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A peer-reviewed drug management journal for managed care and hospital decision-makers

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Efficacy of new drugs compared to older ones not dramatic, study says

by Tracey Walker

The effectiveness of new drugs compared with that of older drugs has fallen since the 1970s, according to a new study in *Health Affairs*.

In the study, researchers randomly selected and analyzed the results of 315 clinical trials that compared a drug to a placebo from 4 medical journals: *New England Journal of Medicine*, *Journal of the American Medical Association*, *Lancet*, and *British Medical Journal* between 1966 and 2010.

RESEARCHERS' FINDINGS

The data extraction was done by research assistants who were kept blind to the purpose of the study and all studies were independently reviewed by 2 different research assistants. Drugs to treat cardiovascular disease, cancer, mental disorders, and respiratory illness, were included.

Researchers found that the average effect size, as measured by the odds ratio (which compares the odds of an outcome resulting from the treatment to the odds of that outcome in absence of the treatment), decreased from a peak of 4.51 (1971-1980) to 1.36 (2001-2010).

Take away

Medical breakthroughs that bestow large benefits above placebo are becoming less common.

Dr Olfson

"In other words, there has been a significant decline over time in the extent to which new drug treatments have been shown to be significantly more effective than placebos to the point that in recent years the average study found only small differences between the active drug and placebo," said lead author Mark Olfson, professor of clinical psychiatry at Columbia University and a research psychiatrist at the New York State Psychiatric Institute, in New York City.

"The results suggest that medical breakthroughs of the sort that confer large benefits above placebo are becoming less common," Dr Olfson told *Formulary*.

"An awareness of the uncommonness of these transformational drug discoveries helps to calibrate expectations for future placebo-clinical trials," he said.

"With apparently declining yield from placebo-controlled studies, now may be a good time to place greater emphasis on studies comparing 2 or more drugs that are known to be effective to evaluate whether there are meaningful differences between them in their tolerability, adherence, safety, or costs," Dr Olfson continued.

MAXIMIZE 'OLDER' THERAPIES

According to Randy Vogenberg, managing principal of Bentelligence, and adjunct professor of pharmacy management at the

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Men's Health Network urges men to get HPV vaccine

by Mark Lowery

The Men's Health Network (MHN) is hoping actor Michael Douglas' assertion that his throat cancer was caused by human papillomavirus (HPV) contracted during oral sex will provoke more males to get the HPV vaccine.

"It's important to vaccinate boys as well as girls for the HPV virus; it is inefficient to vaccinate only one partner against a condition that is spread the way HPV is," said Salvatore J. Giorgianni, Jr, PharmD, chair, Men's Health Caucus Constituency of the American Public Health Association, and Science Advisor, MHN.

"Many young people do not consider oral-genital and other extravaginal activity as sexual activity. Sexually active persons of all ages should understand that these activities carry many of the risks associated with sexual intercourse, such as the transmission of HPV and should engage in safe practices, including as indicated, vaccination," said Dr Giorgianni.

> According to Centers for Disease Control and Prevention, HPV is the most common sexually transmitted infection in the United States.

According to Centers for Disease Control and Prevention, HPV is the most common sexually transmitted infection in the United States. There are an estimated 26,000 HPV-attributable cancers annually in the United States, with about 17,000 occurring in women and about 9,000 in men.

HPV VACCINE RECOMMENDATIONS

HPV vaccine has been recommended for routine vaccination of 11- and 12-year-old girls since 2006 and for 11- and 12-year-old boys since 2011.

Armin Brott, author of "*The Military Father*" and host of the nationally-syndicated "Positive Parenting" radio show, said it's especially important for men to be vaccinated since half of the oral cancers in the United States are diagnosed in men and boys and 75% caused by HPV.

"But that's just the beginning of the devastation caused by HPV," Brott said. "Researchers are now investigating possible links between HPV infection and increased heart disease and stroke risk." ■

News Capsules continued from page 207

University of Rhode Island, Kingston, R.I., many plans and PBMs already have been looking to maximize generic or "older" therapies over the last few years.

"Purchasers of healthcare are less involved in the clinical details but similarly have sought to reduce the cost trend or 'bend the cost curve' due to economic pressures from the recession," Vogenberg told *Formulary*.

"As part of riding the generic wave, plans and PBMs have become increasingly aggressive in promoting step therapy strategies as well as optimizing first-line generic-only treatments," he said.

> Plans and PBMs have become quite aggressive in promoting step therapy and optimizing first-line generic-only treatments.

RETHINKING TREATMENT STRATEGIES

Now that providers are in shared or full-risk arrangements on commercial and exchange/Medicare plan products, they too have been rethinking treatment strategies, according to Vogenberg.

"One of the best examples has been in oncology where the minimal incremental clinical benefit versus the increasingly higher per product cost is resulting in greater use of first-line generic treatments for most patients which deliver good outcomes. This is especially true now that earlier diagnoses and treatment is so common," he said.

"Interestingly, these approaches do align patient interests along with the provider and purchaser of coverage—employer, union, and municipality—better than in the past," Vogenberg continued.

"I expect that the successes in oncology will move into immunology—rheumatoid arthritis and multiple sclerosis—quickly as large medical groups and ACOs seek to maximize outcomes at the lowest cost possible for pharmacologic therapies."

Reuters recently reported that US pharmaceutical companies have spent more than $50 billion every year since the mid-2000s to discover new drugs. ■

Long-term data reinforce safety profile of dabigatran etexilate mesylate

by Tracey Walker


Dr Smith

Results from the RELY-ABLE trial, the RE-LY extension study, support the long-term safety profile of dabigatran etexilate mesylate (Pradaxa, Boehringer Ingelheim Pharmaceuticals) 150 mg twice daily in patients with nonvalvular atrial fibrillation (NVAF), according to a study published in *Circulation*.

The RELY-ABLE trial was designed to evaluate the long-term safety of ongoing dabigatran etexilate mesylate therapy in patients with NVAF, following RE-LY. Patients enrolled in RELY-ABLE continued dabigatran etexilate mesylate therapy, as dosed in RE-LY, for an additional 2.3 years, bringing the mean duration of treatment to 4.3 years. A total of 5,851 patients participated in the extension study: 2,937 received dabigatran etexilate mesylate 150 mg twice daily and 2,914 received dabigatran 110 mg twice daily.

Rates of major bleeding, the primary end point, were 3.74% (n=238) per year with dabigatran etexilate mesylate 150 mg and 2.99% (n=190) per year with dabigatran 110 mg (HR 1.26, 95% CI: 1.04-1.53). Major gastrointestinal bleeding occurred at rates of 1.54% (n=98) per year with dabigatran etexilate mesylate 150 mg and 1.56% (n=99) per year with dabigatran 110 mg.

Secondary end points included other key safety outcomes, such as total bleeding and life-threatening bleeding, and showed similar results as RE-LY, with no new safety findings.

> An estimated 2.3 million Americans have atrial fibrillation, making it one of the most common heart rhythm disorders.

"The encouraging long-term safety results from RELY-ABLE add to the growing body of data reinforcing Pradaxa as an important treatment option for patients with NVAF," John Smith, MD, PhD, senior vice president, clinical development and medical affairs, Boehringer Ingelheim Pharmaceuticals, told *Formulary*.

An estimated 2.3 million Americans have atrial fibrillation (AFib), making it one of the most common heart rhythm disorders. "It is projected that 5.6 million US adults will have AFib by 2050, so we believe the need for OACs [oral anticoagulants] will continue to increase in the coming years," Dr Smith said. "The primary goal of anticoagulant therapy in patients with Afib is to reduce the risk of a clot forming in the heart and traveling to the brain, causing an ischemic stroke."

Nearly 9 out of 10 strokes caused by AFib are ischemic strokes.

Dabigatran etexilate mesylate is the first treatment among the new generation of OACs to be evaluated in a large set of NVAF patients for more than 4 years. "Data from RELY-ABLE also contribute to the evidence supporting the safety profile of Pradaxa, including the most recent analyses of real-world safety data from the FDA Mini-Sentinel initiative," Dr Smith said. ■

Take 2 to 3 minutes to identify CVD patients for more counseling

by Mark Lowery

Face-to-face interaction between pharmacists and patients will be key to the success or failure of the federal government's Million Hearts initiative to prevent heart attacks and strokes, Salvatore Giorgianni, PharmD, told participants during the June 3 *State of Men's Heart Webinar*.

Dr Giorgianni is a scientific advisor for Men's Health Network, which sponsored the webinar along with Million Hearts—an initiative by the Centers for Disease Control and Prevention (CDC) to avert 1 million heart attacks and strokes by 2017.

Men's Health Network encourages providers to celebrate Men's Health Month in June, by participating in health screenings, health fairs, and other health education activities.

"Pharmacists can have a profound effect and a profound impact on the cardiovascular health of men and women in their communities," Dr Giorgianni said, noting historically poor compliance rates involving high blood pressure and high cholesterol medicines.

He urged pharmacists to build better relationships with providers, to offer targeted education and screen-

ing programs, and to red-flag patients receiving cardiovascular prescriptions for additional counseling. "It takes 2-3 minutes," he said. "That's all it really takes."

He pointed to studies such as the 1996 Asheville Project, which demonstrated that medical adherence rates rise dramatically and overall medical costs decline when pharmacists are involved in face-to-face consultations and follow-up.

"I talk to patients, when I'm doing [MTM], and they'll tell me 'I don't take that medication anymore. I don't have the condition anymore.' Many don't realize that these are medicines that they need to continue to take," Dr Giorgianni said.

> ■ Smoking and high blood pressure are the 2 main causes of heart attacks and strokes in men.

Thomas Frieden, MD, MPH, director, CDC, said 1 out of 3 men have some form of cardiovascular disease and 1,000 men die every day due to heart attacks or strokes.

"Too many men have some form of cardiovascular disease and are at risk," he said.

Frieden identified the 2 main causes of heart attacks and strokes in men as smoking and high blood pressure. He said the community portion of Million Hearts would focus on tobacco control, sodium reduction, and trans fat elimination.

Since many men are goal-oriented, Dr Giorgianni suggested that pharmacists encourage male patients by pointing out successes.

"Find something, anything, that they are doing right," he said. "Reinforce it."

CDC and Centers for Medicare and Medicaid Services are the co-leaders of Million Hearts within HHS, working with the Administration for Community Living, National Institutes of Health, the Agency for Healthcare Research and Quality, FDA, the Health Resources and Services Administration, and the Substance Abuse and Mental Health Services Administration, the Office of the National Coordinator, and the US Department of Veterans Affairs. Key private-sector partners include the American Heart Association, and YMCA, among others. ■

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Training, advising pediatricians in antibiotic usage improves compliance with prescription guidelines

by Tracey Walker


Dr Gerber

Educating pediatricians in their offices, auditing their prescription patterns, and leveraging a shared electronic health record, encourages them to choose more appropriate antibiotics for children with common respiratory infections, according to a study published in the June 12 issue of the *Journal of the American Medical Association*.

Study leader Jeffrey S. Gerber, MD, PhD, an infectious diseases specialist at The Children's Hospital of Philadelphia (CHOP), and colleagues conducted a cluster-randomized trial, and randomized 18 pediatric primary care practices in CHOP's primary care network in New Jersey and Pennsylvania into 2 groups. One group received the intervention (an hour-long clinician-education session at the practice office, followed by audit and feedback of antibiotic prescribing) and a control group that did not receive the educational session, audit, and feedback. The study encompassed nearly 1.3 million office visits by some 185,000 patients to 162 clinicians over a study period of 32 months, from 2008 to 2011.

Among the intervention practices, broad-spectrum antibiotic prescribing decreased from 26.8% to 14.3%, or nearly half, compared to a decrease from 28.4% to 22.6% in the control group. For children with pneumonia, the inappropriate broad-spectrum prescriptions declined by 75% among practices receiving the intervention.

The researchers followed the effects of the intervention program for only 12 months, according to Dr Gerber, so it is not known how long the benefits persist. In addition, the study team did not examine whether there were differences between the intervention and control groups in the outcomes of their patients' infections.

The study concentrated on whether the pediatricians prescribed narrow-spectrum antibiotics, as recommended, or broad-spectrum antibiotics for acute bacterial respiratory infections such as pneumonia, acute sinusitis, and streptococcal pharyngitis (or "strep throat"). All are common conditions for which children receive antibiotics.

"Using a relatively simple intervention, we were able to improve antibiotic prescribing to children with common outpatient infections," Dr Gerber told *Formulary*. "Overall, the intervention nearly halved prescribing of broad-spectrum antibiotics, which are typically not indicated, for children at acute primary care encounters, and decreased the use of off-guideline antibiotics for children with pneumonia by 75% by 1 year after the intervention.

> Unnecessary prescribing for viral infections, which don't benefit from any antibiotic use, is well documented and has been declining.

LEVERAGING THE EHR

"Our results demonstrate the ability to leverage an electronic health record to ensure that children receive guideline-recommended care," Dr Gerber continued. "Although our study did not directly examine clinical outcomes and costs, this approach has the potential to improve clinical outcomes while reducing healthcare costs."

