will lead to death.[1] Pulmonary arterial hypertension is characterized by constriction in the diameter of the pulmonary arterial lumen.[2] Since there is less space for blood to pass through, pressure begins to build up in the pulmonary artery. As a result, stress is exerted on the right side of the heart which can lead to heart failure and death. Due to its low prevalence, health care practitioners only have a few options for treating PAH: prostacyclins and prostacyclin analogues which cause dilation of blood vessels and a decrease in platelet adhesion, endothelin receptor antagonists which prevent endothelin from constricting blood vessels or PDE-5 inhibitors which lead to vasodilation.[2,3,4] Other medications are typically used in conjunction with these options, such as diuretics, digoxin, calcium channel blockers and anticoagulants.[4]

In their more widely advertised role, PDE-5 inhibitors are indicated to treat erectile dysfunction through their vasodilation activity. Sildenafil, under the brand name of Viagra®, is a PDE-5 inhibitor currently indicated to treat erectile dysfunction.[5] Under the brand name Revatio®, sildenafil is indicated for PAH as well. It is important to note that in November 2012, generic versions of sildenafil became available to the public. The intent of using sildenafil in PAH patients is to dilate the pulmonary artery and ultimately relieve some of the stress on the heart.[1] Current studies have indicated that sildenafil is an effective treatment for PAH. Through a review of current literature, the writers hope to review the presentation and dangers of PAH and describe when sildenafil monotherapy is an appropriate treatment.

Pulmonary Arterial Hypertension

Pulmonary arterial hypertension is classified into three categories based on etiology: idiopathic, familial or associated. Both familial and idiopathic PAH can be present at birth or develop later in life. Associated PAH occurs when the disease is secondary to other pre-existing conditions such as autoimmune disease, congenital heart and lung disease, portal hypertension, the use of drugs similar in structure to amphetamines and Human Immunodeficiency Virus (HIV) infection among other conditions.[1]

While the pathophysiology of PAH is not fully understood, its basic mechanisms have been identified. In patients with PAH, there is evidence of irregular expression of potassium channels in the endothelium and smooth muscle cells in the pulmonary artery. This irregular function can lead to an inhibited expression of the vasodilators nitric oxide and prostacyclin. Conversely, it can also lead to the overproduction of vasoconstrictors, thromboxane A2 and endothelin-1. These changes result in increased vasoconstriction, inflammation and thrombosis. In PAH patients, high cellular proliferation is present in the vascular wall of the pulmonary artery.[2,3] This leads to increased pressure and stress on the right ventricle of the heart; stress which, in time, can lead to heart failure and death.

Family history is an effective tool in identifying patients who have a higher risk of acquiring PAH.[1] While no age, ethnic or racial group is categorized as high risk, PAH does on average affect more women than men. Additionally, PAH is more prevalent in patients with associated conditions such as autoimmune disease, congenital heart and lung disease, portal hypertension, HIV infection and the use of some drugs such as fenfluramine, cocaine or amphetamines. Patients with PAH may present with side effects similar to other heart and lung conditions such as chest pain, dizziness, fainting, fatigue, swelling, and shortness of breath and lightheadedness while exercising. Since signs and symptoms are not specific to PAH, the disease may be advanced at time of diagnosis.[4] Perfusion lung scan, echocardiogram, right heart catheterization, electrocardiogram and chest x-rays are all indicative in the diagnosis of PAH.

Sildenafil and General Prescribing Information

Sildenafil inhibits PDE-5 in smooth muscle of pulmonary vasculature where PDE-5 is responsible for the degradation of cyclic guanosine monophosphate (cGMP). Increased cGMP concentration results in pulmonary vasculature relaxation. This occurs when PDE-5 breaks down cGMP that forms in response to increased nitric oxide. Increased intracellular

cGMP inhibits calcium entry into the cell, which results in smooth muscle relaxation. Sildenafil is available as both an intravenous injection (IV) and an oral medication. If administering as an IV, the dose of sildenafil is 10 mg IV bolus three times per day; if taking the oral formulation, the dose is 20 mg by mouth three times per day (four to six hours apart) without regard to meals. The onset of action is about 60 minutes, and its duration of action is two to four hours. Sudden cessation of sildenafil could result in an exacerbation of PAH. There is no dose adjustment needed in renal impairment or in hepatic impairment with Child-Pugh class A or B. This drug is a major substrate of CYP3A4 and a minor substrate of CYP1A2, CYP2C19, CYP2D6, and CYP2E1. It is also a weak inhibitor of CYP2C9 and CYP3A4. Therefore, dose adjustments are required when using potent CYP3A4 inhibitors, except with erythromycin. Concomitant use of sildenafil and itraconazole/ketoconazole is not recommended; concurrent use with protease inhibitors and organic nitrates is contraindicated. Sildenafil should be used with caution in patients over 65 years of age, and this drug is Pregnancy Category B. Chronic use in children is not recommended. Patients should avoid drinking grapefruit juice while taking this drug.[5]

Additionally, blood pressure and heart rate should be monitored as hypotension may develop while taking sildenafil. Patients at increased risk of hypotension are those taking an antihypertensive medication or those with aortic stenosis, hypertrophic obstructive cardiomyopathy or fluid depletion. If the patient develops pulmonary edema when taking this drug, sildenafil should be discontinued as this could be pulmonary veno-occlusive disease. Sildenafil should be used with caution in people taking alpha-blockers, bosentan, nitrates and other erectile dysfunction drugs. Adverse effects such as flushing, diarrhea, myalgia and visual disturbances may be increased with adult doses >100 mg/24 hours. Over 10 percent of patients experience a headache and dyspepsia. Other common adverse effects are erythema, dizziness, insomnia, increased liver function tests (LFTs), urinary tract infection and dyspnea.[5]

Selected Clinical Trials

Impact of First-line Sildenafil Monotreatment for Pulmonary Arterial Hypertension, a study conducted by the Keio and Kyorin University Hospitals, analyzed the efficacy of sildenafil as a monotreatment for PAH. Fifty-seven patients with New York Heart Association functional class (NYHA FC) ratings of I, II, or III were enrolled; four patients dropped out of the study due to high cost of off-label use, and seven patients with Eisenmenger Syndrome were dismissed because of their differing clinical characteristics from other patients with PAH. The remaining patients were given 20 mg sildenafil three times daily as a monotreatment from January 2003 to December 2010. A 6-minute walk distance (6MWD; an independent predictor of death in patients with PAH) and B-type natriuretic peptide (BNP) levels were evaluated before treatment began and again during follow-up.[6]

It was found that the BNP tended to be lower after sildenafil treatment, but the results were not significant. Hemodynamic parameters, however, such as the pulmonary vascular resistance (14.6±8.7 versus 11.6± 8.6 Wood units, P<0.05), mean pulmonary arterial pressure (PAP: 52.1±14.0 versus 45.7±15.7 mmHg, P<0.01), mean right atrial pressure (RA: 8.0±5.5 versus 6.4±4.4 mmHg, P<0.05), and cardiac output (CO: 3.7±1.6 versus 4.2±1.9 L/min, P<0.05), improved significantly following sildenafil treatment in the enrolled patients as a whole. These results are indicative of sildenafil's positive cardiovascular effects, which result in improved cardiac function. NYHA FC either improved (n=12, 26.1 percent) or was maintained (n=30, 65.2 percent) in 42 of 46 patients; NYHA FC worsened in four patients (8.7 percent). Due to the NYHA FC maintenance or improvement rate of 91.3 percent, the study concluded that sildenafil demonstrated superior efficacy as a monotreatment for PAH. Critiques of this study included its lack of control group and small study population.[6]

Clinical Efficacy of Sildenafil in Primary Pulmonary Hypertension, a randomized, double-blind crossover study, compared the efficacy of sildenafil with placebo in patients with primary pulmonary hypertension. Change in exercise time on a treadmill was used as a primary endpoint. Patients were randomized into a placebo group or sildenafil group with doses ranging from 25 to 100 mg three times daily based on body weight. A baseline evaluation was done before treatment began, and again after six weeks of treatment. After the six-week evaluation, patients were crossed over to the therapy alternative to their current treatment (i.e. the sildenafil group ceased sildenafil treatment and began the placebo regimen, and vice versa). A final evaluation was performed after another six weeks of treatment.[7]

Twenty-two patients completed the study. Exercise time increased by 44 percent from 475 ± 168 seconds at the end of placebo phase to 686 ± 224 seconds at the end of sildenafil phase ($p < 0.0001$). It was also noted that cardiac index improved from 2.80 ± 0.9 l/m^2 to 3.45 ± 1.1 l/m^2 ($p < 0.0001$). Pulmonary artery systolic pressure decreased from 105.23 ± 17.82 mm Hg to 98.50 ± 24.38 mmHg, but these results were found to be insignificant. Patients also reported significant improvements in dyspnea and fatigue in a Quality of Life questionnaire. From these results it was concluded that sildenafil significantly improves exercise tolerance, cardiac index, and quality of life in patients with primary pulmonary hypertension. No serious side effects were noted. While these results reflect those of other studies, the authors acknowledged that a larger study population, longer treatment duration, and a washout period between crossover treatment would help lend credibility to these findings.[7]

