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

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Cover Article

Medication use in autism spectrum disorders: What is the evidence?

Jacintha S. Cauffield, PharmD, BCPS

161 Autism spectrum disorders (ASD) are complex neurodevelopmental disorders that involve significant social functional impairment and behavioral inflexibility. Autism is the most severe form of ASD and includes significant impairment in communication skills. Treatment of ASD is complex and involves a comprehensive educational interventional plan. Medications are used only as adjuncts, and only in cases in which maladaptive behaviors are severe or life-threatening, or to enable a patient to participate in their behavioral therapies. The most commonly used medications include second-generation antipsychotics (SGAs), selective serotonin reuptake inhibitors (SSRIs), and psychostimulants. Risperidone and aripiprazole are the only medications to carry an FDA indication to treat ASD-related symptoms. There is interest in using newer agents, such as atomoxetine, galantamine, rivastigmine, and memantine, to treat ASD-associated symptoms, but data are lacking to support their use.

Focus On

Ponatinib: An oral tyrosine kinase inhibitor for treatment of CML and Ph+ALL

Brett Feret, PharmD

169 Ponatinib is an oral tyrosine kinase inhibitor (TKI) that was approved by FDA on December 14, 2012, for the treatment of adult patients with chronic-phase, accelerated-phase, or blast-phase chronic myelogenous leukemia (CML) that is resistant or intolerant to previous TKI therapy, and for Philadelphia chromosome (Ph)–positive acute lymphoblastic leukemia (Ph+ALL). CML accounts for a little over 10% of adult leukemias. In 2013, an estimated 5,920 cases will be diagnosed in the United States. Many patients are now showing resistance to standard TKI therapy. A major mechanism of resistance is mutation of the BCR-ABL kinase domain. One of the most common mutations (up to 20% of patients) is the T315I substitution, which leads to resistance to all the current TKIs. Ponatinib has demonstrated significant cytogenic and hematologic responses in patients with either CML or Ph+ ALL, including those with the T315I mutation in both phase 1 and 2 clinical trials. Ponatinib is given orally once daily and has significant adverse effects, including boxed warnings for both hepatotoxicity and arterial thrombosis.

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Agents in late-stage development for the treatment of infectious diseases

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Dietary fiber lowers risk of first stroke

by Tracey Walker

Greater dietary fiber intake is significantly associated with lower risk of first stroke, according to a recent study published in *Stroke*.

Using data from 8 large studies conducted around the world, Diane Threapleton, PhD candidate, Nutritional Epidemiology Group, University of Leeds, United Kingdom, and colleagues, found that within the usual range of fiber intakes (from about 10 g to 30 g per day), the more fiber people had eaten, the lower their risk of stroke. For each increase of 7 grams per day, the risk of stroke was reduced by 7%.

"This study has looked at all the large studies which had reported on the links between the amount of dietary fiber people eat and whether they are then more or less likely to experience a stroke in later life," Threapleton told *Formulary*.


Threapleton

"We systematically reviewed any relevant studies published between 1990 and 2011 and statistically combined the information from these different studies using meta-analysis. All the studies we included had statistically adjusted for potential confounding factors such as smoking, age, and Body Mass Index," she said.

Take away

Greater dietary fiber intake is significantly associated with lower risk of first stroke.

IMPACT IS GREAT

"To our knowledge, this is the first time this analysis has been done," Threapleton continued. "[The 7% risk reduction] sounds like quite a small reduction in risk, but because stroke affects so many people, lowering risk by 7% could potentially impact many thousands of individuals."

> The 7% risk reduction sounds small, but because stroke affects so many people, this could impact thousands of individuals.

Physicians should be aware that on average, intake of dietary fiber in the United States is much lower than recommended goals—about half of what is advised, according to Threapleton.

"Reaching the fiber goal is likely to have all sorts of health benefits, and we think that reducing long-term stroke risk should be added to that list," she said.

The risk reduction the researchers saw related to an increase in fiber of 7 g per day. According to Threapleton, 7 grams of extra fiber per day is easily achievable by eating 1 serving of whole-grain breakfast cereal and 2 servings of fruit or vegetables, for example, or by eating 1 serving of whole grain bread and 1 serving of pulses (lentils/beans).

"Our study suggests that eating a diet with plenty of fiber-rich foods may assist in stroke prevention in the long term," Threapleton said.

"Wholesale changes to diet are often not necessary, and just replacing refined carbohydrates with the higher fiber, less refined versions as well as aiming for increased fruit and vegetable intakes will take the average patient a long way toward achieving the fiber goals," she continued. ■

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Don't offer glutamine, antioxidants to critically ill patients

Formulary staff


Dr Heyland

For critically ill adults with multiorgan failure, early supplementation with glutamine or antioxidants does not improve clinical outcomes, and glutamine may increase the mortality rate of this patient population, according to a study published in the April 18 issue of the *New England Journal of Medicine*.