According to Dr Gerber, unnecessary prescribing for viral infections, which don't benefit from any antibiotic use, is well documented and has been declining. "However, inappropriate prescribing also occurs for bacterial infections, particularly when broad-spectrum antibiotics are used to treat infections for which narrow-spectrum antibiotics are indicated and recommended. We wanted to find a way to help address this emerging problem," he said.

"Just as there are many types of bacteria that can cause infections, there are also many different types of antibiotics," he added. "'Narrow-spectrum' antibiotics treat very few types of bacteria while 'broad-spectrum' antibiotics can treat many different types of bacteria."

Broad-spectrum antibiotics are not "stronger" against the bacteria that cause common respiratory tract infections in children than narrow-spectrum drugs; both types can kill these germs, according to Dr Gerber.

But use of broad-spectrum antibiotics will unnecessarily expose the patient to drugs that are more likely to 1) kill "good" bacteria that live in and on the patient, which can be harmful or 2) create an environment that permits the creation or selection for antibiotic resistant germs, which can complicate the treatment of subsequent infections.

"Therefore, when prescribing antibiotics, it is important to choose an agent that targets the offending pathogen [germ] but as few other types of bacteria as possible," he said.

"By partnering with pediatricians and leveraging a shared, electronic heath record, we were able to improve antibiotic prescribing to children with common infections," Dr Gerber said. "It is our hope that this relatively simple intervention can be applied to other practices and patient populations to help improve patient care." ■

PEER-REVIEWED

The current state of HIV therapy

Jessica A. Benzer, PharmD; Ted K. Riley, PharmD;
Jean C. Lee, PharmD, BCPS, AAHIVP

Abstract

Incidence of human immunodeficiency virus (HIV) has decreased dramatically since its emergence in the early 1980s, but it remains a worldwide epidemic. There is a reduction in newly diagnosed patients, but prevalence is increasing due to a longer life expectancy, which is attributed in part to highly effective antiretroviral therapies. Newly approved and investigational antiretroviral therapies provide additional options for the healthcare team to prevent progression of disease as well as transmission of HIV. Early detection and prevention of HIV is still paramount with the use of in-home HIV testing as well as antiretrovirals for pre-exposure prophylaxis. While many advances in HIV diagnosis and treatment have been made, the importance of education and risk avoidance cannot be underestimated. (*Formulary*. 2013; 48:213-223.)

The number of people newly infected with HIV has declined, but it remains a worldwide epidemic. Prevalence continues to rise with current estimates of 34 million people living with HIV or acquired immunodeficiency syndrome (AIDS), up from 29.4 million in 2001, due to new infections as well as patients living longer. Worldwide in 2011, 1.7 million people died of AIDS.[1] In the United States the prevalence is estimated to be 1.2 million, with approximately 1 in 5 people infected who are undiagnosed and unaware.[2] Although the HIV mortality rate has decreased 80% since its peak in 1995, HIV was the sixth leading cause of death for those aged 25 to 44 in 2009.[3] Deaths have declined in part due to increased treatment options and utilization of highly effective antiretroviral medications.

Eradication of HIV is currently not feasible due to latent infection of CD4 cells; therefore, the goals of therapy include reducing morbidity and prolonging life, restoring and preserving immune function, decreasing opportunistic infections, decreasing viral load, limiting adverse events (AEs), and preventing further transmission. Preventing the emergence of resistance is also imperative. This can be best accomplished by achieving maximal and durable suppression of plasma viremia, which often requires the use of preferably 3 antiretroviral drugs (ARVs). The increasing availability of ARVs and development of new drug classes makes this a more feasible goal for all patients. Predictors of success include a rapid reduction in viral load, increased potency of the regimen, low baseline viremia, higher baseline CD4 count, and adherence to medication regimens.[4] It has been estimated that in order to maintain viral load suppression, high medication adherence rates of greater than 95% may be required. Poor virologic and immunologic responses to ARVs lead to the development of drug-resistant virus.[5]

INITIATION OF TREATMENT

In February 2013, the Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents provided an update to the Guidelines for the Use of Antiretroviral Agents in HIV-1–Infected Adults and Adolescents with recommendations on the initiation of antiretroviral therapy (ART) in treatment-naive patients. Recommended changes were made to reflect emerging data outlining the benefit of therapy in reducing transmission and the harmful effects of ongoing HIV replication on disease progression. These recommendations and their associated strengths are shown in Table 1.[4]

When deciding to initiate treatment, patients need to be educated on the importance of adherence along with the benefits and risks associated with ART (strength of recommendation: AIII; see Table 1. page 214). Evidence has shown that untreated HIV infection can lead to the development of other diseases including cardiovascular disease, kidney disease, liver disease, neurologic complications, and malignancies.[4] Patients may choose to postpone therapy, and providers may elect to defer therapy on the basis of clinical or psychosocial factors such as lack of prescription drug coverage, depression, literacy level, and ability

Drs Benzer and Riley are PGY-1 pharmacy residents, Pharmaceutical Services, Mercy Health Saint Mary's, Grand Rapids, Mich. **Dr Lee** is a clinical pharmacist – HIV Medicine, Special Immunology Services & Infectious Disease, Mercy Health Saint Mary's, Grand Rapids, Mich.

Disclosure Information: Drs Benzer and Riley report no financial disclosures as related to products discussed in this article. Dr Lee reports that she served on the Advisory Board with Gilead Sciences.

Table 1

Recommendations for initiating antiretroviral therapy in treatment-naive patients

Recommendation	Strength*
Based on CD4 count:	
CD4 count <350 cells/mm^3	AI
CD4 count 350 to 500 cells/mm^3	AII
CD4 count >500 cells/mm^3	BIII
Transmission risk:	
Perinatal transmission	AI
Heterosexual transmission	AI
Other transmission groups	AIII
Regardless of CD4 count:	
History of an AIDS-defining illness	AI
HIV-associated nephropathy	AII
HIV/hepatitis B virus co-infection	AII

* Rating for recommendations

Strength of recommendation	Quality of evidence
A: Strong	I: Data from randomized controlled trials
B: Moderate	II: Data from well-designed non-randomized trials or observational cohort trials with long-term clinical outcomes
C: Optional	III: Expert opinion

Formulary/Source: 4

and willingness to initiate therapy and follow medication regimens.[4]

Antiretroviral therapy should consist of 2 nucleoside reverse transcriptase inhibitors (NRTIs) and at least 1 ARV from another class, including a non-nucleoside reverse transcriptase inhibitor (NNRTI), integrase strand transfer inhibitor (INSTI), or protease inhibitor (PI) for initial therapy. The Panel recommends the following as preferred regimens for treatment-naive patients.[4] Their strengths of recommendation follow in parentheses.

- efavirenz/tenofovir disoproxil fumarate/emtricitabine (AI)
- ritonavir-boosted atazanavir + tenofovir disoproxil fumarate/emtricitabine (AI)
- ritonavir-boosted darunavir + tenofovir disoproxil fumarate/emtricitabine (AI)
- raltegravir + tenofovir disoproxil fumarate/emtricitabine (AI)

The selection of a regimen should be individualized on the basis of virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, and comorbid conditions. Recommended alternative and other regimens are also included in the guidelines.[4]

ANTIRETROVIRAL AGENTS AND CURRENT TARGETS OF THERAPY

ARVs target specific processes necessary for the replication of the HIV virus in the human host. Upon entry in the body the virus has contained within its outer shell or capsid all of the necessary elements, such as viral ribonucleic acid (RNA), for replication. The outer layer of the capsid is a protein receptor (gp120) that has affinity for CD4 receptors. These CD4 receptors, found on a number of cells in the body, have particular importance on CD4 T lymphocytes. An interaction between the gp120 receptor and the co-receptors

Continued on page 217

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Continued from page 214

CXCR4 and CCR5 on the CD4 cell reveals the gp41, thus allowing the fusion of the viral envelope to the CD4 plasma membrane. Once in the cytoplasm, viral reverse transcriptase transcribes the RNA into deoxyribonucleic acid (DNA) for transport into the cell nucleus and integration into the host cell's genome. After HIV DNA is integrated into the host cell's DNA, replication is induced. Once the lymphocyte is activated transcription of the viral DNA occurs, resulting in multiple copies of viral RNA. This RNA then codes or translates for the viral proteins and enzymes. An HIV enzyme protease cuts the long chains of HIV proteins into smaller individual proteins. As the smaller HIV proteins assemble with copies of viral RNA genetic material, a new virus particle is formed. These immature virions then mature to become active.[6]

Nucleoside reverse transcriptase inhibitors (NRTIs)

The NRTIs work by competing with nucleosides for incorporation into the viral DNA, thereby inhibiting the activity of HIV reverse transcriptase. This leads to chain termination and prevents replication.[6] Currently available agents include abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir, and zidovudine. A lack of CYP metabolism leads to fewer drug interactions; however, due to renal clearance, dose adjustments are required for renal insufficiency. All NRTIs may be administered without regard to food with the exception of didanosine.[4] When given alone, it requires administration on an empty stomach; however, when given with tenofovir, this food restriction is eliminated.[7] Class side effects include lactic acidosis and hepatomegaly.[4] It should be noted that although the package inserts list these as class effects, they generally occur in very low incidence with certain agents (abacavir, emtricitabine, lamivudine, tenofovir). Some NRTIs also cause peripheral neuropathy (didanosine, stavudine), and are thus not commonly used in practice.[4]

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

The NNRTIs bind directly to reverse transcriptase and impede the RNA-dependent and DNA-dependent DNA polymerase activities.[6] Currently available agents include delavirdine, efavirenz, etravirine, nevirapine, and rilpivirine. Class side effects include rash and hepatotoxicity. A small percentage of patients experience a severe rash, including Stevens-Johnson syndrome. Nevirapine in particular has been associated with hepatotoxicity, especially in patients with higher CD4 counts, and is contraindicated in females with CD4 counts >250 cells/mm^3 and males with CD4 counts >400 cells/mm^3.[8] Efavirenz and rilpivirine have been associated with neurologic and psychiatric AEs. A recent study looking at the results of the ECHO and THRIVE trials showed that rilpivirine was associated with fewer neurological and psychiatric AEs than efavirenz over 48 weeks in treatment-naive, HIV-1–infected adults.[9] The NNRTIs are all extensively metabolized by CYP3A and, with the exception of rilpivirine, are either CYP3A inhibitors or inducers. Therefore, as the potential for drug interactions is high, caution should be used when these agents are used in conjunction with potent CYP inhibitors, inducers, or substrates. It is vital to refer to package inserts or other reference materials when initiating or changing therapy. There is no food restriction with nevirapine administration. Efavirenz should be administered on an empty stomach to reduce potential side effects, and it is recommended to administer rilpivirine and etravirine with a meal.[4]

■ As all PIs are substrates and inhibitors of CYP enzymes, specifically CYP3A, caution is advised if coadministered with medications known to be substrates, inhibitors, or inducers of these CYP enzymes.

Protease inhibitors (PIs)

These PIs inhibit HIV protease used to cleave proteins for final assembly of new virions, which subsequently induces the formation of immature noninfectious viral particles.[6] The currently available agents include atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir. Side effects include gastrointestinal upset, lipodystrophy, dyslipidemia, hyperglycemia, and hepatotoxicity. As all PIs are substrates and inhibitors of CYP enzymes, specifically CYP3A, caution is advised if coadministered with medications known to be substrates, inhibitors, or inducers of these CYP enzymes. Most PIs should be administered with food (atazanavir, darunavir, nelfinavir, ritonavir, saquinavir). Both fosamprenavir and tipranavir should be administered with food if given with ritonavir tablets.[4]

CCR5 inhibitors

The CCR5 co-receptor antagonist inhibits fusion of HIV with the host cell by inhibiting the interaction between the gp120 viral glycoprotein and the CCR5 receptor.[10] Maraviroc is currently the only available

agent in this class. It is indicated for patients who carry CCR5 tropic virus; therefore, testing for co-receptor tropism is required prior to initiation. The co-receptor tropism assay reports the result as R5 (virus that utilizes the CCR5 receptor), X4 (virus that utilizes the alternate receptor CXCR4), or dual/mixed virus (which utilizes either or both receptors to enter the CD4 cell). The most commonly reported side effects include dizziness and muscle pain.[4] Although a single case of hepatotoxicity with allergic features was reported a cross-protocol analysis revealed no significant difference in hepatic toxicity between maraviroc and control groups.[11,12] Concerns about CCR5 antagonists and malignancy were also addressed in a cross-protocol analysis, which showed no association.[13] Maraviroc is metabolized by CYP3A, and the dose must be adjusted if given with CYP3A inhibitors or inducers. Maraviroc may be administered without regard to meals.[11]

Fusion inhibitors

The fusion inhibitor functions by inhibiting fusion of viral and cellular membranes and thus entry into the CD4 cell. It binds to the first heptad-repeat (HR1) in the gp41 subunit of the viral envelope glycoprotein and prevents conformational changes required for fusion of the viral and cellular membranes. Enfuvirtide is the only currently available fusion inhibitor and is available as a subcutaneous injection.