Sildenafil Citrate Therapy for Pulmonary Arterial Hypertension, a double-blind, placebo-controlled study conducted by the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER) Study Group, used the 6MWD test indicating a change in exercise capacity as a primary end point of sildenafil efficacy. Placebo or sildenafil treatment (20, 40, or 80 mg) orally three times daily for 12 weeks was randomly assigned to 278 patients with PAH class II or III. Among the 265 patients who completed the study, an increase in the 6MWD was observed in all groups receiving sildenafil in comparison to the placebo. Improvement was noted at week

four and maintained at weeks eight and twelve. The observed treatment-related increases of 45 to 50 meters is similar to the increases observed with other PAH medications such as intravenous epoprostenol (47 m), inhaled iloprost (36 m), and oral bosentan (44 m), and is higher than the increase seen with the use of subcutaneous trepostinil (16 m). There was no evidence of a dose-response relationship associated with exercise capacity. It is possible that this is due to complete 5-PDE inhibition at the lowest dose.[8]

Patients receiving sildenafil treatment also experienced improvements in functional class. After twelve weeks of treatment, seven percent of patients receiving placebo noted an improvement of at least one functional class. The proportions of FC improvements for those receiving treatment were 28 percent for those receiving 20 mg of sildenafil (P=0.003), 36 percent for those receiving 40 mg (P<0.001), and 42 percent for those receiving 80 mg (P<0.001). A significant decrease from baseline in mean pulmonary-artery pressure and pulmonary vascular resistance was also noted in those taking sildenafil from the placebo group. The proportion of hospitalizations for worsening PAH was greater in the placebo group than in the combined sildenafil treatment groups (P=0.02).[8]

Adverse events experienced (such as headache, dyspepsia and back pain) were mild to moderate in intensity for all treatment groups.[8]

Two hundred seventy-seven patients were enrolled in a 12-week, double-blind, randomized, placebo-controlled trial (SUPER-1), a continuation of the original SUPER study. Two hundred fifty-nine patients completed the study and entered into an open-label, uncontrolled extension study (SUPER-2) that continued until the last patient had completed three years of sildenafil treatment. The median duration of sildenafil treatment was 1,242 days. Patients were titrated to a dose of 80 mg of sildenafil three times daily for treatment of PAH. As in previous studies, the 6MWD test was used as a primary endpoint. At three years post-baseline, 127 patients (49 percent) had an increased 6MWD. Sixty-four percent of patients either improved or maintained their functional class; 81 patients noted improvement, while 86 patients maintained their current level of functioning. Treatment with sildenafil was generally well-tolerated, and noted adverse events were of mild to moderate severity. The study authors acknowledged that an increased treatment duration would be necessary to support these findings of efficacy.[9]

While more thorough and lengthy studies would further validate recent findings, all current evidence suggests that sildenafil is an effective treatment for PAH. It has been shown to significantly improve pulmonary vascular resistance, mean pulmonary arterial pressure, mean right atrial pressure, cardiac output, exercise capacity, FC and quality of life. Sildenafil was found to be generally well-tolerated among all patients studied, with mild to moderate side effects.

Because most studies were aimed at assessing sildenafil's efficacy as a monotherapy compared to placebo, more studies regarding specific dosing effectiveness would be helpful in determining the optimal dosage for PAH treatment. Given current findings, however, the recommended daily dose for PAH treatment remains at 20 mg three times daily.[5] There is no evidence suggesting that sildenafil treatment has a decreased efficacy or increased adverse effects in comparison to other PAH therapies.

Pharmaceutical Application

It is important for health care professionals, especially pharmacists, to be knowledgeable about sildenafil and PAH. Because sildenafil has many drug interactions and possible adverse events associated with its use, pharmacists can play a vital role in therapy by counseling patients when they receive this medication. Although PAH is not a common condition, pharmacists need to be aware of PAH and to know the signs and symptoms of PAH as well as how to treat it in order to improve the patient's quality of life. Sildenafil can significantly improve the quality of life of a patient with PAH and should be considered as an option for treatment in a PAH patient. Specifically, sildenafil is one of two treatment options indicated for functional class II patients with PAH, and one of five treatment options indicated for functional class III patients.[10]

Conclusion

Pulmonary arterial hypertension is the constriction of the pulmonary arterial lumen that can result in stress on the right side of the heart which ultimately leads to heart failure and death. There are only a few treatment options for PAH, and sildenafil, a PDE-5 inhibitor, is one of the options due to its ability to dilate the pulmonary artery. Through various studies, sildenafil has been proven to be effective in treating PAH as monotherapy with mild to moderate adverse events while improving dyspnea, fatigue and quality of life. It is important for pharmacists and other health care professionals to understand PAH as a disease state and to counsel patients on appropriate treatment options, including sildenafil.

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Comparing the GLP-1 Receptor Agonists: Byetta®, Victoza® and once-weekly Bydureon™

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Abstract

Type 2 diabetes mellitus (T2DM) has traditionally been managed with oral medications. However, in the last few years, subcutaneous glucagon-like peptide-1 (GLP-1) receptor agonists have risen to fame. These agents serve as a reliable addition to current monotherapy. GLP-1 receptor agonists offer a significant reduction in hemoglobin A1C (HbA1c), fasting plasma glucose, and have the added benefit of weight loss. They work primarily by enhancing glucose-dependent insulin secretion while inhibiting glucagon secretion. The available GLP-1 agonists are Byetta® (exenatide), Victoza® (liraglutide), and Bydureon™ (exenatide extended-release). Studies suggest that they are similar in safety and efficacy, with the longer acting GLP-1 receptor agonists, liraglutide and extended-release exenatide, proving to be slightly more efficacious in terms of HbA1c and weight reduction. All three products have unique half-lives, dosing schedules, efficacies, side effects and contraindications.

Introduction

GLP-1 Receptor Agonists and Their Role in Therapy

Glucagon-like peptide-1 (GLP-1) receptor agonists have made a prominent appearance in the management of type 2 diabetes mellitus (T2DM) over recent years. Byetta® (exenatide), Victoza® (liraglutide), and once-weekly Bydureon™ (extended-release exenatide) are the only GLP-1 agonists currently on the market. By acting as an agonist on the GLP-1 receptor, they increase insulin secretion by pancreatic beta cells and inhibit glucagon secretion from pancreatic alpha cells.[1] GLP-1 agonists have become a popular treatment option in T2DM for their glucose and body weight lowering properties.[2] Both the American Association of Clinical Endocrinologists (AACE) and American Diabetes Association (ADA) guidelines recommend GLP-1 agonists as add-on therapy for those who do not achieve adequate control on oral monotherapy.[3,4]

GLP-1 is an incretin hormone secreted by the ileum, colon and rectum. GLP-1 is produced within minutes of ingesting food and is rapidly degraded by dipeptidyl peptidase-4 (DPP-4). The GLP-1 receptor is a G-protein coupled receptor found primarily on pancreatic alpha and beta cells. Activation of the GLP-1 receptor in the pancreas results in increased insulin secretion from beta cells and suppressed glucagon secretion from alpha cells via a second messenger signal transduction system involving cyclic adenosine monophosphate.[5] The existence of incretins was first realized when physicians noted that ingested glucose correlated to a larger and more prolonged increase in insulin compared to intravenous glucose. As seen in Table 1, GLP-1 receptor agonists also slow gastric emptying, increase satiety and acutely increase disposal of glucose in the periphery. Also, long-term use leads to pancreatic beta cell proliferation and an increase in overall insulin synthesis.[2] In patients with T2DM, the incretin effect is impaired and incretin hormone activity is reduced, thus interfering with post-prandial insulin production.[1] This is a very important finding since the incretin effect contributes to nearly two-thirds of insulin secretion in those with normal glucose tolerance. Endogenous GLP-1 undoubtedly plays a significant role in glucose homeostasis following oral glucose consumption. Endogenous GLP-1 is rapidly metabolized by DPP-4, resulting in a half-life of only one to two minutes. Therefore, much attention has been given to understanding the pharmacokinetic properties of GLP-1 receptor agonists and making them more resistant to DPP-4 degradation as a way of prolonging their half-lives.[1,6]

Clinical trials have compared the addition of either a GLP-1 agonist or insulin to oral monotherapy in those patients with inadequately controlled T2DM.[7,8,9] These studies show that adding a GLP-1 receptor agonist to oral monotherapy lowers HbA1c as much or even greater than the addition of insulin.[7,8,9]

In addition, GLP-1 agonists do not cause hypoglycemia and actually promote weight loss;[6] as such, they are used in par-

Table 1. Why Choose GLP-1 Receptor Agonists.[1,2,3,4]