Canadian researchers wanted to evaluate the use of early glutamine and antioxidant supplementation in critically ill patients to determine if it would positively affect 28-day mortality. In a large, double-blinded, multicentered randomized trial with intention-to-treat analysis, they randomly assigned more than 1,200 critically ill patients in 40 intensive care units (ICUs) in Canada, the United States, and Europe to receive supplements of glutamine, antioxidants, both, or placebo. Patients had multiorgan failure and were receiving mechanical ventilation. Supplementation, provided both intravenously and enterally, began within 24 hours of ICU admission. Primary outcome was 28-day mortality.

Study lead author Daren Heyland MD, MSc, scientific director, clinical evaluation research unit, Kingston General Hospital, Kingston, Ontario, Canada, and colleagues found that a higher percentage of patients who received glutamine died within the 28-day period (32.4% vs 27.2%; adjusted odds ratio [OR], 1.28; P=0.05). Also, mortality at 6 months was significantly higher among those patients who received glutamine than among those who didn't. The rates of organ failure and infectious complications were not affected by glutamine. Antioxidant supplementation did not affect 28-day mortality (30.8%, vs 28.8% with no antioxidants; adjusted OR, 1.09; 95% CI, 0.86–1.40; P=.48) or on the secondary end points of in-hospital mortality and mortality at 6 months. The groups did not differ with respect to serious adverse events (P=.83).

"The most important finding from the study is the glutamine supplementation in this patient population—critically ill patients with multiorgan failure—was harmful. In addition, antioxidant supplementation did not seem to be beneficial or harmful," Dr Heyland, told *Formulary*. "Glutamine supplementation should not be offered to such patients." ■

Care management programs key to managing complexities of hepatitis C medication adherence

by Mari Edlin

The standard of care for hepatitis C (HCV) was uprooted in 2011. Prevailing treatment involved a combination of 2 drugs—pegylated-interferon and anti-viral ribavirin—taken for 1 year. Two new protease inhibitors, boceprevir and telaprevir, joined the regimen.

While the multidrug combination reduces treatment timelines to 24 to 48 weeks, its complexity also hampers adherence.

Patients only take telaprevir for the first 12 weeks of treatment on a specific dosing schedule. An additional 12 or 36 weeks of peginterferon alfa and ribavirin is also required.

A clinical study from Weill Cornell Medical College known as ADVANCE, comparing patients on standard 2-drug therapy to those on a 12-week course with the triple combination therapy of protease inhibitors followed by standard care, found a sustained response of 44% versus 79%, respectively. In other words, telaprevir with peginterferon-ribavirin, as compared with peginterferon-ribavirin alone, was associated with better outcomes.

HCV patients typically have adherence issues with the prevailing therapy because of side effects, and the added complexity of self-management of multiple drugs exacerbates the problem. Patient lack of adherence with interferon is often attributed to depression, pain, fatigue, chronic pain, and flu-like side effects.

The inherent complexity of managing hepatitis C patients has rallied specialty pharmacies, many of which have developed care management programs targeting HCV.

Andrew Muir, MD, director of gastroenterology and hepatology research at Duke University School of Medicine, says one of the biggest challenges for HCV is the large number of people who do not know they are infected. And once the condition is detected, most don't know how long they have had it.

"Since liver damage is not always related to how long someone has had HCV," Dr Muir said, "there is an opportunity to develop a liver wellness strategy, not just related to drugs but also to care coordination and affordability."

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Table 1

FDA-approved combination therapy

Boceprevir + Pegylated Interferon + Ribavirin
Telaprevir+ Pegylated Interferon + Ribavirin
Pegasys + Copegus (peginterferon alfa-2a + ribavirin)
PegIntron + Rebetol (peginterferon alfa-2b + ribavirin)
Roferon A + Ribavirin (standard interferon alfa-2a + ribavirin)
Intron A + Rebetol (standard Interferon alfa-2b + ribavirin)
Infergen + Ribavirin (consensus Interferon + ribavirin)

*Formulary/*Source: www.hivandhepatitis.com

Paul Turner, MD, therapeutic strategy lead for Quintiles, a biopharmaceutical services company based in Durham, N.C., anticipates that the advent of new therapies and recommended testing by the Centers for Disease Control and Prevention (CDC) will raise awareness. Although HCV does not have strong awareness campaigns like HIV does, more Americans now die of HCV than HIV and AIDS.

Last year, the CDC recommended that everyone born during the years 1945 through 1965 receive a 1-time blood test for HCV to potentially uncover an estimated 800,000 undiagnosed cases of the disease. The CDC says that baby boomers are 5 times more likely than other adults to be infected.