The most commonly reported AEs are injection-site reactions including redness, swelling, pain, hardened skin, and bumps. There are no clinically relevant drug interactions with enfuvirtide, and due to subcutaneous administration it can be administered without regard to meals.[14]

Currently in the management of HIV, this agent is generally reserved for salvage therapy due to its side-effect profile and the availability of newer highly effective oral agents.[15]

Integrase strand transfer inhibitors (INSTIs)

INSTIs obstruct integrase by binding in the catalytic core domain of the enzyme and competing for binding with the host DNA. This prevents integrase from inserting the viral genome into the host DNA. The currently available individual agent is raltegravir, with common AEs of insomnia, headache, nausea, and fatigue. Raltegravir is mainly metabolized via a UDP-glucuronosyltransferases (UGT) 1A1-mediated glucuronidation pathway. Decreased plasma concentrations may occur if coadministered with drugs that strongly induce UGT1A1 such as rifampin.[16] With recent reports of myopathy associated with raltegravir, it should be used with caution in individuals with increased risk of myopathy or rhabdomyolysis[17], such as those receiving concomitant therapy with statins and fibric acid derivatives. Raltegravir may be administered without regard to meals.[16]

A new INSTI, elvitegravir, is currently only available as combination with emtricitabine, tenofovir, and cobicistat, known as Stribild. It requires a pharmacokinetic booster, cobicistat, for viral activity.[18]

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NEWER THERAPIES

Recent approvals of ARVs have focused on single-tablet regimens. Prior to this, efavirenz/emtricitabine/tenofovir (Atripla) was the only medication that was composed of 3 ARVs that could be taken as 1 tablet once daily. In May 2011, FDA approved rilpivirine, and in August 2011, the second single-tablet regimen was approved as emtricitabine/rilpivirine/tenofovir (Complera). This was joined by elvitegravir/cobicistat/emtricitabine/tenofovir (Stribild) in August 2012 as the third single-tablet regimen.[19]

Rilpivirine

Rilpivirine a newer NNRTI, has the advantage of having a smaller pill size compared to other ARVs. In the ECHO and THRIVE trials, rilpivirine was shown to have noninferior efficacy compared to efavirenz, with a higher virologic failure rate but a more favorable safety and tolerability profile in treatment-naive patients.[20] A distinct advantage for rilpivirine is the lower rate of CNS side effects that are commonly seen with efavirenz.[9] In these studies, patients with a baseline HIV-1 RNA >100,000 c/mL and CD4 counts <200 cells/mm^3 experienced higher virologic failure rates[20] prompting label indication of use in those with HIV-1 RNA <100,000 c/mL.[21] Rilpivirine primarily undergoes oxidative metabolism mediated by the CYP3A system; hence, monitoring for drug interactions are important. Its exposure is approximately 40% lower when taken in a fasted condition compared with a normal caloric meal (533 kcal).[21] Rilpivirine was shown in the ECHO and THRIVE trials to be better tolerated than efavirenz, but 10% of patients treated with rilpivirine experienced treatment failure, which were mostly virologic failure. The E138K mu-

Table 2

Phase 3 studies comparing dolutegravir

Study	Dolutegravir	Comparator	Efficacy	Safety	Other
SINGLE: Treatment naïve	50 mg QD + abacavir/ lamivudine (n=414)	EFV/ emtricitabine/ tenofovir QD (n=419)	At 48 weeks (<50 c/mL): DTG: 88% EFV: 81% (*P*=.003) CD4 response change from baseline (cells/ mm^3): DTG: 267 EFV: 208 (*P*<.001)	Both well tolerated. Overall AEs leading to discontinuations: DTG: 2% EFV: 10%	DTG showed superiority
SPRING-2: Treatment naïve	50 mg QD + either abacavir/ lamivudine or tenofovir/ emtricitabine (n=411)	RAL 400 mg BID + either abacavir/ lamivudine or tenofovir/ emtricitabine (n=411)	At 48 weeks (<50 c/mL): DTG: 88% RAL: 85% (*P*<.05) Median CD4 increased by 230 cells/μL in each arm	Most common AEs: nausea, headache, nasopharyngitis, diarrhea	No treatment-emergent resistance with DTG. Resistance seen with RAL.
VIKING-3: Treatment experienced with INSTI. Open label.	50 mg BID + optimized background regimen (n=183)		At 24 weeks (<50 c/mL): DTG: 63% (n=114)	Most common AEs (5% each): diarrhea, nausea, headache	
SAILING: Treatment experienced but INSTI naïve	DTG 50 mg QD + BR (n=354)	RAL 400 mg BID + BR (n=361)	At 24 weeks (<50 c/mL): DTG: 79% RAL: 70% (*P*=0.003) CD4 response change from baseline(cells/ mm^3): DTG: 99 EFV: 93	Well tolerated. Overall AEs: DTG: 20% RAL: 23% Most common AEs: GI (diarrhea, nausea, vomiting)	DTG showed superiority

Abbreviations: AEs, adverse events; BID, twice daily; BR, background regimen; DTG, dolutegravir; EFV, efavirenz; GI, gastrointestinal; INSTI, integrase strand transfer inhibitor; QD, once daily; RAL, raltegravir.

Formulary/Sources: 26,27,28,29

tation was the most common and affects susceptibility to all other available NNRTIs.[23] Coadministration of rilpivirine with medications that elevate gastric pH such as proton pump inhibitors, H_2 antagonists, and antacids may decrease the serum concentration of rilpivirine, resulting in potential virologic failure and possible resistance. Rilpivirine must be taken 4 hours before or 2 hours after antacids as well as 4 hours before or 12 hours after an H_2 receptor antagonist. The use of rilpivirine with proton pump inhibitors is contraindicated.[21] Providers must weigh these considerations carefully with each patient individually.

> Dolutegravir has been shown to have a high genetic barrier, exhibiting a different resistance profile and activity against isolates resistant to current INSTIs.

The combination of emtricitabine/rilpivirine/tenofovir, as Complera, is another single-tablet regimen option. Renal dose adjustment is not required; however the combination should not be used in patients with creatinine clearance (CrCl) <50mL/min. It is recommended that this ARV be taken with a meal. Again, as this agent includes rilpivirine, caution is recommended with the use of concomitant strong CYP inhibitors and acid-reducing agents.[22]

Elvitegravir/cobicistat/emtricitabine/tenofovir

As the most recently approved INSTI-based single-tablet regimen of elvitegravir/cobicistat/emtricitabine/tenofovir for treatment-naïve patients, elvitegravir utilizes cobicistat, a strong inhibitor of CYP3A, as a pharmacokinetic boosting agent. Caution is warranted with concomitant medications that are substrates, inducers, or inhibitors of CYP3A as both elvitegravir and cobicistat are metabolized by CYP3A, and cobicistat is metabolized to a minor extent by CYP2D6. This ARV is not recommended to be initiated in patients with CrCl <70 mL/min and should be discontinued when CrCl <50 mL/min. Generally this elevation in serum creatinine occurs within the first few weeks of therapy, which then stabilizes. There is a boxed warning of lactic acidosis and severe hepatomegaly with steatosis and post-treatment exacerbation of hepatitis B in patients who have discontinued emtricitabine or tenofovir. The most common side effects in clinical trials were nausea (16%) and diarrhea (12%). No dosage adjustment or changes of administration times are necessary if taken with proton pump inhibitors or H_2 antagonists; however, it is recommended to separate elvitegravir/cobicistat/emtricitabine/tenofovir and antacids by at least 2 hours. Patients should take the medication with food to enhance absorption.[23] In September 2012, the DHHS Panel made the recommendation of use of the product as an alternative regimen for ART-naïve HIV-infected patients with CrCl >70 mL/min (strength of recommendation: BI).[4] Currently, neither elvitegravir nor cobicistat are available as separate agents.

ANTIRETROVIRALS ON THE HORIZON

Dolutegravir

Dolutegravir is a once daily unboosted INSTI, distinctive from the currently licensed raltegravir and elvitegraivr, by way of low variability in its pharmacokinetics and a predicable dose-response relationship. It has been shown to have a high genetic barrier, exhibiting a different resistance profile and activity against isolates resistant to current INSTIs. Dolutegravir has shown in vitro activity against HIV-1 and HIV-2, which was independent of HIV subtype. Mainly metabolized by glucuronidation utilizing UGT1A1, with a minor role of CYP3A4, potential drug interactions may occur. It has a terminal elimination half-life of 13 to 15 hours, supporting the once daily dosing, and food administration does not alter drug exposure.[24] Dolutegravir has been shown to inhibit renal tubular secretion of creatinine, leading to an increased serum creatinine. This effect is due to inhibition of the organic cation transporter 2.[25]

Drug interactions with dolutegravir have been investigated. Coadministration with an antacid resulted in a 30% reduction in dolutegravir AUC and 70% reduction

INFOGRAPH

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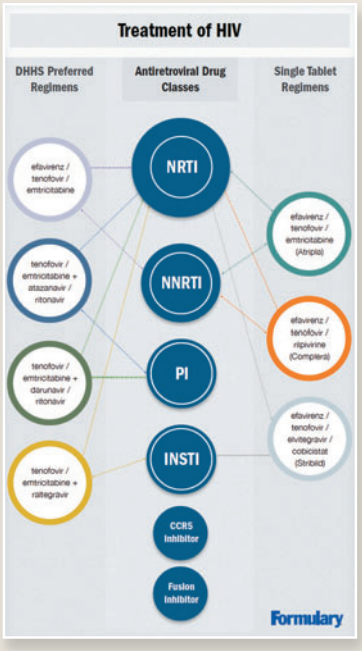

Table 3

Recent studies utilizing tenofovir or emtricitabine/tenofovir for pre-exposure prophylaxis

Study	Patient population	Medication	HIV reduction rate compared to placebo
iPrEx	MSM, transgender women (US, S. America, Africa, Thailand)	FTC/TDF QD (n=1,251) Placebo (n=1,248)	44%
Partners PrEP	Serodiscordant heterosexual couples (Kenya, Uganda)	TDF QD (n=1,584) FTC/TDF QD (n=1,579) Placebo (n=1,584)	Women: 71%; Men: 63% Women: 66%; Men: 84%
TDF2	Heterosexual males and females (Botswana)	FTC/TDF QD (n=611) Placebo (n=608)	62%
FEM-PrEP	Women (Kenya, South Africa, Tanzania)	FTC/TDF QD (n=1,062) Placebo (n=1,058)	Study stopped due to lack of efficacy

Abbreviations: FTC/TDF, emtricitabine/tenofovir; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; QD, once daily; TDF, tenofovir.

Formulary/Source: 38,39,40,41

in C_{max}. There was no significant effect on dolutegravir when combined with tenofovir, with only a slight increase in tenofovir exposure. There is no effect of dolutegravir on lopinavir/ritonavir or darunavir/ritonavir; however ,there was reduction in both AUC (22%) and C_{max} (11%) when coadministered with darunavir/ritonavir. Both boosted and unboosted atazanavir resulted in an increase in dolutegravir concentrations, with no effect on atazanavir itself. Etravirine significantly reduced dolutegravir concentrations (AUC 71%, C_{max} 52%), but was attenuated with the addition of darunavir/ritonavir.[24]

Recent phase 3 studies (Table 2, page 219) with dolutegravir showed that it was well tolerated and exhibited superiority over efavirenz/emtricitabine/tenofovir[26] and non-inferiority to raltegravir[27] in treatment-naive patients. Dolutegravir was also shown to be well tolerated in treatment experienced patients[28] and showed superiority when compared to raltegravir.[29]

MK-1439

This novel NNRTI was shown to be active given once daily in HIV-positive patients.[30] MK-1439 is metabolized by CYP3A4/5 and was shown to neither induce nor inhibit CYP3A metabolism. It has activity against the most prevalent NNRTI-resistant viruses,[31] and the elimination half-life of 10 to 16 hours in HIV-positive patients supports once daily dosing.[30]

Tenofovir alafenamide

Tenofovir alafenamide (TAF) is a novel oral bioavailable prodrug of tenofovir (TDV), which exhibits antiretroviral activity against reverse transcriptase.[32] The currently available agent tenofovir disoproxil (TDF, Viread®) is also a prodrug to TDV. Both agents are converted by different pathways to the active parent compound, TDV.[33] At much lower doses, TAF has been shown to

have superior efficacy compared to TDF 300 mg, with approximately 80% to 97% lower plasma TDV concentrations and higher intracellular concentrations.[32] TAF has been studied in combination with other agents (emtricitabine, elvitegravir, and cobicistat) as a single-tablet regimen[34] and in combination with emtricitabine, darunavir, and cobicistat.[35]

HIV PREVENTION AND EARLY DETECTION

Pre-exposure prophylaxis (PrEP)