Actions of GLP-1 Agonists	Advantages	Disadvantages
ACUTE • Enhances glucose-dependent insulin secretion • Inhibits glucagon secretion • Slows rate of gastric emptying • Increases satiety • May increase glucose disposal in the periphery **CHRONIC** • Stimulates insulin synthesis • Increases beta cell proliferation • Promotes resistance to apoptosis	• Weight Loss • Limited hypoglycemia • Large decrease in HbA1c	• Gastrointestinal side effects • Route of administration (injection) • High Cost • Possible acute pancreatitis • C-cell hyperplasia/ medullary thyroid tumors (liraglutide and extended-release exenatide) • Long-term safety unknown

ticular in patients at high risk of hypoglycemia or when weight loss is deemed appropriate.[10] Although GLP-1 receptor agonists do not cause hypoglycemia, they may increase the frequency of sulfonylurea-induced hypoglycemia when given in combination. Physicians should therefore consider reducing the sulfonylurea dose when initiating GLP-1 receptor agonist therapy.[11] A review article by Marre and Penfornis suggests that there may be a benefit to using GLP-1 agonists as an initial treatment for T2DM due to possible protective effects on pancreatic beta cells in addition to positive effects on cardiovascular markers, including high-density lipoprotein (HDL) levels, triglyceride levels, and diastolic blood pressure.[1]

Available Options

Byetta® (exenatide) was the first incretin mimetic to be introduced to the market in April 2005.[12] Exenatide is a synthetic form of exendin-4, which is a natural GLP-1 present in the saliva of the Gila monster.[1] It is 53 percent homologous to human GLP-1, but has a half-life of 2.4 hours as compared to the one to two minute half-life of endogenous GLP-1. Byetta® is administered subcutaneously (SQ) twice-daily, up to 60 minutes prior to breakfast and dinner (with at least six hours between the two doses), due to its ability to reduce post-prandial glucose (PPG) concentrations for approximately five to eight hours.[13,14] Exenatide appears to be well-tolerated. The frequent adverse effect is nausea, which tends to subside or become less severe as treatment progresses.[11] To combat the gastrointestinal side effects, doses are initiated at 5 mcg twice-daily and titrated up to 10 mcg twice-daily in accordance with tolerability.[1,15] Exenatide is renally eliminated, therefore the product is not recommended in individuals with a CrCl < 30 mL/min.[13]

Another side effect of exenatide is immunogenicity. Anti-exenatide antibodies are reported to develop in 61 percent of patients after a 26 week administration period. High levels of anti-exenatide antibodies in patients were found to be associated with smaller mean HbA1c reductions.[16]

Victoza® (liraglutide) was approved by the Food and Drug Administration (FDA) in January 2010.[12] Liraglutide is 97 percent homologous to native human GLP-1 with only an amino acid substitution of arginine for lysine at position 35 and the addition of a fatty acid chain at position 26. These minor modifications from endogenous GLP-1 increase half-life by promoting protein binding and facilitating self-association into heptamers, thus slowing absorption and preventing DPP-4 degradation.[13,17] The extended half-life of 11 to 15 hours allows for once-daily dosing.[17] Victoza® may be administered without respect to food.[18]

Liraglutide use is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2. Unlike exenatide, decreased renal function has proven to have little effect on the pharmacokinetics of liraglutide, but because it is a relatively new drug caution should still be used when treating renally impaired patients.[18]

A study of the immunogenicity of liraglutide has shown the development of anti-liraglutide antibodies in 8.3 percent of patients using liraglutide 1.8 mg after a 26 week period. The presence of anti-liraglutide antibodies does not change the glycemic response to liraglutide, as evidenced by similar reductions in HbA1c in patients with and without the antibodies.[16] Although these antibodies do not seem to alter the efficacy, 40 percent of those patients developing antibodies have developed infections, most commonly upper respiratory tract infections.[18,19] The six Liraglutide Effect and Action in Diabetes (LEAD-6) trials included investigations comparing the immunogenic responses of both exenatide and liraglutide. They reported a greater immunogenic response with exenatide compared to liraglutide and concluded that this effect was due to the greater difference between amino acid sequences between exenatide and endogenous human GLP-1.

Once-weekly exenatide (Bydureon™) was approved in January 2012.[12] Bydureon™ contains the same active ingredient as the original exenatide twice-daily (Byetta®) formulation. The extended-release characteristics come from the drug being encapsulated in microspheres of medical grade poly-(D,L-lactide-co-glycolide). The exenatide-containing microspheres slowly degrade in the body following SQ injection and release the drug in a sustained-release manner. This provides for a low initial release rate while maintaining consistent therapeutic levels over a dosing interval. Bydureon™ comes as a dry powder and must be reconstituted by the patient. Both twice-daily exenatide and liraglutide come as solutions that are ready for injection. Unlike the twice-daily product, once-weekly exenatide can be taken at any time of day without regard to meals.[20] As with Victoza®, Bydureon™ is contraindicated in patients with a personal or family history of medullary thyroid carcinoma.[21]

Literature Review

Recent trials have shown that both once-weekly exenatide and once-daily liraglutide are superior to twice-daily exenatide when added to the treatment regimen of inadequately controlled type 2 diabetics.[3,19,22] Two leading studies comparing efficacy of the different GLP-1 agonists are detailed below. The first is the LEAD-6 trial, which compared exenatide administered twice-daily (Byetta®) and liraglutide (Victoza®).[19] The second is the DURATION-1 trial, which compared exenatide administered twice-daily (Byetta®) and exenatide administered once-weekly (Bydureon™).[22]

Exenatide twice-daily versus liraglutide once-daily (Byetta® versus Victoza®)[19]

Changes in HbA1c from baseline were measured in a 26 week randomized, open-label, active comparator, parallel-group, multinational trial comparing liraglutide 1.8 mg SQ once-daily to exenatide 10 µg SQ twice-daily.[19] Inclusion criteria included age between 18 and 80 years, diagnosis of T2DM, HbA1c between 7 and 11 percent, body mass index (BMI) of 45 kg/m^2 or less and no history of impaired liver or renal function, clinically significant cardiovascular disease, retinopathy or maculopathy requiring acute treatment, uncontrolled hypertension (as described by being ≥ 180/100

mmHg), or cancer, as well as having been on stable treatment with maximally tolerated doses of metformin, sulfonylurea, or both for at least three months with no previous use of insulin, exenatide or liraglutide.

After randomization, participants underwent a two-week liraglutide dose escalation period or a four-week exenatide dose escalation period followed by a 22 to 24 week maintenance period. During the maintenance period, dose reduction was not allowed and any participants who had intolerance to the required study doses were removed from the study. Exenatide was administered zero to 60 minutes before breakfast and dinner (or before each of the two main daily meals that are at least six hours or more apart), and liraglutide participants were encouraged to take liraglutide at the same time each day.

The primary efficacy endpoint was the difference in HbA1c from baseline to 26 weeks. Secondary efficacy endpoints included the proportion of patients reaching HbA1c targets, changes in fasting plasma glucose, self-measured seven-point plasma glucose profiles, β-cell function, glucagon, blood pressure and lipid profiles. Safety variables included adverse events, vital signs, electrocardiogram, biochemical and hematological measures and patient reported hypoglycemic episodes.

A total of 464 participants were randomly assigned to each treatment group. Withdrawal rates were not significantly different between the two treatment groups; the most common reason for withdrawal was adverse events. There were no statistically significant differences in baseline therapy, BMI, nationality or age. There was a statistically significant difference of race between the two treatment groups; however, it is possible that this significance was due to the small number of non-Caucasian participants in the study. The decrease in HbA1c values from baseline to week 26 was significantly greater in the liraglutide group. The proportion of participants achieving HbA1c targets was also significantly higher in the liraglutide group. Both the amount and proportion of participants experiencing weight loss were similar between the groups. Overall treatment satisfaction was reported to be significantly better in the liraglutide group; however, liraglutide was found to have more serious adverse events despite having an overall lower frequency of adverse events. The incidence of nausea was initially found to be similar between the groups, but was lower with liraglutide at week 26.[19]

It is important to note that despite these positive results, the open-label design may have affected the outcome by creating bias in the study and possibly affecting patient expectations and adherence to therapy. Additionally, the study was not properly powered to assess differences between treatments for rare clinical safety adverse events. Another issue is that the majority of participants were Caucasian. This makes it difficult to extrapolate the data to a more varied population, even though there were no significant differences in baseline characteristics of the participants. Even with the limitations to the trial, it provides a direct comparison of efficacy and safety between liraglutide and exenatide over a 26-week period. Although additional studies are needed to investigate long-term clinical benefits of liraglutide, the results show that once-daily liraglutide provides a significantly greater reduction in HbA1c and treatment satisfaction compared to twice-daily exenatide. Liraglutide was also associated with lower incidence of nausea (3 percent of treatment group) compared to exenatide (9 percent of treatment group).

Exenatide once-weekly versus twice-daily (Bydureon™ versus Byetta®)[22]

Efficacy, safety and tolerability of once-weekly and twice-daily formulations of exenatide were compared in a 303 subject randomized, comparator-controlled, open-label trial. Inclusion criteria were age of at least 16 years and diagnosis of T2DM that had been treated for at least two months prior to screening. Following the lead-in, the 295 patients remaining were divided into a 2 mg once-weekly exenatide group and a twice-daily 10 μg exenatide group. During the trial, patients self-administered exenatide after proper training. Patients did not receive instruction on nutritional or caloric restriction during the course of the study.[22]

The study tested the hypothesis that the change in HbA1c from baseline achieved with once-weekly exenatide is non-inferior to that of twice-daily exenatide at the end of 30 weeks of treatment. Secondary endpoints included safety and tolerability, analysis of fasting and PPG concentrations, body weight, fasting glucagon, fasting lipids, blood pressure, and exenatide pharmacokinetics. The proportion of patients achieving target HbA1c concentrations of 7.0 percent or less, 6.5 percent or less, and 6.0 percent or less was also recorded during the study.