Approximately 3.2 million Americans have chronic HCV virus infection, with an estimated 40,000 new infections per year, according to the World Health Organization. By 2029, total annual medical costs in the United States for people with the condition are expected to more than double, from $30 billion in 2009 to approximately $85 billion.

TRIPLE THERAPY

Express Scripts, a pharmacy benefits manager (PBM) headquartered in St. Louis, has adopted adherence initiatives for HCV. Mary Dorholt, vice president, clinical practice lead for specialty pharmacy, said the programs fit into a consumer-based, behavioral sciences approach to healthcare.

Patients might be prescribed telaprevir 3 times a day, 7 to 9 hours apart, always taken with food. A meal or snack containing about 20 grams of fat within 30 minutes before each dose is recommended. Treatment would include ribavirin twice a day and a weekly injection of interferon.

"We are helping patients to better understand how to manage side effects from therapy, such as scheduling doses so they won't interfere with a work schedule; partnering patients with someone who can support their therapy; anticipating when patients need drug refills; and solving member cost issues," Dorholt says.

Express Scripts' care management program targeting HCV provides specialty pharmacist support to patients, including a log to schedule blood tests that help regulate drug dosage and length of therapy. The results dictate how the PBM can facilitate ongoing treatment education and follow-up.

Patients also receive a treatment diary to document when they take medications, dosages, side effects and the medications they are taking to manage side effects.

In addition, a new video-based virtual coaching tool provides patients with information on how a protease inhibitor works to prevent the virus from reproducing, along with instructions on how to schedule doses, what types of food to take with medications and the time required in between doses.

The Express Scripts Drug Trend Report 2012 indicated that total drug trend for the HCV therapy at the end of 2011 was 194.8%, more than 10 times the total trend for any other specialty therapy class, with the average cost per prescription rising to $3,370.99 (up from $1,389.04 in 2010). The increase in utilization for drugs slowed during 2012, resulting in a total trend of 33.7%.

SELF-MANAGEMENT

"The triple therapy and its significant side effects make self-management difficult," said Sumit Dutta, MD, senior vice president and chief medical officer of Catamaran, a PBM based in Lisle, Ill.

Dr Dutta says that specialty pharmacy is an ideal model for not only managing the disease itself, but also associated conditions such as depression.

Catamaran pharmacists contact patients prior to shipment of medication to offer counseling. Educational materials on side effects are included in shipments. Patients also receive calls from nurses at least 2 times during the first month of therapy to discuss side effects and barriers to adherence and continue during the next 3 months as needed.

The PBM's systems document laboratory information, such as viral load levels and hemoglobin, to gauge treatment response and anemia.

Over a 6-month period, a comparison of 2 groups—program enrollees and those not enrolled—showed a 5% increase in the medication possession rate using the model.

HIGH-TOUCH PROGRAM

Walgreens Specialty Pharmacy maintained medication adherence rates of 93% to 95% when moving patients from

Interferon-free hepatitis C treatments

The industry is moving quickly toward transforming therapy once again by bringing interferon-free options to market for patients with genotypes 1, 2, and 3 hepatitis C. The therapy for type 1 is expected by 2015, the latter 2 for 2014. According to GBI Research, the market for interferon-free treatments could increase to $15 billion by 2015.

Gilead Sciences is one of the organizations developing an option to treat patients with genotypes 2 and 3 HCV. In early April, the company applied for FDA approval for its oral pill sofosbuvir taken in combination with ribavirin. Gilead said a late-stage trial testing of the drug showed no detectable virus level in 73% of study patients after 16 weeks of therapy.

Santaris Pharma A/S, a clinical-stage biopharmaceutical company, conducted a phase 2a trial for miravirsen, the first microRNA-targeted drug for genotype 1 to enter clinical trials. The results, reported in the online edition of the *New England Journal of Medicine* on March 27, 2013, indicate that 4 out of 9 patients treated at the highest dose of miravirsen (7 mg per kilogram of weight) became HCV RNA-undetectable with just 5 weekly doses and without any discontinuation related to adverse effects.

Paul Turner, MD, therapeutic strategy lead for Quintiles, a biopharmaceutical services company, attributes the current decrease in utilization of HCV medications to a trend in warehousing patients until new interferon-free therapies are available. They are expected to cause fewer side effects and can be taken for a shorter duration and fewer times a day.

Because HCV may take years to show any evidence of liver damage, Dr Turner said it might be safe for some patients to wait until the arrival of interferon-free solutions.