In July 2012 the FDA approved once daily use of the combination of emtricitabine/tenofovir disoproxil (Truvada) for PrEP in sexually active adults at high risk for acquiring HIV.[36] It is the first drug to be approved for this indication. Patients need to be counseled that taking this medication does not replace safe sexual practices to avoid acquiring HIV.[37] A number of studies have been conducted to support the use of tenofovir in PrEP (Table 3, page 221). Studies were conducted internationally in both men who have sex with men (MSM) and heterosexual populations. HIV reduction rates with the use of tenofovir or emtricitabine/tenofovir compared to placebo ranged from 44% to 84%.[38–40] One study conducted in African women was stopped due to lack of efficacy likely due to low adherence rates.[41] Based on these trial results, the Centers for Disease Control and Prevention has published interim guidance for the use of PrEP for MSM and heterosexual populations.[42,43]

Home HIV testing

Although there are home HIV tests available for the public, OraQuick, approved in July 2012, is the first over-the-counter test for HIV designed for confidential in-home testing with results within 20 minutes. Through an oral swab of the upper and lower gums of the mouth, the test will detect the presence of HIV-1 and HIV-2 antibodies. Researchers compared the results of the OraQuick In-Home HIV Test with laboratory tests performed by a trained professional on 4,999 people. The laboratory results showed 96 people tested HIV-positive and 4,903 were HIV negative. In comparison, the test was 99.9% effective in reporting negative results with 1 false positive. Additionally, 91.7% of the HIV-positive participants were correctly identified with this test.[44]

As a positive test result indicates that the patient may have HIV, a consult and confirmatory test is needed with a healthcare professional. It may take antibodies up to 3 months to develop, so it is recommended that patients with a negative result repeat the test at least 3 months after the last 'risk' event.[45]

CONCLUSION

The many significant advances in the treatment of HIV that have occurred in the past few years have had a major impact on patient survival. Newly developed, highly active antiretroviral therapies and regimens allow for single-tablet, once-daily dosing or significantly reduce overall pill burden, which show promise for improving patient adherence to prescribed medication therapy. Strict adherence is vital for suppression of viral loads and to slow progression of disease and development of resistant virus. The availability of at-home testing may lead to an increase in the number of HIV diagnoses among the approximately 1 in 5 patients who are unaware of their infection status. Pre-exposure prophylaxis of uninfected sexual partners of HIV-positive patients has been shown to decrease transmission rates given medication therapy is strictly adhered to. Medications currently in development show promise in giving providers and patients more options to help maintain progression-free survival. It is difficult to predict advances in diagnosis and therapy that may occur over the coming decade—however, if the previous decade provides any insight, we can expect many significant and life-enhancing advances for our patients. ■

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Current trends in specialty drug utilization and management: Payer interventions in the shadow of a burgeoning pipeline

Kjel A. Johnson, PharmD, BCPS, FCCP, FAMCP

Abstract

The overall cost of medical benefits, provider-adminstered specialty drugs is roughly a quarter of a billion dollars per 1 million commercial lives, and the trend for the top 25 most costly drugs was 16%, a significant increase over last year's virtually flat trend. Payers are increasingly interested in developing management programs to improve quality and cost of care of these drugs. Improving drug mix to favor lower cost, but equally effective products, is accomplished through prior-authorization and reimbursement strategies. A year-over-year increase in average sales price-based reimbursement was seen this year, although this can be problematic if used as a straight percentage across all drugs as it encourages the selection of high-cost therapies. Copays are being used less while payers are using higher percentage coinsurances when compared to previous years. Payers now realize that the provider's office is the lowest cost distribution channel and are developing site-of-service programs for this distribution channel. Utilization management programs are now nearly ubiquitous, with a 22% increase in the portion of lives that are subjected to prior-authorization programs versus last year. The pipeline for these products is robust, and this is reflected in the increase in use of unspecified Healthcare Common Procedure Coding System codes seen recently. If the pipeline is any predictor of the future, the clinical and financial challenges surrounding these medical benefit injectable products will only continue to expand, as will payer management strategies. (*Formulary*. 2013; 48:224–228.)

Specialty pharmaceuticals are continuing to play an increasingly large role in managed care plan budgets and are certainly deserving of the increased payer attention they are receiving, according to a recent trend report.

The report, *Medical Pharmacy & Oncology Trend Report,* from ICORE Healthcare—a subsidiary of Magellan Pharmacy Solutions, looks specifically at the medical benefit, under which almost half of all specialty pharmaceutical costs are currently managed and paid.[1]

It showed that costs for the top 25 specialty medications increased by 16% compared to the previous year. In addition to increasing price and utilization, this significant increase in trend was likely due to the fact that none of these high-cost, top-25 specialty drugs lost patent protection. Quantitatively, the annual spend for these drugs, which includes key therapeutic classes such as oncology and rheumatology across all sites of service, was approximately $255 million per 1 million lives. And while a lack of specialty medications coming off patent is a driver of this recent trend, a robust pipeline of promising specialty agents is expected to continue the annual trend of ~15%.

COST DRIVERS

A number of cost drivers that contribute to the rising specialty drug spend have been identified within the managed care infrastructure. Among these cost drivers are drug mix, the degree of provider reimbursement, member benefit design, distribution channel, the extent of utilization management, and the degree of operational effectiveness in paying claims correctly. Because these drivers are inter-related and are often overlapping components of specialty trend, they each serve as targets for payer-led management interventions.

Drug Mix. In the recent past, the impact of drug mix on medical benefit specialty trend was improving because numerous unbranded or generic alternatives were available. Such opportunities for optimizing the use of lower-cost alternatives, while still real and valuable, have been complicated by unique, first-in-class therapies entering the market on an ongoing basis. Payer response to this phenomenon has been several-fold, with prior authorization (PA) and strategic reimbursement frequently used to drive favorable drug mix. For example, the number of plans reimbursing by a variable-fee schedule (ie, arranging a greater margin for providers on lower-cost alternatives) nearly doubled according to the report. And, more therapies are offering rebates or upfront discounts today than ever before, providing another incentive to optimize drug mix.

Reimbursement. Although reimbursement is a seemingly easy target for payer cost-management initiatives, managed care decision-makers are becoming savvier regarding the impact of narrowing providers' margins on the administration of specialty injectables paid under the medical benefit. By tightening reimbursement

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and making it unprofitable for physicians to administer specialty drugs in their offices, members are often directed to receive these services in facilities where costs are ultimately higher for all parties involved; in fact, they are often more than twice the cost of office-administered infusions. Furthermore, when members receive drug administration services in facilities other than their physicians' offices, it can fragment their care and create a potential for reduced quality. There was a year-over-year increase in plans using an average sales price (ASP)-based reimbursement logic, which tends to ensure that physicians receive an adequate margin on specialty drugs administered in their offices. We presume that this trend is reflective of an effort to keep drug administration services in the low-cost, high-quality physician's office setting through more favorable reimbursement for providers.

Benefit Design. In terms of benefit design, the report found an increase in the proportion of plans using coinsurance instead of copays for specialty drugs covered under the medical benefit. Coinsurance was more prevalent among larger health plans (≥500,000 lives), which employ it for more than half of their members versus approximately one-third for smaller health plans. Considering the high cost of these specialty medications—with an average claim cost of approximately $2,500—this trend represents payers' desire to increase cost contribution from the member. Furthermore, the percentage of drug cost for which the member is responsible via coinsurance has also risen, from an average of 20% in the previous report to the current average of 26%. Copays, although becoming less prevalent overall for specialty pharmaceuticals covered under the medical benefit, also increased from an average of $46 to an average of $75 in the most recent report. While these actions demonstrate payers' willingness to shift more financial responsibility to the patient, they must be ever mindful of the impact of cost-sharing on therapeutic adherence; studies demonstrate that annual out-of-pocket expenses exceeding $2,500 can have a distinctly adverse effect on compliance.[2]

In conjunction with the increased cost-sharing imposed on specialty medications, payers are demonstrating more willingness to manage the once-sacrosanct realm of oncology, and this increased willingness to manage extends beyond traditional UM practices.

For example, the most recent report indicated that the overwhelming majority of health plans (74%) today recognize palliative care programs as being critical for high-quality end-of-life care and for mitigating ineffective and often detrimental end-line therapy.

Distribution Channel. As described previously, the physician's office is the single most economical site of care for the administration of infusible specialty drugs. Recent findings from the report show that payers generally embrace this assertion, because the physician's office is the most common (~50%) distribution channel for specialty drugs covered under the medical benefit. Conversely, the hospital inpatient setting—widely recognized as one of the least economical settings for the administration of specialty injectables—was the least common (13%) distribution channel used for these drug administrations.

Looking specifically at chemotherapies infused in the physician's office, 60% of the volume is billed via a buy-and-bill process. Specialty pharmacies have also been challenged to serve as a distribution channel for the provider's office and currently provide approximately one-third of the chemotherapeutic drugs infused in this setting. However, specialty pharmacy acquisition costs for these drugs are 17% higher on a weighted average basis than in the physician's office, and approximately 20% of drugs shipped to a physician's office remain unused due to changes in dosing, duration of therapy, or insurance coverage.[3] When the drug is unused, the drug is still billed to the payer because it has been shipped by the specialty pharmacy and cannot be sent back. This leads to waste and unnecessary cost. As such, traditional provider buy-and-bill administration remains the most cost-effective channel, according to currently available data.

Despite these findings, one-third of respondents surveyed in the report state that they are seeing oncology practices in their service area being purchased by hospital systems. However, drugs infused in practices under these circumstances are no longer submitted as physician's office claims, which more than doubles the cost of these drugs for employers and payors. Furthermore, as health systems around the country proceed to purchase large provider practices, the viability of these arrangements from a legal standpoint has come into question. Thus, a shift in distribution channel, or site of service, is a looming threat to the cost structure of current and future infused drugs.

Utilization. In an effort to curb specialty drug costs and improve the quality of care, health plans increased their use of utilization management programs for provider-administered injectables from approximately 70% in our last report to 92% of covered lives in the most recent report. Again demonstrating payers' willingness to more aggressively manage cancer care, more than 4 out of 5 plans currently require PA on chemotherapies, presumably due to their high cost and potential for misuse. FDA indication and compendia listing remained as the most common criteria for this PA in the latest report. Other predominant forms of utilization management for cancer therapies include National Comprehensive Cancer Network (NCCN) guideline adherence, genetic tests prior to initial therapy, claims edits for appropriate diagnosis, and retrospective drug utilization review.[4]

Operational Costs. Operational inefficiencies account for a noteworthy portion of the cost of specialty pharmaceuticals, with billing errors alone contributing 3% to 5% of the cost of provider-administered infusions. As such, post-claim edits were conducted for the majority of covered lives (61%) in the report. Eighty-eight percent of the time, these edits were conducted via internal health plan staff, while only 12% of the time they were conducted by an outside vendor, indicating that additional recovery opportunity may be possible. Regardless of the administration, these post-claim edits are advisable as a means of mitigating billing errors, fraud, waste, and off-standard-of-care use.

PIPELINE IMPACT

Reiterating a previous concept, the introduction of innovative new therapies from the drug pipeline—for which no therapeutic equivalents exist—has impacted drug mix and has driven costs upward in the absence of lower-cost alternatives. These first-in-class agents for previously unaddressed conditions, such as melanoma, offer significant therapeutic promise but often also give payers no other recourse than to offer liberal coverage of the high-cost entries.

Because of this pipeline, a significant increase in the number of specialty products billed under unclassified Healthcare Common Procedure Coding System (HCPCS) codes (eg, J3490, J3590, J9999, etc) can be used as a surrogate marker of the number of pipeline therapies entering the market. The report found that 2.5% of specialty medications are currently billed under such "dump codes," an 8-fold increase over the previous year.

Moreover, in 2012, nearly 600 agents were being evaluated in phase 2 or 3 clinical trials for 10 leading cancer types. The tandem of non-small cell lung cancer and breast cancer alone accounted for 227 of these investigational therapies. Furthermore, these study agents represent only the cancer specialty drug pipeline, with hundreds more injectables in development across other therapeutic classes. Despite this abundance of potential new therapies, some believe relief to the specialty trend may come from biosimilars also in the pipeline. The near-term impact of the introduction of biosimilars on specialty drug trend is likely to be minimal, because many biosimilar manufacturers have deemed soon to be off-patent biologics to be unreplicable and modest biosimilar discounts are expected due to market dominance of the innovator products. In addition, FDA guidance for the approval of these agents is still in its fledgling stages, leading to uncertain impact of these biosimilars on the market.

CONSIDERATIONS ON MANAGING COSTS, IMPROVING QUALITY OF CARE

As outlined herein, numerous factors have contributed to the rapidly escalating trend and costs of specialty medications in recent years, centering upon the cost-drivers outlined above. Drug mix and specifically the introduction of new therapies from the pipeline continue to shape expenditures, with the research-laden chemotherapeutics accounting for more than one-third of the overall spend. In addition to the economic ramifications of these factors, certain components of the specialty drug dynamic may also adversely impact quality of care. One key cost driver among specialty drugs in particular, distribution channel or site of service, has significant implications on patient quality of care and experience. In addition to increasing costs for all stakeholders with the exception of hospitals, disrupting the continuity of care and introducing inconveniences that may impact therapeutic adherence may cause even greater issues in the long-term. Meanwhile, operational cost drivers, such as fraud, waste, and billing errors, simply constitute an avoidable and indisputable drain on financial resources.