Withdrawal rates during the 30 week assessment, as well as baseline demographics, were not found to be statistically significant between the groups. Both treatment groups had significant reductions in HbA1c by week six with the mean reduction being significantly greater with exenatide once-weekly after ten weeks. This trend continued through the remainder of the study. The mean difference of HbA1c levels from baseline was 1.9 for once-weekly dosing and 1.5 in twice-daily dosing. This reduction was found to be statistically significant for both groups. The HbA1c reductions were consistent across all treatment background therapies for patients in both groups, and did not notably vary with sex or age. It was also found that once-weekly dosing yielded a greater proportion of patients achieving a HbA1c level of less than 7.0 percent compared to the twice-daily dosing. Both groups experienced significant reductions in body weight. The most common adverse events in once-weekly dosing were nausea and injection site pruritus, while the most common adverse effects in twice-daily dosing were nausea and vomiting. The incidence of nausea was found to be significantly less in the once-weekly dosing. The authors concluded that both treatment regimens significantly reduced baseline HbA1c and body weight at the end of the 30 week treatment. The significantly greater reduction in HbA1c observed for once-weekly exenatide was thought to be due in part to the continuous exposure of exenatide resulting in greater sup-

pression of fasting glucagon and a corresponding reduction in fasting glucose levels. It is also possible that the open-label study biased the patients' expectations and adherence to therapy, although this bias could have potentially affected both forms of treatment. Despite this limitation, the reduction in HbA1c is consistent with a previous double-blind placebo controlled study of extended-release exenatide conducted by Kim et al. in 2007.[24]

Cost-effectiveness

As these medications are relatively new to the market and are available as brand-only products, many may question the cost-effectiveness of such treatment. According to a 2011 article coming out of Europe, the improved life-expectancy, reduced complication rates, and improved quality of life seen with liraglutide make it a cost-effective choice in comparison to twice-daily exenatide, despite the slightly higher lifetime cost.[25] There are no published studies on the cost-effectiveness of once-weekly exenatide. Despite an increased price, Bydureon™ offers even further improvements in clinical outcomes (weight loss and decreased HbA1c) and therefore may be a cost-effective alternative.

Pharmacist Counseling

Patients using GLP-1 agonists for the treatment of T2DM should be aware of their gastrointestinal side effects. Nausea, the most common side effect, typically peaks within eight weeks of treatment and usually resolves in 14 to 16 weeks.[10] Vomiting, diarrhea or decreased appetite may also occur. Those experiencing increased urination, severe abdominal pain, difficulty swallowing, breathing problems, hypoglycemia, or persistent nausea, diarrhea or dizziness should contact their physician. Patients should be counseled on the dosing regimen of their particular therapy. Diet, exercise, glucose monitoring and regular lab testing should be a part of the treatment regimen for all T2DM patients. If a patient misses a dose of Byetta® or Victoza®, they should skip that dose and take the next dose at the normally scheduled time. Doses should not be doubled. [14,18] If a dose of Bydureon™ is missed, it should be taken as soon as possible unless the next regularly scheduled dose is less than three days away. In other words, two doses of Bydureon™ should not be administered within a three day period.[21]

The Future and Investigational Drugs

A once-monthly formulation of exenatide is currently being developed. Phase 3 clinical trials are currently in consideration, although side effects and dosing concerns have been raised.[12] There are several other GLP-1 agonists in the late stages of development. These include lixisenatide, dulaglutide, albiglutide and taspoglutide. Albiglutide is unique in that it is a recombinant GLP-1/albumin conjugate. It is conjugated with albumin to yield a longer half-life than Victoza® and Byetta®.[2]

Conclusion

Since the introduction of Byetta® in 2005, GLP-1 receptor agonists have become an increasingly popular therapy option in the maintenance of T2DM. The class has a great deal to offer with proven efficacy in lowering fasting plasma glucose and HbA1c as well as minimal side effects and weight loss. Although all three products are similar in their safety and efficacy profiles, studies suggest that liraglutide and extended-release exenatide are more effective in lowering HbA1c and body weight compared to twice-daily exenatide. Extended release exenatide offers the additional benefit of only being administered once-weekly perhaps improving patient compliance and improved drug-related outcomes. The GLP-1 receptor agonists have demonstrated significant therapeutic benefits when added to the medication regimen of type 2 diabetics inadequately controlled on initial monotherapy options.

Table 2. Approved GLP-1 Agonists.[11,14,15,18,19,21,22,23]

	Exenatide (Byetta®)	Exenatide (Bydureon™)	Liraglutide (Victoza®)
Half-life	2.4 hours	2.4 hours, with sustained release of drug from microspheres	11-15 hours
Dosing Interval	BID	Once-weekly	QD
Decrease in HbA1c	0.8-1.1	1.9	1.1-1.6
Decrease in Fasting BG (mmol/L)	1.16	2.12	1.82
Side effects	Nausea (lessens with time) Headache Diarrhea Anti-exenatide antibodies Pancreatitis	Nausea (lessens with time) Headache Diarrhea Anti-exenatide antibodies Pancreatitis	Nausea (lessens with time) Headache Diarrhea Anti-liraglutide antibodies Infections Pancreatitis
Black Box Warnings	None	Dose and duration dependent thyroid C-cell tumors observed in animal studies	Dose and duration dependent thyroid C-cell tumors observed in animal studies
Weight-loss (lbs.)	4.5	5.3	5

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Truvada® Recommended by FDA Committee for Pre-exposure Prophylaxis in High-Risk HIV-Negative Individuals

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Abstract

Once-daily combination tenofofovir disoproxil fumarate (TDF) and emtricitabine (FTC) has received Food and Drug Administration (FDA) approval for use in pre-exposure prophylaxis (PrEP) against Human Immunodeficiency Virus (HIV) infection in high-risk individuals. In clinical trials, FTC/TDF has been shown to reduce the risk of HIV acquisition by 62 percent in sexually active heterosexual men and women. Similarly, use of FTC/TDF demonstrated a 44 percent reduction in HIV infection within the men who have sex with men population.[7] When used compliantly and in conjunction with safe sex practices, it appears that FTC/TDF can play an important role in reducing the impact and incidence of HIV infection.

Introduction

On July 16, 2012, the United States Food and Drug Administration approved Truvada®, a combination of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC), as the first drug indicated for pre-exposure prophylaxis (PrEP) against Human Immunodeficiency Virus (HIV) infection in high-risk adults.[1] Although neither drug component is new, once-daily combination FTC 200 mg/TDF 300 mg has been shown to decrease the chance of HIV infection by approximately 62 percent.[2] When taken as directed and used as part of a comprehensive set of safe-sex practices, FTC/TDF appears to demonstrate significant potential in reducing the incidence of HIV transmission both within the United States and worldwide.

Typical HIV patients present with varying symptoms depending on the stage of infection. In the first few weeks, an HIV infected individual may appear asymptomatic, or experience flu-like symptoms including fever, headache, rash or sore throat. As the infection progresses, plasma CD4+ counts decrease, resulting in a loss of immune function, increasing vulnerability to opportunistic infections, and ultimately leading to acquired immunodeficiency syndrome (AIDS).[3] FTC/TDF acts as a combination reverse transcriptase inhibitor (NRTI). Both FTC and TDF are pro-drugs that are converted to active nucleoside/nucleotide analogs in the body, which then compete for incorporation into HIV DNA. Incorporation of the active drug causes termination of HIV DNA chain growth and inhibits activity of viral reverse transcriptase, which prevents disease development by blocking both viral genome incorporation into host cell DNA and viral replication.[4]

Those at the highest risk for HIV infection include men who have sex with men, African-Americans, and young individuals aged 13 to 29 years. Since there is currently no cure for HIV, the associated health complications may be avoided by preventing infection with the virus. FTC/TDF may prove to be an effective tool in reducing HIV transmission within high risk populations by preventing infection before exposure to the virus even occurs. Additionally, sexual partners of HIV infected individuals may also benefit from PrEP with FTC/TDF. It is therefore worthwhile for the modern-day pharmacist to have a strong background on HIV treatment and prevention methods, as well as become educated on the side effects and counseling points associated with FTC/TDF.[5]

Efficacy in Research

Several trials have been published in the New England Journal of Medicine evaluating the efficacy of PrEP with FTC/TDF. These studies showed promising results in several populations, including single heterosexual men and women, heterosexual couples and men who have sex with men. Within these populations, FTC/TDF use provided a significant reduction in the incidence of HIV as compared to placebo.[2,6,7]

The Partners PrEP study, a randomized, double-blind, placebo-controlled trial performed by Baeten et al., evaluated the protective effects of once daily FTC/TDF in heterosexual, HIV-1-serodiscordant couples (one partner was infected with HIV-1 while the other was not). To be included in the study population, heterosexual couples were required to be HIV-serodiscordant, free of hepatitis B virus, not pregnant or breast-feeding, and had not received any previous antiretroviral medications. After enrollment, the HIV-seronegative participants of 4,747 couples were randomly assigned to receive 300 mg TDF daily, FTC/TDF (300 mg/200 mg) daily, or placebo for a period up to 36 months. At the conclusion of the trial, researchers found a 75 percent reduction in HIV acquisition due to FTC/TDF as compared to placebo ($p<0.001$). Furthermore, there was no significant difference between the TDF monotherapy and FTC/TDF combination therapy groups ($p=0.23$).[6]

The TDF2 study, a randomized trial by Thigpen et al., examined the effects of daily FTC/TDF versus placebo in sexually active men and women from Botswana. To be eligible for inclusion, participants were required to be between 18 and 39 years of age, HIV seronegative, free of chronic illnesses and hepatitis B virus and not pregnant or breast-feeding. After enrollment, a total of 1,219 study participants were randomized and followed for 1,563 person-years (median, 1.1 years; maximum, 3.7 years) with monthly HIV testing. Upon conclusion, the intent-to-treat analysis of FTC/TDF

provided a 62.2 percent reduction in HIV infection as compared to placebo (p=0.03). In the as-treated analysis, data was limited to participants who became infected within 30 days of their last self-reported dose of medication, yielding a total of four infections within the FTC/TDF group and a protective efficacy of 77.9 percent (p=0.01). However, within the treatment group, mean plasma drug levels were significantly lower in participants that became infected as compared to plasma levels of participants that did not become infected (0.3 ng/mL versus 30.6 ng/mL for TDF, p=0.007; and 0.5 ng/mL vs 103.3 ng/mL for FTC, p=0.009). Therefore, these results show that while FTC/TDF can provide a significant reduction in the risk of HIV infection, its efficacy in PrEP is largely dependent on adherence to the medication regimen.[2]

FTC/TDF has also shown desirable efficacy of HIV prophylaxis in the men who have sex with men population. In the iPrEx study, a randomized, placebo-controlled trial by Grant et al., 2,499 HIV-negative men or transgender women who have sex with men were randomly assigned to receive once daily FTC/TDF or placebo.[7] Participants were then tested for HIV infection monthly and were followed for 3,324 person-years (median, 1.2 years; maximum, 2.8 years). During the follow-up period, a total of 100 participants became infected; 36 in the FTC/TDF group and 64 in the placebo group, resulting in a 44 percent reduction in HIV infection (p=0.005).[7] Furthermore, within the treatment group, plasma levels of FTC/TDF were detected in 9 percent of infected subjects, whereas detectable levels were discovered in 51 percent of non-infected subjects. Similar to other studies, these results further demonstrate the importance of adherence, as there is a strong relationship between detectable plasma levels of FTC/TDF and its prophylactic effect. [2,7]

The Partners PrEP, TDF2, and iPrEx studies all shared a common limitation in that each study included participants with an acute HIV infection that was missed during the enrollment process.[2,6,7] The Partners PrEP enrolled 14 participants with current HIV infection of which eight received either TDF or FTC/TDF.[6] TDF2 study enrolled a total of three infected participants of which two were entered into the treatment group.[2] In the iPrEX study, 10 participants were found to have plasma HIV RNA after enrollment of which five had symptoms of acute viral syndrome at enrollment.[7] A major concern with initiating FTC/TDF therapy in an HIV positive patient is the risk of retroviral resistance. In the TDF2 study, one enrolled HIV-infected participant receiving FTC/TDF, developed reverse transcriptase resistance mutations at high levels of approximately 100 percent, thereby limiting use of reverse transcriptase medications as an HIV treatment therapy.[2] Of the participants enrolled with HIV infection in the Partners PrEP study, two developed resistance.[6] To avoid the issue of resistance, acute HIV infections can be screened for, not only overt symptoms but also testing for HIV antibodies if no symptoms are present, and additional testing for HIV RNA if possible when HIV antibodies results are negative.[7]

It is important to recognize that each of the three clinical trials performed included a comprehensive package of HIV prevention services in addition to the FTC/TDF therapy. These services included risk reduction (RR) counseling, screening and treatment of sexually transmitted infections (STIs) and free condoms.[2,6,7] Participants in the Partners PrEP study also received condom counseling and referral for male circumcision.[6] The TDF2 study performed individualized counseling on RR during quarterly visits and at any other visits upon request.[2] When using FTC/TDF as PrEP HIV, prevention services are an integral part of the therapy and must be included in order to best prevent HIV infections.

Special Considerations

FTC/TDF is a renally cleared drug, and precautions must be taken with patients who are using FTC/TDF for PrEP and have impaired renal function. If the patient's renal function is <60 mL/min, FTC/TDF use is not recommended.[8] The patient's creatinine clearance (CrCl) should be measured every three months initially, then every six months.[9]

Based on a lack of clinical studies, FTC/TDF is not recommended for pregnant or lactating women. In the TDF2 study, women could not continue with the study if they had a positive pregnancy test; however, of the 107 pregnancies, neither the rate of pregnancy nor the rate of fetal loss differed between the study groups (p=0.58, and p=1.00, respectively).[2] The Partners PrEP trial also excluded women who became pregnant but were allowed to return after the pregnancy.[5] Both FTC and TDF are currently used to prevent perinatal transmission from HIV-infected women to their newborns. Currently, there is no evidence of adverse effects on fetuses exposed to FTC and TDF; however, the data is not complete because the combination of FTC/TDF has not been clinically tested yet due to pregnant women being removed from clinical studies, so health care providers should use their best clinical judgment. Pregnancy tests should be done routinely every two to three months in women taking FTC/TDF for PrEP.[9]

Bone mineral density loss is another side effect that must be taken into consideration. Currently, long-term studies have not been performed to determine the exact effects of FTC/TDF when used as PrEP on bone mineral density. The TDF2 study did look at bone mineral density in a subset of the participants. The results showed a decline in bone mineral density in the forearm, hip, and lumbar spine in participants who received FTC/TDF versus placebo (p=0.004 at the forearm, p<0.001 at hip and lumbar spine).[2] These results do not show long-term effects of FTC/TDF on bone mineral density, and more studies need to be done to determine these long-term effects. Therefore, patients taking FTC/TDF should receive regular bone mineral density tests.

Pharmacist Information

Use of FTC/TDF as PrEP is aimed at high risk individuals including those with HIV-positive partners or those who engage in sexual activity within a high prevalence area and have one or more of the following characteristics: inconsistent or no condom use, diagnosis of STI, exchange of sex commodities, use of illicit drugs or alcohol dependence, incarceration or partner of unknown HIV status and any of the above risks.[8] FTC/TDF should not be used as PrEP for

HIV if the patient is already HIV-positive or if HIV status is unknown.[8] An HIV test must be performed before taking FTC/TDF for PrEP as well as every three months during therapy to avoid the possibility of drug resistance.[8] At each three month visit, clinicians should test patients for hepatitis B infection and STIs. No more than 90 pills should be dispensed at a time to ensure FTC/TDF PrEP is not being taken concurrently with an undiagnosed HIV infection.[9]

A vital counseling point for the pharmacist to emphasize to the patient taking FTC/TDF for PrEP is the importance of compliance. Medication adherence counseling should be given every time the patient comes in for no more than a 90 day supply of FTC/TDF. The Partners PrEP study, TDF2 study, and iPrEx study all discovered that detectable amounts of FTC/TDF in the plasma led to a decrease in HIV risk.[2,6,7] In addition, another trial looking at the use of FTC/TDF as PrEP for prevention of HIV had to stop entirely due to low levels of medication adherence.[9] Help patients develop a routine to ensure their medication is being taken properly to ensure they do not acquire HIV.

An integral part of PrEP is combining the use of FTC/TDF with other standard prevention interventions including risk-reduction counseling, the use of condoms, medication adherence counseling and testing for STIs.[9] When it comes to RR counseling, studies have been done to identify the optimum style that results in the greatest success in preventing the spread of HIV.

Project RESPECT, a multicenter randomized controlled trial, looked into three different RR counseling styles in order to determine the most efficacious approach.[10] Participants received either enhanced counseling (four session interviews of 200 minutes total), brief counseling (two sessions of 40 minutes total), or didactic messages (two sessions without engagement of ten minutes total). Development of STIs was lower in the enhanced counseling as well as brief counseling arm (11.5 percent and 12 percent) compared to the didactic messages arm (relative risk 14.6 percent, 0.81; 95 percent confidence interval, 0.67-0.98).[10] These results are clinically significant in that even spending as few as two 20-minute sessions with a patient, engaging him or her through a more conversational way of counseling can improve healthy RR habits. Based on these results, pharmacists should make an effort to create a dialogue between their patients, particularly those at risk, about the importance of condom use as well as avoiding risky behaviors such as multiple partners, using injectable drugs and engaging in anal intercourse.