Managed care decision-makers are faced with myriad different options to combat this trend in specialty spending, many of which also serve to improve quality of care. For example, a recent analysis demonstrated that 14% of oncologists were not conforming to NCCN guidelines in the treatment of their patients, leading to a divergence from evidence-based medicine and potentially resulting in ineffective therapy and undesirable and unnecessary adverse events.[5] In response to scenarios such as these, utilization management is virtually ubiquitous in managed care oncology, with 82% of plans using PA. Regardless of the specific approach, it is reasonable to assume that all of the aforementioned cost drivers should be addressed to some extent when developing a comprehensive, integrated approach to managing specialty drug costs. If the pipeline is any indication, the clinical and financial issues surrounding specialty pharmaceuticals will only continue to expand into the foreseeable future. In fact, our expectations are that these drug costs will eclipse traditional drug costs within the next several years. ■

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AREDS gets another look: Removing beta-carotene, adding lutein/zeaxanthin shows clear benefits

By Lynda Charters

Investigators had already determined that the Age-Related Eye Disease Study (AREDS) formulation slowed the progression to advanced age-related macular degeneration (AMD), with a 25% decrease in the likelihood of progression to advanced AMD compared with placebo.

Emily Y. Chew, MD, described those results for the AREDS Research Group at the annual meeting of the Association for Research in Vision and Ophthalmology in Seattle. She is the deputy director, Division of Epidemiology and Clinical Applications, and the deputy clinical director, at the National Eye Institute, National Institutes of Health, Bethesda, Md.

In the AREDS2, a multicenter, double-masked, randomized trial with a 2 × 2 factorial design, the primary analysis evaluated the treatment effects in patients randomly assigned to either daily placebo or addition of the omega-3 long-chain polyunsaturated fatty acids (1 g), docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA); 10 mg of lutein and 2 mg of zeaxanthin, or both to the original AREDS formulation (500 mg vitamin C, 400 international units of vitamin E, 15 mg beta-carotene, 80 mg of zinc, and 2 mg copper). Lutein and zeaxanthin, according to Dr Chew, are components of the macular pigment, which might be involved in the pathogenesis of AMD. DHA and EPA, also components of the retina, might be instrumental in controlling inflammation.

In the secondary analysis, investigators studied the effects of the AREDS formulation without beta-carotene and the AREDS formulation with low zinc (25 mg). Beta-carotene was identified in 2 randomized trials to cause lung cancer in smokers. The lower dose of zinc was evaluated because nutritional data suggested that the body absorbs only a lower amount of the mineral.

Dr Chew

STUDY RESULTS

The findings of the study were published online on May 5, 2013, by the *Journal of the American Medical Association (http://jama.jamanetwork.com/article.aspx?articleid=1684847)*. A total of 4,203 patients (median age, 74 years) were enrolled in AREDS and followed for almost 5 years.

The primary analysis, which included half of the study population, showed that none of the effects of 3 treatment groups compared with placebo had a significant effect in stopping progression to advanced AMD.

Dr Chew reported that a beneficial effect of lutein/zeaxanthin was identified when the entire study population was included, specifically, lutein/zeaxanthin decreased the risk of progression to advanced neovascular AMD by 10%; in the secondary analysis, patients who had the lowest dietary intake of lutein/zeaxanthin had a 26% decrease in the risk of disease progression.

Subgroup analysis showed additional benefits. The patients who took the AREDS formulation with lutein/zeaxanthin and no beta-carotene had a decrease in their risk of about 18% of developing advanced AMD over the course of study compared with those who took the AREDS formulation with beta-carotene and no lutein/zeaxanthin as well as a 22% decrease in progression to neovascular AMD, Dr Chew said.

Adding DHA and EPA to the AREDS formulation, using a lower dose of zinc, and eliminating beta-carotene from the formulation did not further reduce the risk of progression to advanced AMD. An important safety issue was the finding that patients who were randomly assigned beta-carotene had an increased incidence of lung cancer (P=0.04) and the majority of these were former smokers. Dr Chew noted the important implications that this finding has for treatment.

"The fact that 8% of the AREDS2 participants were smokers and about 50% were former smokers underscores the importance of this finding as a public health issue," she said. "Long-term use of AREDS supplements appears safe and protective against advanced AMD. While zinc is an important component of the AREDS formulation, based on evidence from AREDS2, it is unclear how much zinc is necessary. Omega-3 fatty acids and beta-carotene clearly do not reduce the risk of progression to advanced AMD. The substitution of beta-carotene by lutein may further improve the formulation."

In 2006, the National Eye Institute started the AREDS2 trials to determine if the original AREDS formulation could be taken a step further to refine its effects with the addition or subtraction of various supplements. While no increased benefit of the formulation was discerned during the primary analyses of comparison of three treatment groups with the placebo group, the secondary analyses of subpopulations of patients provided clinical guidelines for modifications of the AREDS supplements.

Dr Chew reported no financial interest in any aspect of this report. ■

Ms Charters is a freelance medical writer based in Framingham, Mass.

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Pipeline preview

Complete response

■ Tivozanib (Aveo) for the treatment of patients with advanced renal cell carcinoma (RCC). In the CRL, FDA stated that the post-study treatment data for tivozanib produced inconsistent progression-free survival and overall survival (OS) results, thus making the TIVO-1 results uninterpretable and inconclusive. FDA recommends that the company conduct an additional clinical study to support approval of tivozanib for the treatment of advanced RCC. In addition, FDA also stated that the proposed dissolution acceptance criterion was not supported by the provided dissolution data, and would need to be updated and resubmitted.

■ Testosterone undecanoate (AVEED, Endo Pharmaceuticals) injection, for men diagnosed with hypogonadism. The complete response letter did not include requests for the company to perform additional clinical studies. FDA outlined the steps necessary to support approval of the New Drug Application and updated the requirement for a Risk Evaluation and Mitigation Strategy (REMS). Specifically, FDA has requested that the REMS include a Medication Guide as well as Elements to Assure Safe Use (ETASU) to mitigate the risks and severe complications related to post-injection reactions. Endo plans to submit a complete response by the end of the third quarter of 2013.

Priority review

■ Metreleptin (AstraZeneca and Bristol-Myers Squibb) for the treatment of metabolic disorders associated with inherited or acquired lipodystrophy.

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New molecular entity

Diclegis

Doxylamine succinate and pyridoxine hydrochloride

DUCHESNAY

Delayed-release formulation combining 10 mg of antihistamine doxylamine succinate and 10 mg of the vitamin B6 analog pyridoxine hydrochloride for women who have not adequately responded to conservative management of nausea and vomiting during pregnancy

In April 2013, FDA approved doxylamine succinate 10 mg, pyridoxine hydrochloride 10 mg (Diclegis, Duchesnay) for the treatment of nausea and vomiting in pregnant women who do not respond to conservative management. Diclegis is a delayed-release formulation combining 10 mg of the antihistamine doxylamine succinate and 10 mg of the vitamin B6 analog pyridoxine hydrochloride. This combination was once marketed in the United States as Bendectin. However, legal suits claiming related birth defects forced the manufacturer to withdraw Bendectin from the market in the 1980s. Doxylamine/pyridoxine has not been studied in women with hyperemesis gravidarum.

■ Doxylamine/pyridoxine is recognized as a pregnancy Category A drug.

Efficacy. A randomized trial with 261 pregnant women compared doxylamine/pyridoxine to placebo for 14 days. The mean gestational age was 9.3 weeks (range 7 to 14 weeks). Sixty percent of women were taking 4 tablets daily and the remaining 40% were similarly split between 2 and 3 tablets daily. The Pregnancy Unique-Quantification of Emesis (PUQE) score was used to quantify efficacy, and the change in score from baseline to day 15 was evaluated. The PUQE score encompasses information about daily vomiting episodes and feelings of nausea. There was a significant difference in the change of PUQE score from baseline in the Diclegis group compared to placebo [-0.7 (-1.2 to -0.2)].

Safety. The same randomized trial described above evaluated the safety of doxylamine/pyridoxine. Somnolence was found to be the only adverse event occurring in greater than 5% of participants and of a higher incidence than in the participants receiving placebo. Other adverse events described in the prescribing information include falls or other accidents that can result from the concurrent use of doxylamine/pyridoxine with other central nervous system depressants. Given the risk of somnolence, women should avoid activities such as driving or operation of heavy machinery until medically cleared. Women should also be advised to avoid other depressants of the central nervous system such as alcohol, other antihistamines, narcotics, or sleep aids as these medications may worsen somnolence.

Two meta-analyses based on observational studies from 1963 to 1991 concluded that there was no increased risk of fetal malformation from exposure to doxylamine succinate and pyridoxine hydrochloride in the first trimester.

The voluntary reporting of post-marketing use of 10 mg of doxylamine plus 10 mg of pyridoxine has provided additional possible side effects that may be related to the drug. The following are listed in the package insert: Dyspnea, palpitation, tachycardia, vertigo, vision blurred, visual disturbances, abdominal distension, abdominal pain, constipation, diarrhea, chest discomfort, fatigue, irritability, malaise, hypersensitivity, dizziness, headache, migraines, paresthesia, psychomotor hyperactivity, anxiety, disorientation, insomnia, nightmares, dysuria, urinary retention, hyperhidrosis, pruritus, rash, and maculo-papular rash. Doxylamine/pyridoxine is contraindicated with monoamine oxidase inhibitors since they can prolong the anticholinergic effects of antihistamines. Avoidance of other sedatives is also recommended.

Dosing. Doxylamine/pyridoxine is recognized as a pregnancy Category A drug. The recommended initial dose of doxylamine/pyridoxine is 2 tablets at bedtime on an empty stomach with a glass of water, taken daily and not on an as needed basis. If after 2 nights symptoms are not adequately controlled, the dose may be increased to 1 tablet in the morning and 2 tablets at bedtime. If on the next day

Pipeline from page 230

- Sofosbuvir (Gilead Sciences), a once-daily oral nucleotide analogue inhibitor for the treatment of chronic hepatitis C virus (HCV) infection.
- Miltefosine (Impavido, Paladin Labs) for the treatment of leishmaniasis, one of the diseases targeted by FDA for innovation and development of new therapies through its tropical disease priority review voucher program.

Orphan drug designations

- SL-401 (Stemline Therapeutics) for the treatment of blastic plasmacytoid dendritic cell neoplasm (BPDCN), a rare and aggressive hematologic malignancy for which there is no effective treatment.
- RV001 (River Vision Development), a human monoclonal antibody teprotumumab, for the treatment of active phase Graves Orbitopathy (GO), also known as thyroid eye disease.

symptoms are still inadequately controlled, the dose can be increased to 1 tablet in the morning, 1 tablet mid-morning, and 2 tablets at bedtime. The maximum recommended dose is 4 tablets daily. It is important to take doxylamine/pyridoxine on an empty stomach due to delayed and reduced absorption. Given the delayed-release formulation these tablets should not be crushed, chewed, or split. There are currently no dose recommendations in patients with renal or hepatic dysfunction as no studies have been conducted in these populations. ■

■ There are currently no dose recommendations in patients with renal or hepatic dysfunction.

The column is researched and compiled by **Diana M. Sobieraj**, *PharmD, assistant professor of Pharmacy Practice, University of Connecticut School of Pharmacy, Storrs, Conn.*

FDA actions *in brief*

Telavancin (**Vibativ**, Theravance) was approved for the treatment of adult patients with hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible isolates of *Staphylococcus aureus* when alternative treatments are not suitable.

A test that identifies the genotype of hepatitis C virus (HCV) that a patient is carrying (**The Abbott RealTime HCV Genotype II**, Abbott Molecular) was approved. The test can differentiate genotypes 1, 1a, 1b, 2, 3, 4, and 5, using a sample of an infected patient's blood plasma or serum, will aid healthcare professionals in determining the appropriate approach to treatment.

Denosumab (**Xgeva**, Amgen) was approved for the treatment of adults and some adolescents with giant cell tumor of the bone (GCTB), a rare and usually noncancerous tumor.

The use of levonorgestrel (**Plan B One-Step**, Teva Women's Health) was approved as a nonprescription product for all women of child-bearing potential. This action complies with the April 5, 2013, order of the United States District Court in New York to make levonorgestrel-containing emergency contraceptives available as an over-the-counter product without age or point of-sale restrictions.

Fluzone Quadrivalent vaccine (Sanofi Pasteur) supplemental biologics license application (sBLA) was approved. Fluzone Quadrivalent vaccine is the first and only 4-strain influenza vaccine option for patients as young as 6 months of age, as well as adolescents and adults.

A Supplemental New Drug Application for micafungin sodium (**Mycamine**, Astellas Pharma) for injection by intravenous infusion was approved for the treatment of pediatric patients aged 4 months and older with candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses, esophageal candidiasis, and prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplants.

New indication for lenalidomide (**Revlimid**, Celgene) was approved for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after 2 prior therapies, one of which included bortezomib.