Conclusion

There is currently no cure for HIV, therefore, all forms of prevention, including FTC/TDF should be implemented to avoid later health ramifications. Currently, trials have been conducted in three populations of high-risk individuals including men who have sex with men, heterosexual individuals and heterosexual couples with one seropositive partner, showing a significant protective effect of FTC/TDF against transmission of HIV. However, the benefit is only seen in combination with safe sex practices and strict compliance. Pharmacists have an important role in patient education of proper use of FTC/TDF. In this way, pharmacists can maximize the protective effects of FTC/TDF, thereby reducing the transmission of HIV and overall impact of the disease.

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Immunization Guidelines for Pregnant Women

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Abstract
There are many misconceptions among the general public regarding the administration of vaccinations during pregnancy. It is imperative for pharmacists to be current regarding guidelines and updates about recommended vaccines. Data from the Centers for Disease Control and Prevention (CDC) indicate that while some vaccines are highly recommended during pregnancy, others have limited safety data or are contraindicated. As new data emerges on the safety and efficacy of immunizations during pregnancy, pharmacists should continue to review the literature to stay up-to-date on vaccination recommendations. The CDC also has information available for pharmacists and other health care professionals regarding the use of other vaccines during pregnancy, including vaccines for travel, not covered in this article.

Background
Administering adult immunizations has become an important role of the pharmacist. The availability of the pharmacist to the public, including weekends and extended hours, places the pharmacist in a unique position in patient care to have a major impact on reducing vaccine-preventable illnesses and deaths.[1] Healthy People 2020 indicates the significance of this topic, as one of its objectives is to "increase immunization rates and reduce preventable infectious diseases."[2] However, despite progress in this endeavor, it is estimated that approximately 42,000 adults and 300 children in the United States will die each year from vaccine-preventable diseases.[2] Some speculate that one of the reasons the United States has fallen short of the national goal is due to misconceptions the public may have about the safety and efficacy of current vaccines. These misconceptions may be magnified during pregnancy, when special concern is taken for the mother and unborn child. As pharmacists have the opportunity to educate patients about the importance of vaccines, and also may be able to administer certain vaccines per state laws, it is imperative for pharmacists to be up-to-date on the current guidelines about recommended vaccines for pregnant women.

There are a few general principles regarding pregnancy and vaccine safety. First, administering live, attenuated viral or live bacterial vaccines is contraindicated in pregnant women due to the theoretical risk of transmitting to the developing fetus.[3,4] Second, considerations of risks and benefits to individual patients in the context of general guidelines must be considered (Table 1). If the patient is at a high risk of disease exposure, if an infection could cause harm to the mother or fetus or if the vaccine is unlikely to cause harm the benefits of vaccinating could outweigh the potential risks.[4] Finally, the mother's current and past medical history, including allergy to any component of the vaccine product, must be taken into consideration when determining whether she should receive a specific vaccine.

Recommended Vaccines
Influenza (Inactivated)
It is recommended by the American College of Obstetricians and Gynecologists (ACOG), the U.S. Advisory Committee on Immunization Practices (ACIP) and the Centers for Disease Control and Prevention (CDC) that women who are pregnant during influenza season should receive an inactivated influenza vaccine during any trimester of pregnancy.[5,6] It is recommended that pregnant women be given the inactivated injectable influenza vaccine instead of the live attenuated influenza vaccine (LAIV) administered as a nasal spray, which is contraindicated during pregnancy.[7]

Certain populations have a higher risk of morbidity and mortality as a result from contracting an influenza infection, one of which are women who are pregnant.[7] During pregnancy, healthy women have a four- to fivefold increase in risk of developing a serious illness requiring hospitalization due to being infected with the influenza virus compared to non-pregnant, healthy females.[6]

There is a limited amount of research on influenza infections in pregnant women due to the exclusion of pregnant patients from controlled, randomized trials and toxicity testing.[7] These limited data indicate that use of the inactivated vaccine during any trimester of pregnancy is effective with no recognized risks to the fetus. However, the possibility of fetal hypoxia due to an anaphylactic reaction of the mother to the vaccine's components (due to an allergy such as an egg allergy) must be considered.[7]

Tetanus, Diphtheria, and Pertussis (Tdap)
Pertussis is a contagious, respiratory illness, also known as whooping cough, which is caused by the bacteria *Bordetella pertussis.*[8] According to the CDC, there has been an increase in the number of outbreaks of pertussis in 2012 throughout the United States, with nearly 34,000 cases reported. Of these cases, 16 deaths have occurred, with the majority of these occurring in infants less than three months old.[9] Tetanus is caused by the bacteria *Clostridium tetani* transmitted through contaminated, punctured, or deep tissue wounds. In the past few years, an average of 29 cases were reported in the United States, with about half of the patients being 50 years of age or older. Most of the cases are due to not receiving the primary vaccine series or not following up with the booster vaccine.[10] The bacteria *Corynebacterium diphtheria* can be acquired through the nasopharynx or cutaneously. Diphtheria occurrence in the United States has greatly decreased in the past few years and is rare in the United States; however, it continues to be endemic in other parts of the world.[11]

Table 1. Summary of Immunization Guidelines for Pregnant Women.[4, 24]

Vaccine	Form	Route	General Recommendation
Hepatitis A	Inactivated	IM	May be used if benefit outweighs risk
Hepatitis B	Inactivated	IM	Recommended in some circumstances
Herpes zoster (shingles)	Live	SC	Contraindicated
Human papillomavirus (HPV)	Inactivated	IM	Not recommended
Influenza, trivalent inactivated	Inactivated	IM, ID	Recommended
Influenza, live attenuated (LAIV)	Live	Nasal spray	Contraindicated
Measles, mumps, rubella (MMR)	Live	SC	Contraindicated
Meningococcal conjugate (MCV4)	Inactivated	IM	Inadequate data for recommendation
Tetanus, diphtheria, pertussis (Tdap)	Inactivated	IM	Recommended
Varicella	Live	SC	Contraindicated

IM = intramuscular; ID = intradermal; SC = subcutaneous

Currently, the CDC recommends that pregnant women who have not been previously vaccinated with Tdap receive one dose of Tdap preferably later in pregnancy (after 20 weeks gestation) to confer the greatest protection to the newborn. If a Td booster is indicated for a pregnant woman for wound management, and she has not previously received a Tdap vaccine, Tdap should be administered. Recently, the ACIP endorsed a provisional recommendation that all pregnant women, regardless of vaccination history, receive a Tdap dose during the third trimester or post-partum; this recommendation has not yet been fully endorsed by the CDC. [12]

If a woman does not receive this vaccine during her pregnancy, it is recommended to be given immediately after delivery while still in the health care facility.[4] Likewise, it is recommended that close contacts of the newborn (immediate and extended family members and caregivers) receive vaccine at least two weeks before interacting with the infant. Due to the re-emergence of pertussis in the United States, this strategy, known as "cocooning," is being advocated to reduce transmission to newborns who are too young to receive the vaccine themselves.[13]

Vaccines That May Be Used In Some Circumstances

Hepatitis A

There are two hepatitis A inactivated vaccines licensed for use in the United States. The safety of these vaccinations during pregnancy has not been completely determined, but the risk could be assumed to be low since it is not a live vaccine.[14] Since there is no definitive evidence on the safety of the vaccine, the risk associated with receiving the vaccination should be compared against the risk for hepatitis A in a pregnant woman who may or may not be at a high risk for exposure to the virus.[15]

Hepatitis B

Hepatitis B virus (HBV) is prevalent worldwide and is responsible for one million deaths per year. There is a higher prevalence in developing countries with limited medical facilities, and it is most common in young adults. The virus can be transmitted perinatally from mother to infant at birth.[16] The impact of perinatal transmission is indicated by the fact that approximately 40 percent of infants born to infected mothers in the United States develop chronic HBV. In order to decrease the risk of transmission during birth, preventive measures, such as screening pregnant women for the presence of the hepatitis B surface antigen (HBsAg), can be instituted.[17] The presence of HBsAg in serum signifies an infection, and the carrier rates for this antigen are 10 to 15 percent.[16] Additional preventive measures include individual case management of women and infants with HBV, immunoprophylaxis given to infants born of infected women, and a continued series of HBV vaccines for the infant.[17] Due to perinatal transmission, it is recommended that pregnant women at high risk of contracting HBV receive the hepatitis B vaccine. Women at high risk include those being evaluated or treated for a sexually transmitted infection (STI), those who have had more than one sex partner in the past six months, those using injection drugs and those who have had intercourse with a HBsAg positive partner.[4] The vaccine is a recombinant DNA or plasma-derived vaccine, containing noninfectious HBsAg, which is given in three doses via the intramuscular route.[16] Limited data infer that fetuses of women who receive the vaccine are at low risk for adverse effects.[4]