Dabrafenib (**Tafinlar**, GlaxoSmithKline) and trametinib (**Mekinist**, GlaxoSmithKline) were approved for patients with advanced (metastatic) or unresectable melanoma. In addition, FDA also approved Tafinlar and Mekinist with a genetic test (THxID-BRAF, bioMérieux S.A) that will help determine if a patient's melanoma cells have the V600E or V600K mutation in the BRAF gene.

Neostigmine methylsulfate (**Bloxiverz**, Flamel Technologies) was approved for the reversal of the effects of non-depolarizing neuromuscular blocking agents after surgery.

Underdosing in obesity—an epidemic: Focus on antibiotics

By Katie S. Buehler, PharmD, BCPS and Abigail M. Yancey, PharmD, BCPS

Abstract

Obesity is associated with an increased risk of infection. Unfortunately clinical trials examining the safety and efficacy of antibiotics in obese patients are deficient. Thus, clinicians predominately rely on pharmacokinetic and pharmacodynamic data for appropriate antibiotic dosing. The current literature for vancomycin, aminoglycosides, beta-lactams, fluoroquinolones, linezolid, and macrolides was reviewed to evaluate appropriate dosing in obese patients. Due to the limited number of studies and various pharmacokinetic parameters of antibiotics, dosing should be based on both patient- and drug-specific factors. (*Formulary.* 2013;48:232–235.)

Obesity is a growing problem in the United States. Currently, 68% of adult Americans are overweight (body mass index [BMI] >25 kg/m^2).[1] Of those, 35% are obese (BMI >30 kg/m^2) and 6% are morbidly obese (BMI >40 kg/m^2) (Table 1, page 233).[1-4] Between 2000 and 2005, the prevalence of a BMI >30 kg/m^2 increased by 24%, BMI >40 kg/m^2 increased by 52%, and BMI >50 kg/m^2 increased by 75%.[3] It is estimated that by 2030, 51% of the population will be obese and 11% will be morbidly obese.[1] Obese patients have an increased risk of infection and a higher mortality rate.[5] We are often confronted with dosing antibiotic agents in obese patients. Unfortunately, trials focusing on optimal dosing in obese patients are scarce. Underdosing antibiotics may increase the risk of treatment failure, unnecessary escalation to broader-spectrum antibiotics, resistance, and possibly death.[5]

Pharmacokinetic studies show that the volume of distribution (V_D) of lipophilic drugs and the clearance of hydrophilic drugs can be increased in obese patients. Water-soluble drugs may distribute to extracellular fluid in adipose tissue, slightly increasing the V_D; however, this difference may not be significant.[4] Hydrophilic medications that are renally eliminated have increased clearance in obese patients.[6] Based on these kinetic findings, it can be difficult to ensure adequate drug concentrations or time above minimum inhibitory concentrations (MIC) in obese patients.

DOSING ANTIBIOTICS

Vancomycin

The Infectious Disease Society of America (IDSA) recommends a dosage of vancomycin of 15 to 20 mg/kg every 8 to 12 hours for most patients with normal renal function.[7] Two institutions compared weight-based dosing regimens and found that obese patients received the IDSA recommended dose in less than 1%, compared with 46% of normal-weight patients.[8] Two additional studies found a shorter half-life and increased clearance in obese patients compared to nonobese patients, with a direct correlation between total body weight (TBW) and both clearance and V_D. These pharmacokinetic changes result in higher cumulative daily doses.[9,10] One institution noted supratherapeutic concentrations in obese patients who were given 15 mg/kg every 8 to 12 hours. The protocol was amended to 10 mg/kg every 12 hours or 15 mg/kg every 24 hours with no dose capping. The revised protocol had significantly higher therapeutic vancomycin troughs (59% versus 35%) and decreased supratherapeutic troughs (18% versus 55%). However, there were increased subtherapeutic troughs (23% versus 9%). Rates of nephrotoxicity were similar in both groups.[11] Based on the high number of subtherapeutic troughs when using ideal body weight (IBW), TBW should be used to determine the appropriate dosage, with an interval based on the patient's renal function; however, initial dose capping may be appropriate. With limited antibiotics to treat methicillin-resistant *Staphylococcus aureus* infections, it is imperative to maintain adequate trough concentrations to prevent the emergence of vancomycin-resistant organisms.[7]

Aminoglycosides

Standardized approaches to weight-based aminoglycoside dosing have been derived from pharmacokinetic trials. Using TBW accepts that drug-specific pharmacokinetic parameters increase in proportion to body size; unfortunately, this tends to overshoot desired therapeutic concentrations and increases the risk for toxicities.[12–14] Using IBW relies solely on a patient's gender and height and tends to underdose and increase risk for treatment failure.[13] Utilizing protocols that emphasize dosing based on the patient's adjusted body weight (IBW + 0.4 [TBW – IBW]), with a frequency based on the patient's renal function and adjusting regimens based on peaks and troughs for conventional dosing and midinterval for extended-interval dosing, may be useful in practice.[12]

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Beta-lactams

Beta-lactam antibiotics are hydrophilic and do not distribute well into adipose tissue. These antibiotics are time-dependent, and underdosing might yield concentrations below the MIC resulting in antibiotic failure.[15] One study of preoperative cefazolin found a positive correlation with TBW and V_D, but no correlation with clearance.[16] A 2 g dose of cefazolin in morbidly obese patients achieved similar adipose and serum concentrations as did a 1 g dose in nonobese patients. In morbidly obese patients, the 2 g dose resulted in a significant decrease in postoperative infections compared to the 1 g dose (10.9%).[17] A study examining cefepime in obese patients found that 2 g must be given every 8 hours to ensure that the percentage of time greater than the MIC (%t>MIC) is at least 60%. Signs of toxicity were not observed.[18]

A case report evaluated piperacillin-tazobactam 3.375 g every 4 hours for treatment of a *Pseudomonas aeruginosa* wound infection in a morbidly obese patient. Serum concentrations were below normal nonobese concentrations for greater than 50% of

Table 1

Weight classifications based on BMI

Body Mass Index (kg/m^2)	Classification
<18.5	Underweight
18.5–24.9	Normal weight
25–29.9	Overweight
30–34.9	Obese class I
35–39.9	Obese class II
>40–49.9 >50	Obese class III Morbid obesity Super obesity

Formulary/Source:Refs 1–4

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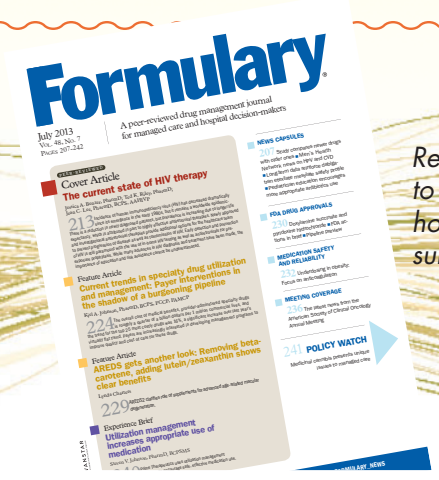

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the dosing interval, and an increased V_D was observed. Based on MICs of 2, 4, 8, 16, 32, 64, and 128 mg/L, %t>MIC were 100%, 100%, 90.9%, 55.4%, 19.88%, 0%, and 0%, respectively.[19] Another case report in which 4 g was used every 6 hours reported an increased V_D and clearance; however, a desirable %t>MIC of 60% was obtained.[20]

One institution implemented therapeutic drug monitoring and found that cefepime 2 g and piperacillin-tazobactam 4 g obtained similar proportion of therapeutic concentrations in critically ill obese and nonobese patients. In patients not receiving continual renal replacement therapy, more obese patients receiving meropenem 1 g had subtherapeutic concentrations compared to nonobese patients (35% versus 0%).[21]

A 1 g dose of ertapenem yielded a higher area under the curve (AUC) in normal-weight patients compared to obese and morbidly obese patients. A nonsignificant decrease in clearance with an increased BMI was seen, suggesting a modest decrease in drug exposure in obese and morbidly obese patients.[22] A post-hoc analysis found no difference in cure rates between obese and nonobese patients treated with ertapenem for a complicated intra-abdominal infection.[23] However, another post-hoc analysis found an increased incidence of surgical-site infection in patients with a BMI ≥30 kg/m^2 compared with those with BMI <30 kg/m^2 (26.7% vs. 12.7%, respectively) after elective colorectal surgery.[24]

Extended or continuous infusions of piperacillin-tazobactam and carbapenems are associated with a lower mortality rate. These regimens have been shown to increase the %t>MIC and the probability of target trough attainment. However, these dosing strategies have not been studied in the obese patient population.[19,25,26] Inconsistent and limited results in therapeutic outcomes suggest that clinicians should consider dosing beta-lactams within the upper limit of normal for obese patients, with the most amount of evidence supporting cefazolin 2 g, cefepime 2 g, and piperacillin-tazobactam 4 g, (4.5 g available in the US) with an interval adjusted for renal function.[16–21,27]

Fluoroquinolones

There are no specific recommendations for dosing fluoroquinolones in obese patients. A statistically significant decrease was noted in maximum plasma concentrations (C_{max}) and AUC in obese patients compared to nonobese patients when administered 400 mg intravenous ciprofloxacin.[28] Drug clearance and V_D were significantly increased; however, no difference was noted in the half-life. Ciprofloxacin distributes less to adipose tissue than other tissues, but partial distribution does occur. When dosing ciprofloxacin based on TBW, one study found higher C_{max} and AUC in obese patients; however, interstitial-space fluid of skeletal muscle and subcutaneous adipose tissue C_{max} and AUC were not significantly greater. Therefore, due to impaired skeletal muscle and adipose tissue penetration, increased dosages of ciprofloxacin may be required in order to appropriately treat some systemic infections.[29] In a case report on a 226-kg patient who received ciprofloxacin 800 mg intravenously every 12 hours, therapeutic serum concentrations were obtained at the given dose.[30] A study that assessed the pharmacokinetics of moxifloxacin in morbidly obese patients noted that the V_D and clearance were not significantly altered.[31] Similar results have been reported with levofloxacin. One case study reported that when a morbidly obese patient was administered a TBW-adjusted levofloxacin dose of 4 mg/kg every 12 hours (750 mg every 12 hours), the C_{max} and clearance were the same as in nonobese patients receiving 750 mg every 24 hours but the AUC was double.[32] Another study compared an intravenous dose of levofloxacin 750 mg in hospitalized and healthy ambulatory care obese patients (BMI >35 mg/m^2). Peak concentrations and V_D were similar to what has been reported in normal-weight patients. Overall, the half-life and AUC were similar to nonobese patients; however, the AUC was significantly lower and the clearance was significantly faster in the healthy patients than in the hospitalized patients, demonstrating potential variability in pharmacokinetics in acute illness.[33] Based on available data, ciprofloxacin may be the only fluoroquinolone affected by obesity, and doses up to 800 mg should be considered in order to achieve adequate tissue penetration.

Linezolid

Multiple small studies have examined linezolid use in obese patients. Although there appears to be a decrease in serum concentrations and increased clearance compared to nonobese patients, this does not appear to affect the efficacy of the drug. Based on the available data, it would be appropriate to continue using traditional 600 mg twice daily dosing in obese patients.[34,35]

Macrolides

Data for macrolides are severely lacking. Erythromycin base was found to have similar peak concentration in obese and nonobese patients.[15] In patients being treated for *Helicobacter pylori* with triple therapy including clarithromycin, patients with a BMI >25 kg/m^2 had lower rates of eradication compared to normal-BMI patients (55% vs. 85.4%).[36] Another study found improved efficacy rates for eradication in obese patients with 14 days of clarithromycin-based triple therapy compared to 7 days (80% versus 67%).[37] Based on these data, it would be feasible to increase the dosage or duration of macrolide treatment.

The IDSA recommends implementing an antimicrobial stewardship program (ASP) as one of the most effective approaches to improving antimicrobial use. Dose optimization based on patient characteristics and pharmacokinetic

and pharmacodynamic properties of antibiotics is one strategy that is recommended. Additional key aspects of an ASP that may help prevent underdosing of antibiotics include education, evidence-based institutional guidelines, and antimicrobial order forms.[38] Some institutions have adopted antibiotic dosing guidelines for obese patients; unfortunately, adherence rates were extremely low for the targeted antibiotics (1.2% to 8%). The authors concluded that additional education is required to improve adherence rates.[39]

Dosing based on TBW assumes that pharmacokinetic parameters increase in proportion to body size, whereas fixed dosing does not.[14] Most of the recommendations for dosing antibiotics are derived from small pharmacokinetic studies or case reports with limited supporting safety data. There is a lack of published data comparing the different grades of obesity and the appropriate dosages to achieve therapeutic concentrations. Because of this, dosing in obesity should be drug specific. Efforts must be made to ensure appropriate prescribing of antibiotics that have increased dosing requirements in obese patients to improve patient outcomes and prevent the emergence of antibiotic resistance. ■

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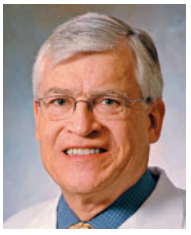
FROM THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY ANNUAL MEETING 2013

Four-year update shows nilotinib induces significantly deeper molecular responses than imatinib

by Mark L. Fuerst


Dr Larson

The 4-year data from the landmark ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials – Newly Diagnosed Patients) trial continues to demonstrate the improved clinical benefit of front-line nilotinib (Tasigna) versus imatinib (Gleevec) in patients with newly diagnosed, Philadelphia chromosome-positive chronic myeloid leukemia (CML) in chronic phase.