Since the vaccine contains a noninfectious antigen for hepatitis B, the vaccine is not contraindicated for pregnant women. If the mother is immunized, the antibodies may passively transfer to the fetus. A study was conducted to test the efficacy of two different dosing regimens during pregnancy, where the first group received two doses of the vaccine and the second group received three doses. Pregnant women who received the three-dose regimen had statistically significantly higher levels of maternal antibodies. The antibody

levels in the infants were higher in the three-dose regimen group at the time of birth; the levels declined in the months following delivery. The vaccine did not cause any significant side effects during the study and the immune response was excellent. This study concluded that the hepatitis B vaccine is safe in pregnancy and has high immunogenic results.[18]

Vaccines That Are Contraindicated/Not Recommended

Measles, Mumps and Rubella (MMR)

Measles, Mumps and Rubella (MMR) is a live, trivalent, attenuated measles, mumps and rubella vaccine. Measles, mumps and rubella are commonly known as childhood diseases that may have some serious and even fatal complications.[19] Measles is a contagious viral infection that most often presents with fever, cough, acute rhinitis, and an erythematous, maculopapular rash.[3,19] Severe side effects often include pneumonia and encephalitis.[3] Mumps is a contagious virus often spread via air droplets, saliva or fomites. It presents with fever, malaise, parotiditis and myalgia.[19] Mumps can lead to further complications including meningoencephalitis and other neurologic complications such as deafness.[3] Rubella, also known as the German measles, can affect children and adults. It often has a mild presentation, but infection during the first trimester can cause serious birth defects, such as congenital rubella syndrome (CRS), which can be cardiac, ophthalmologic, auditory and/or neurologic in nature.[19]

As the MMR vaccine is a live, attenuated vaccine, it is contraindicated during pregnancy.[3,4] Women should be informed to avoid pregnancy for at least 28 days after receiving the MMR vaccination. However, routine pregnancy testing before administering the MMR vaccine is not recommended.[4] A woman who conceives within four weeks of administration of the MMR vaccine should be counseled on the theoretical risk of CRS; receipt of the vaccine should not be the basis to terminate a pregnancy.[3,4] Rubella-susceptible women who are not vaccinated because they may be pregnant should be counseled about the risk of CRS and educated to avoid exposure to rubella; they should be vaccinated as soon as they are no longer pregnant.[4] Pharmacists can educate all women of childbearing potential on the importance of MMR vaccination before pregnancy.

Herpes zoster (zoster)

The live attenuated vaccine used to prevent shingles is contraindicated for use in pregnant women. Although most women in the age group recommended to receive the zoster vaccine are not likely to bear children due to decreased fertility, it can be beneficial to educate high risk patients. If a woman capable of becoming pregnant receives the vaccine, she should wait 28 days following administration of the zoster vaccine to conceive. If a pregnant woman has inadvertently received the live attenuated vaccine within one month of conception, in most cases, the decision to terminate a pregnancy should not be completely based on the administration of the zoster vaccine during pregnancy.[4]

Varicella

The varicella virus causes the highly contagious childhood disease commonly known as chicken-pox. It rarely causes serious complications, but in some cases it can cause encephalitis and pneumonia. Typically, the risk of serious events increases with age.[3]

Since the varicella vaccine contains the live, attenuated varicella zoster virus, it is contraindicated in pregnancy.[3,4] Currently, the effect of the varicella vaccine on the fetus is unknown. Non-pregnant women receiving the vaccination should avoid becoming pregnant for one month after the injection. Women who conceive within four weeks of receipt of the vaccine should be counseled on theoretical risks to the fetus; pregnancy termination based on exposure to the vaccine is not warranted. [4]

If a susceptible pregnant woman is exposed to the varicella virus, administration of the varicella zoster immune globulin (VZIG) should be strongly considered due to a higher risk of severe varicella and complications.[4] According to the CDC guidelines, "Administration of VZIG to these women has not been found to prevent viremia, fetal infection, congenital varicella syndrome or neonatal varicella. Thus, the primary indication for VZIG in pregnant women is to prevent complications of varicella in the mother rather than to protect the fetus."[4]

Human papillomavirus (HPV)

About twenty million Americans are currently infected by the human papillomavirus (HPV), and each year 6 million more are infected. The vaccine may help prevent the occurrence of cervical cancer, which affects about 12,000 women in the United States each year. There are two versions of the vaccine available in the United States. The vaccine is given in a three-dose series and is recommended for individuals aged nine to 26 years.[20] The CDC states that the HPV vaccine is not recommended for pregnant women. If a woman discovers she is pregnant between doses of the vaccine, it is preferred that she wait until the end of her pregnancy to receive the next dose; however, no medical interventions are needed.[4,21] A pregnancy test is not required before administration of the HPV vaccine.[4]

Inadequate data

Meningococcal Conjugate (MCV4)

Meningococcal disease, caused by the pathogen *Neisseria meningitidis,* is one of the leading causes of bacterial meningitis in the United States.[22] *N. meningitidis* is a gram negative diplococcus bacterium that commonly colonizes in the respiratory tract. It is transmitted by air droplets or contact with respiratory tract secretions.[23] Approximately 2400 to 3000 cases occur each year, and it is estimated that 10 to 14 percent of cases are fatal, despite the timely administration of antibiotic therapy.[22] Other serious sequelae include hearing loss, neurologic disorders and the potential for the loss of a limb.[23]

Meningococcal conjugate is a tetravalent meningococcal vaccine containing polysaccharide serogroups A, C, Y, and W-135 conjugated to diphtheria toxoid. It has been approved by the U.S. Food and Drug Administration for active immunization of adolescents and adults 11 to 55 years of age.[23] Routine vaccination is recommended for high-risk individuals

including, but not limited to, military recruits, patients with anatomic or functional asplenia, patients with terminal complement component deficiencies and college students living in dormitories.[3] However, currently there is no data available on the safety of MCV4 during pregnancy.[4]

Conclusion

While general guidelines have been presented here, the risks and benefits of administering specific vaccines during pregnancy must be determined for each patient.[3] Table 1 summarizes the general recommendations presented in this article.

Pharmacists can educate patients about the vaccines recommended for use during pregnancy as well as the importance of vaccinating other family members. Pharmacists can also administer specific vaccines per state laws and protocols. Finally, pharmacists can help protect the public's health by reporting any exposures to vaccines during pregnancy, or any known outcomes to mother or child, to the respective vaccine manufacturers to be recorded in their pregnancy registries. Through education, reporting and provision of services, pharmacists can promote public health and primary prevention.

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Endometriosis: The Etiology and Recommended Treatment

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Abstract
Endometriosis is a gynecological condition that occurs in women between the ages of 15 and 49 years, in which endometrial cells grow outside the uterus. Normally, endometrial cells form the endometrium and respond to hormones throughout the menstrual cycle, but when endometrial cells are located outside the endometrium, painful bleeding and other side effects may occur. Treatment of endometriosis is usually symptomatic relief, including the use of oral contraceptives and other hormone replacement options, as well as non-steroidal anti-inflammatory drugs. To ensure that patients receive the appropriate treatment for this condition, pharmacists should be able to recognize the signs and symptoms of endometriosis and refer patients to physicians. Pharmacists also play a key role in patient education about the medications and surgical treatments to manage the symptoms and pain associated with endometriosis.

Introduction

Endometriosis is a gynecological condition in which endometrial cells grow outside the uterus. This condition commonly affects women between the ages of 15 and 49 years. The endometrial cells typically form the endometrium, or lining of the uterus, and respond to hormones, such as estrogen, throughout the menstrual cycle. These hormones stimulate menstrual bleeding after a woman's typical menstrual cycle.[1] When endometrial cells are located outside the uterus, they respond to hormones in the same manner leading to bleeding which can be extremely painful.[2] However, some women with endometriosis may be asymptomatic and these cases often go undiagnosed. Other cases of endometriosis may go undiagnosed due to inappropriate diagnosis as a different disease or conditions such as premenstrual syndrome (PMS). Endometriosis commonly occurs on the outside surface of the uterus, the vagina, fallopian tubes, rectum, behind the cervix and on the ovaries.[3] The growth, swelling, and breakdown of endometrial tissue outside the uterus can cause lesions which can permanently scar. Awareness of the risks, causes and symptoms of endometriosis may lead to a more effective treatment outcome and, in turn, improve the patient's quality of life.

Risk Factors and Causes of Endometriosis

The growth of endometriosis is dependent upon hormones, especially estrogen. However, hormones are not responsible for the proliferation of the endometrial cells outside the uterus. One possible cause of endometriosis is retrograde menstruation, a condition where uterine lining is present in the fallopian tubes and potentially the abdomen, rather than the vaginal cavity. Although many women experience retrograde menstruation, most women avoid endometriosis with the help of their immune system. Women affected by endometriosis may have abnormal functioning of their immune system, in which the immune system allows endometrial cells to begin growing on other organs. The lymphatic system may carry endometrial cells to other organs as well which results in growth further from the uterus.[3]

Endometriosis can occur in any woman of child bearing age. However, some women are at a higher risk of developing endometriosis. A major risk factor in developing the disease is the presence of familial history of endometriosis in a primary female relative. An irregular menstruation cycle can also increase a woman's risk of developing endometriosis. A woman who experiences early onset of menstruation before 12 years of age may have an increased risk of developing the condition. The risk of endometriosis also increases for women experiencing menstrual bleeding for more than seven consecutive days. This prolonged bleeding time may be an indication of bleeding from physiologically different areas of the body other than the uterus. If a woman cannot or chooses not to have children, her risk of developing endometriosis increases; pregnancy typically decreases the progression of the condition due to a decreased amount of estrogen.[2] A woman's uterus may have a physiological defect or abnormal development potentially causing endometriosis to occur.[3] There is no single cause or risk factor responsible for the development of endometriosis, but it is important for women to be informed of the potential risks they have for developing the condition.