"Front-line nilotinib compared with imatinib affords a higher proportion of patients the opportunity to achieve deep molecular responses, a key eligibility criterion for participation in studies of treatment-free remission," said lead author Richard A. Larson, MD, of the University of Chicago, at the American Society of Clinical Oncology annual meeting in Chicago.

> "Nilotinib provided greater protection from progression to advanced phase and induced more rapid, deeper molecular responses. Treatment-emergent mutations were less frequent on nilotinib."

STUDY

ENESTnd is a phase 3 randomized, open-label, multicenter trial comparing the efficacy and safety of the 2 tyrosine kinase inhibitors. The study enrolled 846 CML patients, who were randomly assigned to receive nilotinib 300 mg twice daily (282 patients), nilotinib 400 mg twice daily (281 patients), or imatinib 400 mg once daily (283 patients).

The primary end point was major molecular response (MMR) at 12 months. Patients in the imatinib arm who had suboptimal response or treatment failure were allowed to escalate dose and/or switch to nilotinib in a separate extension study.

AN UPDATE OF DATA

An update of data from years 3 to 4 of the study found significantly higher rates of molecular response and deep molecular responses were achieved in the nilotinib versus the imatinib arms. "The difference in the rates of deep molecular response continued to be significantly higher for nilotinib, with the difference in favor of nilotinib increasing from year 1 to year 4," said Dr Larson.

Among patients who achieved MMR, more patients achieved deep molecular responses on the nilotinib 300-mg arm (76%) and nilotinib 400-mg arm (73%) compared with the imatinib arm (56%) ($P<.0001$ for both nilotinib arms versus imatinib). No patient in any arm progressed after achieving deep molecular response.

Significantly fewer patients progressed to accelerated phase/blast crisis on nilotinib versus imatinib, he said. No new progressions (excluding clonal evolution) occurred between years 3 and 4. All progressions on core treatment occurred before the 2-year data cutoff. Including clonal evolution, 3 (1.1%), 5 (1.8%), and 17 (6.0%) progressions occurred on core treatment in the nilotinib 300 mg, nilotinib 400 mg, and imatinib arms, respectively ($P=.0009$ and .0085 for nilotinib 300-mg arm and nilotinib 400-mg arm versus imatinib, respectively).

Between years 3 and 4 of the study, in the nilotinib 300-mg arm there was 1 new case of clonal evolution on core treatment and 2 patients had newly emergent BCR-ABL mutations, and 1 patient on imatinib had a new BCR-ABL mutation.

"Nilotinib displayed good tolerability, with a safety profile consistent with that of previous reports and no new safety signals observed," Dr Larson said, noting that few new patients experienced selected cardiac and vascular events on nilotinib (3 on the nilotinib 300-mg arm and 6 on nilotinib 400-mg arm) between years 3 and 4.

CONCLUSION

In conclusion, Dr Larson said "nilotinib provided greater protection from progression to advanced phase and induced more rapid, deeper molecular responses. Treatment-emergent mutations were less frequent on nilotinib."

Dr Larson is a consultant for Novartis Pharmaceuticals and has received research funding from Novartis Pharmaceuticals. Several of his co-authors are consultant/advisers for Novartis Pharmaceuticals, Bristol-Myers Squibb, Ariad, and Pfizer. ■

Mark L. Fuerst is a freelance health and medical writer based in Brooklyn, N.Y.

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FROM THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY ANNUAL MEETING 2013

Nilotinib leads to sustained responses in CML patients with residual disease on imatinib

by Mark L. Fuerst

For chronic myeloid leukemia (CML) patients with minimal residual disease on long-term imatinib (Gleevec) therapy, switching to nilotinib (Tasigna) can lead to deep, sustained responses.

The 2-year results from the ENESTcmr (Evaluating Nilotinib Efficacy and Safety in Clinical Trials – Complete Molecular Response) trial show that switching to nilotinib leads to deeper molecular responses in patients who still had evidence of residual disease after long-term therapy with imatinib.

"Significantly more patients achieved confirmed undetectable BCR-ABL in 2 consecutive assessments by 24 months [22.1%] with the switch to nilotinib versus those remaining on imatinib [8.7%]," said lead investigator Nelson Spector, MD, of Federal University of Rio de Janeiro, Rio de Janeiro, Brazil, at the American Society of Clinical Oncology annual meeting in Chicago.

> Deep molecular responses were more likely to be sustained in 3 consecutive assessments with nilotinib treatment (15.3% vs 9.7%).

DIFFERENCE DOUBLES

The difference between groups by 24 months has doubled since the 12-month analysis, Dr Spector said. Significantly more patients treated with nilotinib achieved the deepest molecular response or undetectable BCR-ABL compared to imatinib, regardless of the BCR-ABL transcript level at baseline. He noted that no patients achieving and maintaining the deepest molecular response have progressed to advanced stages of CML.

ENESTcmr is an open-label, randomized, prospective, multicenter phase 3 study of 207 patients who received either nilotinib 400 mg twice daily (104 patients) or standard-dose imatinib in 400 mg or 600 mg doses once daily (103 patients).

STUDY DESIGN

The study was designed to compare the kinetics of molecular response for patients with Philadelphia chromosome-positive CML in chronic phase who had achieved complete cytogenetic response, but were still BCR-ABL positive after at least 2 years of treatment with imatinib. The primary end point was the rate of confirmed best complete molecular response by 12 months of therapy with either tyrosine kinase inhibitor.

"The increase in the rate of confirmed undetectable BCR-ABL in 2 consecutive assessments was 3 times higher with nilotinib [9.6%] than with imatinib [2.9%] from month 12 to 24," said Dr Spector.

Significantly more patients in the nilotinib arm (42.9%) achieved the deepest molecular response than in the imatinib arm (20.8%), and the difference between the arms increased over time from 12 to 24 months.

"Improved responses with nilotinib were particularly notable in patients lacking major molecular response [MMR] at study start," he said.

Most patients remained on study at 24 months. At the time of discontinuation, 10 of 24 patients (41.7%) who discontinued from the nilotinib arm had a deep molecular response compared to none in the imatinib arm.

Most drug-related adverse events occurred in the first 12 months, Dr Spector said. Half of the events leading to discontinuation in the nilotinib arm were grade 1-2.

Dr Spector said nilotinib should be considered as a leading option for frontline therapy "because it allows many patients to achieve deeper, earlier responses that are associated with improved long-term outcomes."

DEEP MOLECULAR RESPONSES

He noted that deep molecular responses were also more likely to be sustained in 3 consecutive assessments with nilotinib treatment (15.3% vs 9.7%). Also, in patients highly selected for imatinib tolerance, "switching to nilotinib was associated with more adverse events than remaining on imatinib, although discontinuation rates decreased from 12 to 24 months," he said.

Dr Spector has received an honorarium from Novartis Pharmaceuticals. Several of his coauthors are consultant/advisers to Novartis Pharmaceuticals, Bristol-Myers Squibb, Pfizer, Teva, Ariad Pharmaceuticals, Roche, and CSL Limited. ■

FROM THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY ANNUAL MEETING 2013

Everolimus combination prolongs PFS in HER2-positive advanced breast cancer

by Mark L. Fuerst

The addition of everolimus, an mTOR inhibitor, to trastuzumab and vinorelbine in heavily pretreated advanced breast cancer patients led to a 22% reduction in the risk of disease progression in the first phase 3 study showing that inhibition of human epidermal growth factor receptor-2 positive (HER2+) receptor and mTOR provides significant benefit in HER2+ advanced breast cancer.

"Trastuzumab has markedly improved outcomes for patients with all stages of HER2+ breast cancer. However, in the metastatic setting, the majority of patients eventually develop resistance to trastuzumab," said lead author Ruth O'Regan, MD, professor and vice-chair for educational affairs, department of hematology and medical oncology at Emory University School of Medicine, at the American Society of Clinical Oncology annual meeting in Chicago.

In subgroup analyses, everolimus seemed to have greater effect on PFS among patients under aged 65 years, those with hormone receptor-negative cancers, and those who had received prior adjuvant or neoadjuvant trastuzumab.

PREVIOUS TRIAL

Previously, a phase 1b trial found a 10 mg dose of everolimus led to clinical activity, with an overall response rate (ORR) of 44% and clinical benefit rate (CBR) of 74%, with a median progression-free survival of 34 weeks. These data were confirmed in phase 2 trial. A phase 1b trial included a 5-mg dose of everolimus plus trastuzumab plus vinorelbine and found promising activity (CBR 50%).

BOLERO-3 (Breast cancer trials of OraLEveROlimus-3) is a phase 3, randomized, double-blind study of everolimus plus trastuzumab and vinorelbine conducted at 159 clinical trial sites globally. The trial included 569 women with HER2+ locally advanced or metastatic breast cancer who were previously treated with a taxane and were resistant to trastuzumab. Participants were randomly assigned to receive either everolimus 5 mg/day orally (284 patients) or placebo (285 patients), plus weekly vinorelbine 25 mg/m2 intravenously and weekly trastuzumab 2 mg/kg intravenously following a loading dose of 4 mg/kg. All patients had prior taxane therapy, and 27% of patients in each group had received prior lapatinib. The dose intensity of the everolimus arm was a little lower than the placebo arm, she said.

The study met its primary end point of improved PFS, Dr O'Regan said, with a median time to progression of 7.0 months in the everolimus combination arm and 5.8 months in the placebo combination arm. Overall survival data are not yet mature, and will be available next year.

Dr O'Regan noted that in subgroup analyses, everolimus seemed to have a greater effect on PFS among patients under aged 65 years, those with hormone receptor-negative cancers, and those who had received prior adjuvant or neoadjuvant trastuzumab. The overall response rate was not significantly different between the 2 groups.

ADVERSE EVENTS

Adverse events were consistent with the known safety profile of everolimus, she said, and were "quite manageable." The most common all-grade adverse reactions were neutropenia, stomatitis, anemia, leukopenia, fatigue, pyrexia, diarrhea, nausea, decreased appetite and constipation. The most common Grade 3-4 adverse reactions were neutropenia, leukopenia, anemia, stomatitis, fatigue, febrile neutropenia, diarrhea, pyrexia, nausea, hyperglycemia, and thrombocytopenia. The Global Health Status was not significantly different in the 2 arms. "The toxicity of everolimus did not affect quality of life," she said.

In conclusion, Dr O'Regan said "the addition of everolimus to trastuzumab and vinorelbine significantly prolongs PFS in patients with trastuzumab-resistant and taxane-pretreated HER2+ advanced breast cancer, resulting in a 22% decrease in risk of disease progression or death. The data support earlier clinical trials that inhibition of the mTOR pathway reverses resistance to trastuzumab, and shows the potential role of everolimus in treating these women."

She noted that 2 agents, pertuzumab and trastuzumab emtansine (T-DM1), have been approved for advanced breast cancer in the last 18 months. "This everolimus combination would be the third line after those agents in the metastatic setting," she said. "With more mature survival data, I hope it will become another treatment option for advanced breast cancer." ■

FROM THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY ANNUAL MEETING 2013

Octreotide LAR extends survival in low hepatic load neuroendocrine tumors

by Mark L. Fuerst

Octreotide LAR not only prolongs time to progression (TTP) but also appears to extend overall survival (OS) in a subgroup of patients with metastatic midgut neuroendocrine tumors (NETs) and a low hepatic load.

"A trend in longer survival in this subgroup is further indication to give octreotide LAR immediately upon diagnosis. The drug should be started as early as possible for these patients," said Rudolf Arnold, MD, professor of gastroenterology at Phillips University Marburg, in Marburg, Germany, at the American Society of Clinical Oncology (ASCO) annual meeting in Chicago.

> "...Newly diagnosed patients should immediately receive octreotide LAR. If there is a survival benefit, then a watch-and-wait strategy is not possible."

Previously, octreotide LAR had shown to lengthen significantly TTP in patients with metastatic midgut NET in the PROMID trial, a placebo-controlled, double blind, prospective, randomized study. The anti-proliferative response was more pronounced in patients with low (≤ 10%) hepatic tumor load, said Dr Arnold.

In that study, octreotide extended TTP to 27 months compared to 7.2 months with placebo. There was no difference in OS in either group. This follow-up study investigated whether this beneficial effect also affects OS.

THE NEW STUDY

The new study included 85 patients from the PROMID trial who were followed until January 2013 at least once a year for about 7 years. Between July 2001 and January 2008, the patients were randomly assigned to receive octreotide LAR (42 patients) or placebo (43 patients). Post-study treatment was left at the discretion of the local investigator. If patients progressed on placebo, they crossed over to octreotide LAR. Data on cause of death and on post-study treatment were documented.

Of the 85 patients, 19 died in the octreotide arm and 22 died in the placebo arm. Median OS was not reached in the treatment arm and was 84 months in the placebo arm (P=.59, HR=0.85). The cause of death was unrelated to the tumor disease in 8 patients. Of 64 patients in the low hepatic load subgroup (HL≤10%), 26 patients died (10 patients in the octreotide LAR arm, 16 patients in the placebo arm) and 15 of 21 patients in the high hepatic load subgroup (HL>10%) died (9 patients in the octreotide LAR arm, 6 patients in the placebo arm) (P=.002, HR=2.7).

In the low hepatic tumor load subgroup, median OS was not reached in the octreotide LAR group versus 80.5 months in the placebo group (P=.14, HR=0.56). In the high hepatic load subgroup, the median OS was 35 months in the octreotide LAR group versus 84 months in the placebo group (P=.14, HR=2.18). TTP was not prolonged in the high hepatic load subgroup, he said.

Dr Arnold noted that placebo patients were allowed to cross over to the treatment arm and that may have influenced the OS benefit. "If we wait longer, we might see a statistically significant difference in OS. In this interim analysis, we saw a trend in favor of longer survival. If patients survive longer, they should receive the active drug sooner," he said.

He added: "I believe that newly diagnosed patients should immediately receive octreotide LAR. If there is a survival benefit, then a watch-and-wait strategy is not possible." Dr Arnold noted that "everyone in the placebo group progressed within 30 months. There is no stabilization of disease. If they all progress, why not treat them immediately?"

There was also a difference between the 2 arms initially. The octreotide LAR arm had a longer time since diagnosis, which might indicate they had more indolent disease.

In conclusion, Dr Arnold said "almost all patients who were randomized at study entry in the placebo group received octreotide LAR after disease progression, but these patients experienced a less favorable OS than those in the low hepatic load subgroup."

ASCO discussant Abby Siegel, MD, medical director of Hepatobiliary Oncology at New York-Presbyterian Hospital/Columbia University Medical Center in New York, commented: "Octreotide LAR is still the standard of care for NETs. Interestingly, the OS of the placebo arm was about 7 years, with the median OS not yet reached in the treatment arm. This gives us a benchmark for our patients." ■

Utilization management programs may increase appropriate use of medication and quality of healthcare

Steven V. Johnson, PharmD, BCPS

Prime Therapeutics LLC (Prime) is headquartered in St. Paul, Minn., and manages pharmacy benefits for health plans, employers, and government programs including Medicare and Medicaid. The company processes claims and delivers medicine to more than 21 million members, offering clinical services for people with complex medical conditions. Prime is collectively owned by 13 Blue Cross and Blue Shield Plans, subsidiaries or affiliates of those plans.

BACKGROUND

Health insurers and payers are increasingly using utilization management (UM) programs to encourage safe and cost-effective medication use. Some utilization management programs use prior authorization (PA), a program that requires members to meet certain criteria before particular drugs are covered under the health plan.

Health insurers and payers are increasingly using these programs to help ensure patients receive the safest and most-effective treatment and to prevent prescribing that is improper or suboptimal for a specific health condition. In addition, PA programs often apply to certain high-cost drugs and/or drugs that have the potential for misuse, and this can help to reduce escalating healthcare costs. Before medications included in the PA program can be covered under a benefit plan, the physician will need to get approval through payers or insurers.

Dr Johnson

EXPERIENCE

Prime recently presented 2 studies at the Academy of Managed Care Pharmacy (AMCP)'s 25th Annual meeting & Expo in San Diego that conclude that utilization management programs may increase the quality of healthcare for patients taking specialty medications.

In the first study, Prime evaluated utilization patterns for natalizumab (Tysabri), a drug FDA approved for Crohn's disease and relapsing forms of multiple sclerosis (MS). Natalizumab exposes patients to the risk of developing progressive multifocal leukoencephalopathy, a rare viral disease that damages the brain and is often fatal. As a result, natalizumab is, in general, only prescribed when the patient has had an inadequate response to or is unable to tolerate an alternative MS therapy.

Prime looked at integrated medical and pharmacy claims among 8.1 million commercially insured members. All members using natalizumab had an MS diagnosis. Researchers found that during the 6-month analysis period, more than half (50.7%) of the patients starting on natalizumab had not tried an alternate MS medication. The percent of members with no alternate MS agent decreased to 39.0% and 26.3% for 24 and 60 months look back, respectively.

Given that 1 in 4 patients hadn't tried another MS treatment prior to natalizumab, Prime concluded that a PA program could be successful in better determining safe and appropriate treatment for patients with MS.

In a separate study, Prime researchers, in collaboration with Florida Blue, evaluated use of linezolid (Zyvox), an antibiotic that the Infectious Disease Society of America recommends should not be used as a first-line treatment for most infections. The society recommends linezolid be reserved to treat drug-resistant strains of enterococcus, staphylococcus, or streptococcus.

In the study, 1.2 million members were exposed to the PA and another 1.1 million members were not. The study found that after 30 days of follow up, the average per member overall costs of care were $4,189 lower for members exposed to the PA submitting a linezolid claim (P=.020). Members submitting a linezolid claim not exposed to the PA had a non-significant 2.8% lower hospitalization rate (P=.582), 3.9% higher ER visit rate (P=.467), and, on average, 1 additional office visit (P=.332) than those who were exposed to the PA program.

Researchers concluded that the linezolid PA program helped ensure appropriate use of the drug and did not negatively impacting patient outcomes. ■

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Medicinal cannabis presents unique issues in managed care

Arthur D. Hodge, Esq. | *Contributor*

Medicinal cannabis, despite its emerging popularity, presents unique issues to managed care and hospital decision-makers. Exactly how does a quasi-legal substance, which has existed outside the sphere of mainstream medicine, become integrated into a traditional hospital and managed care setting?

CULTURAL EMERGENCE OF MEDICAL CANNABIS

Suddenly, medical cannabis is pervasive in certain areas of the United States. While it is far outside the scope of this article, some background on recent developments is necessary to understand how the plant's medical components are used. There are different varieties of cannabis (popularly called "strains") that are developed by cannabis growers to feature various characteristics. Hybrid and new strains are constantly emerging, touted as helpful to a particular ailment by the grower.

Unfortunately, the recent explosion of medical cannabis has led to abuses by some growers who use pesticides or scent oils to improve appeal of their cannabis. If medical cannabis is to be responsibly administered in a hospital or managed care setting, attention must be made to the strain and potency and adjusted according to a patient's needs, and testing of cannabis for strength and mold/pesticides by third-party laboratories should be used to ensure safe and accurate dispensation.

As a quasi-legal substance, in addition to the variables presented in the strains, potency, and method of ingestion, medical cannabis remains an outsider when it comes to mainstream hospital and managed care. The common method of ingestion —smoking—is not tolerated inside a hospital. Thus, developments in the method of ingestion of medical cannabis appear, in my opinion, to be a prerequisite to mainstream use of medical cannabis in a hospital setting.

EMERGENCE OF MEDICAL CANNABIS

Many proclaim that cannabis will be legal for medicinal and recreational purposes in the reasonably near future. In states allowing medical cannabis, patients seek various strains of cannabis reported to be effective for a particular ailment. Cannabis concentrates, such as hash oil and wax, are used in "smoke-free" devices without flame, creating a "vapor" that is inhaled. Medical cannabis patients have their own particular strains that they choose and develop a preferred method of ingesting the medicine.

If a hospital or care facility allows use of medical cannabis, it is unclear at this time how the variety and dosage of medical cannabis is determined. In California, the physician prescribes cannabis use, and the patient is on his or her own to determine what strain to use, how to ingest the medicine, and where to obtain it. Suggestions to patients that lead to selection of a patient's preferred variety of medical cannabis are typically made by the dispensary staff, based upon the available varieties and reported experiences of other patients. Each strain of cannabis has distinct features (color, density, smell), and potency varies depending upon where the harvest was made on the plant (closer to top center "main cola" is typically stronger than lower branches on cannabis plants).

FEDERAL LAW

At this time, there is no question that the laws concerning medical cannabis are unsettled. Cannabis is illegal under federal law as a Schedule I controlled substance. Any person using cannabis for medical purposes is in violation of federal law. Many do not realize that there are ongoing federal prosecutions in California of dispensary operators and landowners, notwithstanding strict compliance with state law.

It was once thought that the federal government would avert its eyes from medical cannabis use in compliance with state laws—a notion propagated by memoranda from the Department of Justice. Property owners still risk forfeiture actions, and dispensary operators who are convicted are being sentenced to federal prison.

The viability of medical cannabis in mainstream medicine remains doubtful unless the federal approach is softened to permit use in compliance with state and local laws. The

Mr Hodge is a California civil litigation attorney whose 20-year practice includes representation of businesses, landowners, and individuals related to medical cannabis, including state/local compliance, land use and zoning, landlord/tenant issues, and property matters.

argument has been advanced that research into effectiveness of medical cannabis is hampered by the Schedule 1 classification of cannabis. Certain cities rely upon federal enforcement to assist their local agencies with property seizure and forfeiture, with a portion of the proceeds going back to the city. It would appear that the dichotomy between federal laws and the laws of states allowing use of cannabis are at odds and must be resolved before significant progress can be made toward sensible medical cannabis laws that do not place patients and caregivers at risk of federal prosecution.

STATE LAW

State laws vary widely, but, in recent years, many states have passed laws allowing medical use of cannabis under a physician's prescription. In my home jurisdiction, the California Supreme Court recently held that state medical cannabis laws do not override local county and cities from establishing their own ordinance schemes regulating use of medical cannabis within their municipalities (*City of Riverside v. Inland Empire Patients Health and Wellness Cente*r [May 6, 2013, S198638]). California state law provides immunity from certain state laws governing use of controlled substances if the qualified patient or caregiver has a prescription for use of medical cannabis from a licensed California physician. This does not guarantee that a patient will be able to obtain medical cannabis, or lawfully cultivate it, under local laws.

In August of 2008, California's Governor Edmund G. Brown (then Attorney General Brown) promulgated "*Guidelines for the Security and Non-Diversion of Marijuana Grown for Medical Use*." The guidelines were an attempt to ensure the security and non-diversion of cannabis grown for medical use. They also were designed to ensure that marijuana grown for medical purposes remains secure and does not find its way to non-patients or illicit markets, in addition to helping law enforcement agencies perform their duties effectively and help patients and primary caregivers understand how they may cultivate, transport, and use medical marijuana under California law. The 2008 guidelines also discuss establishment of cooperatives or collectives, operated in a non-profit manner, and procedures to follow to help ensure cannabis is not diverted to illicit markets. The 2008 guidelines have been reviewed and judicially ratified by several appellate courts.

LOCAL MUNICIPAL LAW

In California, there are several approaches taken by counties and cities concerning regulation of medical cannabis. It is important in California to recognize what ordinance framework a particular municipality has adopted. There are many cities and counties that have adopted a total ban of medical cannabis dispensaries. Each jurisdiction uses its inherent power to enact zoning and business regulation laws concerning the use of land and buildings.

TOTAL BAN APPROACH

In some jurisdictions, any storage or cultivation of any quantity of medical cannabis is deemed a nuisance under municipal law, subjecting the dispensary and property owner to a nuisance abatement action. I represented a medical cannabis collective based in the City of Agoura Hills, where the right of the city to enact a total ban of all cannabis use, including personal use and home cultivation, was upheld by the Second District of the Court of Appeal (*Conejo Wellness Center v. City of Agoura Hills* [2013] 214 Cal. App. 4th 1534).

In a "total ban" jurisdiction, use of cannabis at a hospital or managed care facility would subject the facility to closure via a nuisance abatement action.

PERSONAL USE ONLY APPROACH

Some jurisdictions allow individuals to possess, cultivate, and use medical cannabis in limited quantities provided that they cultivate it themselves. Many localities have tacitly adopted this framework even though the letter of their municipal law states all use of cannabis is forbidden. In these jurisdictions, it is not possible to lawfully dispense or obtain medical cannabis, and use of cannabis at a hospital or managed care facility would subject the facility to prosecution as a nuisance.

DISPENSARY/COLLECTIVE BAN APPROACH

Several California cities have banned medical marijuana dispensaries, but, by definition, a "medical marijuana dispensary" does not include a licensed clinic, healthcare facility, residential care facility for people with chronic life-threatening illness or the elderly, or a residential hospice. Within this framework of local laws, permission is given to certain licensed facilities to *provide* medical cannabis to patients. However, there is no clear provision as to where and how medical cannabis is *obtained* by patients and caregivers. In some of these jurisdictions, the city code is silent as to personal use of medical cannabis, presumably allowing it so long as it is otherwise lawfully obtained.

CONCLUSION

The emergence of medical cannabis as an alternative to mainstream medicine cannot be denied. Yet, a hospital or managed care facility may place itself at risk of legal prosecution, or possibly even federal intervention, for obtaining the medicine and administering or dispensing it to a patient. The inconsistent patchwork of state laws cannot succeed without cooperation from the federal government by way of a stand-down of prosecuting medical cannabis use by those abiding by state and local laws. ■

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