Symptoms of Endometriosis

Not all women that have endometriosis experience symptoms. However, recognition of the main symptoms of endometriosis is important in early diagnosis of a woman with the disease. The most common symptom of endometriosis is pain and cramping in the pelvic region especially prior to and during menstrual bleeding. Pain may also occur during bowel movements, during urination or as cramping in the lower back. Menstrual bleeding may become heavier than normal. Sexually active women may experience dyspareunia, or pain during sexual intercourse. Endometriosis can lead to infertility and miscarriage. If a woman is having trouble becoming pregnant or carrying a fetus to full term, she may have endometriosis.[3] If a woman is experiencing these symptoms, she should schedule an appointment with her doctor to have a pelvic exam.

Pharmacologic Treatment of Endometriosis

There are several strategies for the treatment of endometriosis. Treatment goals include controlling pain, slowing endometrial growth, and restoring or preserving fertility. Treatment options depend on a variety of factors, including severity of symptoms, size and location of growths, the degree of scarring and extent of the disease, if the patient wishes to conceive and at what age.[3] The American College of

Obstetricians and Gynecologists updated guidelines in 2010, which detail treatment strategies for each type of patient based on the previously listed factors.[4] First line agents for the treatment of dysmenorrhea, include non-steroidal anti-inflammatory drugs (NSAIDs) and combined oral contraceptives, which are hormone replacement medications that contain both estrogen and progestin. Medroxyprogesterone acetate, danazol and aromatase inhibitors are agents used for noncyclic chronic pelvic pain (defined as pain in the pelvic region lasting more than three months) and as second line treatment for dysmenorrhea. Agents that can be used second or third line for dyspareunia and dysmenorrhea are levonorgestrel intrauterine system and gonadotropin-releasing hormone (GnRH) agonists.[5]

Combined oral contraceptives can be used as a first line treatment with or without NSAIDs for relief of endometriosis related pain in women who are not trying to conceive at the time of treatment. Although they are associated with a 20 to 25 percent failure rate in the treatment of pelvic pain associated with endometriosis, combined oral contraceptives are preferred over danazol or GnRH agonists because they are generally well-tolerated.[5] Combined oral contraceptives work in relieving this pain by inhibiting ovulation, decreasing gonadotropin levels, and reducing menstrual flow and buildup of the endometrium during the menstrual cycle.[6] While oral contraceptives can be beneficial when used on a continuous basis to prevent menstruation, the endometrial growth that was decreased throughout treatment tends to reverse when treatment is stopped. This makes oral contraceptives a difficult treatment choice for anyone who wishes to become pregnant, because the patient will have to discontinue the drug before being able to conceive.[3]

Progestin only products, such as medroxyprogesterone acetate, are also a viable option for the treatment of endometriosis as an alternative to combined oral contraceptives. These drugs work by halting menstruation and the further growth of the endometrium, which will help relieve the signs and symptoms of endometriosis. Although not considered the treatment of choice, other hormonal treatments of endometriosis include GnRH agonists and antagonists. These products can be used to block the production of ovarian-stimulating hormones, leading to lower estrogen levels, which causes the endometrial growths to shrink. GnRH agonists, such as leuprolide and nagarelin, inhibit luteinizing hormone (LH) and follicle stimulating hormone (FSH) secretion, after an initial hormone flare. Continuous administration of GnRH agonists suppresses gonadotropin release through a negative feedback mechanism to the hypothalamus. GnRH antagonists have a more immediate inhibition of FSH and LH secretion. Unlike GnRH agonists, GnRH antagonists work by directly inhibiting FSH and LH release, and do not require a feedback mechanism. Examples of GnRH antagonists include ganirelix and cetrorelix.[7]

Another treatment option for endometriosis is danazol, a testosterone product that works by blocking the production of ovarian-stimulating hormones and therefore preventing menstruation. Danazol has also been shown to suppress the growth of the endometrium, making it a very effective treatment for endometriosis. However, danazol is not considered first-line due to undesirable side effects including alopecia and acne.[8]

Non-steroidal anti-inflammatory drugs are commonly prescribed as a first-line treatment for women experiencing dysmenorrhea and pain caused by endometriosis.[5,9] Non-steroidal anti-inflammatory drugs effectively inhibit cyclooxygenase (COX) enzymes, thereby inhibiting the production of prostaglandins, a likely cause of endometriosis-related pain. However, NSAIDs have no effect in decreasing or removing any endometrial deposits.[9]

Recently, it has been noted that the COX enzymes, more specifically the COX-2 isoform, are involved in regulation of cell growth and apoptosis. Activation of the non-steroidal anti-inflammatory growth factor (NAG-1) by NSAIDs effectively decreases cell proliferation and enhances apoptosis in cells, including endometrial cells.[10, 11] A 2008 in vitro study investigated cell proliferation and apoptosis response of endometrial cells to treatment with various concentrations of celecoxib in patients with endometriosis. At dosages of 50, 75 and 100 micromolar (μM), there was a significant effect on cell apoptosis induction versus control, with p values <0.05, <0.001, and <0.001, respectively. At these same concentrations, there was also a significant decrease in cell proliferation versus control, with p values <0.05, <0.01, and <0.001, respectively.[11] In addition to its effects on cell proliferation and apoptosis, celecoxib has also been shown to inhibit implantation of endometrial tissue. Like other COX inhibitors, COX-2 inhibitors additionally provide pain relief. The results of these data suggest that selective COX-2 inhibitors are an option for effective treatment, and even prevention, of endometriosis.[10]

For the reduction of dysmenorrhea and pain symptoms, NSAIDs must be taken a few days before or on the first day of menses.[5] Common side effects of NSAIDs include headache, dizziness, drowsiness, nausea, diarrhea, and GI irritation.[5, 9] Selective COX-2 inhibitors have fewer GI effects, but the potential risk for cardiovascular thrombotic disease may be increased.[10]

Laparoscopic Procedures

Laparoscopies for the diagnosis and treatment of endometriosis comprise 25 to 35 percent of all laparoscopic procedures yearly. Surgical treatment, such as laparoscopy, is not typically first-line treatment. Indications for this surgery include ineffective pain control or relief with NSAIDs, severe pain that lasts several months, and pain that requires one to miss school/work or requires hospitalization.[12]

Laparoscopy treatment can include: fulguration, ablation, and excision; excision or drainage and ablation; or laparoscopic presacral neurectomy (LPSN) of the tissues and cysts. The latter, LPSN, nerve-pathway interruption, also aids in control of pain by removal of the presacral nerves.[5] No studies have investigated the therapeutic outcome differences between the laparoscopic procedures, but individual treat-

ments have been investigated for recurrence of endometriosis and pain. In a study comparing laser treatment of endometriosis, including nerve transection, to aspiration of fluid, 20 out of 32 patients and seven of 31 patients, respectively, reported symptom improvement/relief six months after surgery. In the laser group, 90 percent of those who stated relief at six months experienced relief at one year, with only 10 percent (two patients) noting a return of symptoms.[13]

Laparoscopic surgery is often an option chosen by women wishing to conceive. Several systematic reviews have shown an increase in rate of pregnancy, nine to 12 months following surgery in one review, and a five-fold increase in pregnancy rate in another review, after laparoscopic surgery. There is some concern about diminishing ovarian reserve with laparoscopic surgeries, and as a result, in vitro fertilization is recommended for women who have endometriosis after repeated laparoscopic procedures.[13]

Recurrence of endometriosis after laparoscopic surgery is common.[12,14] Three important factors found to be determinant of repeat surgery were: older age, post-operative pregnancy and symptomatic improvement. Women who experienced pelvic pain rather than fertility problems were more likely to undergo or require another surgery. Location of endometrial tissues and cysts also played a significant role in whether or not another surgery would be required.[14]

The risks associated with laparoscopic surgery are not different than risks associated with any other surgical procedure, including anesthesia risk, infection, hemorrhage, potential damage to internal organs and new adhesions.[5]

Pharmacist's Role

Endometriosis is a disease that affects many women among various age groups, so it is important that pharmacists understand the pathology of the disease and also treatment options and goals. While pharmacists cannot directly diagnose endometriosis, it is important to recognize signs and symptoms of the disease so that they can refer patients that present with questions about these symptoms to their physician. There are many different treatment options for this disease so it is necessary for pharmacists to collaborate with patients and physicians to help the patient receive the best individualized treatment. Pharmacists should be able to educate the patients on potential treatment options and also be able to explain possible side effects and risks associated with each treatment. Even for those patients who choose surgery as a treatment, pharmacists have a role in helping patients with their post-surgery management of medications.

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