"It depends on clinical factors for each patient in terms of warehousing. If a simpler solution or more potent therapy becomes available in the near future, it may be beneficial to 'wait and see,'" said Glen Pietrandoni, senior manager for HIV/AIDS and HCV pharmacy services, Walgreens Specialty Pharmacy.

double therapy to the more complicated triple therapy regimen, said Rick Miller, director, clinical services for the pharmacy.

"Our ConnectedCare high-touch, clinical program for diseases requiring specialty pharmaceuticals, such as hepatitis C, focuses on ensuring that patients understand how and when to take their medications, assesses barriers to adherence, manages issues related to side effects and educates patients about therapy expectations," he said.

Walgreens also collects and reviews lab data to determine if a patient's response to therapy could lead to recommendations for discontinuing medications, Miller said.

Walgreens' program utilizes care management services via a call center but has supplemented triage by identifying 77 health system and retail locations closely associated with physicians to provide face-to-face intervention.

Walgreens Specialty Pharmacy sponsors national HCV screening days at its retail stores targeting those markets with a larger baby boomer population. ■

Actavis to sell generic reformulated OxyContin in 2014

Formulary staff

Actavis will be able to sell defined quantities of a generic version or an authorized generic version of reformulated OxyContin as early as next year, according to a prepared statement from Purdue Pharma L.P., the manufacturer of the opioid analgesic.

Purdue Pharma L.P. and Actavis Inc. have settled patent infringement lawsuits that included patents for its abuse-deterrent reformulated OxyContin (oxycodone HCl controlled-release) Tablets CII.

This announcement came 10 days after FDA's announcement that the Agency would not approve any generic versions of the original OxyContin formulation, as the benefits no longer outweigh the risks. FDA also approved updated labeling for reformulated OxyContin, indicating that the product has physical and chemical properties that are expected to make misuse and abuse via injection difficult and to reduce abuse via the intranasal route.

"Today's agreement [between Purdue and Actavis] will promote competition and allow for availability of generic formulations of reformulated OxyContin. At the same time, this resolution relieves us of the risks, distractions and costs of continued litigation. We are pleased that this matter has been resolved in a manner that respects the inventions we have incorporated into the reformulated OxyContin tablets," said John H. Stewart, president and CEO of Purdue.

Last month, FDA approved updated labeling for reformulated OxyContin tablets. The new labeling indicates that the product has physical and chemical properties that are expected to make misuse and abuse difficult.

"The recent FDA approval of the updated labeling . . . serves as a victory for both consumers and healthcare providers because increased incidences of overdoses and/or death attributed to OxyContin use was viewed by both sides as a public health concern that was quickly becoming an epidemic," said *Formulary* advisor Abimbola Farinde, PharmD, MS, clinical staff pharmacist, Clear Lake Regional Medical Center, in Webster, Texas. "By deterring potential abuse with the reformulated version of OxyContin, countless lives may be saved while at the same time promoting the appropriate use of this medication." ■

Researchers find small benefit from antibiotics for patients with respiratory infections

by Tracey Walker

Physicians would need to prescribe antibiotics to more than 12,000 patients diagnosed with common colds to prevent 1 hospital admission for pneumonia, according to a study published in the March/April issue of the *Annals of Family Medicine*.

"Common colds are extremely unlikely to progress to more serious bacterial infections," study lead author Sharon B. Meropol, MD, PhD, of Case Western Reserve University School of Medicine, Rainbow Babies and Children's Hospital, Cleveland, Ohio, told *Formulary*. "This should reassure doctors and patients that antibiotics are usually not needed or helpful.

> Avoiding unnecessary antibiotic use, slowing the development of resistance, and preserving antibiotics' effectiveness as long as possible are urgent public health issues.

"Doctors frequently prescribe antibiotics for nonspecific respiratory infections, or common colds, which are almost always caused by viruses," Dr Meropol continued. "Presumably they and/or their patients feel that antibiotics are likely to prevent progression to a serious bacterial illness. We wanted to further explore the real risks to enable more informed decision-making about antibiotic use in the future."

In addition, when an adverse event is reported after medication use, it is frequently blamed on the drug, but it might have occurred with or without the drug—by chance alone or by the patient's underlying medical condition, according to Dr Meropol.

"We wanted to get a better estimate of the true risks of antibiotic use, comparing similar groups of patients who were treated versus who were not treated with antibiotics," she said.

Using anonymous data from electronic medical records in the United Kingdom, Dr Meropol, assistant professor of pediatrics and epidemiology and biostatistics, and colleagues found a group of patients who were diagnosed with nonspecific respiratory tract infections—common colds—during a visit to their primary care doctors.

Approximately two thirds (65%) of the patients received antibiotic prescriptions and the rest did not. "For these patients, we checked for hospital admissions within 2 weeks after the visit, for pneumonia, and for certain severe reactions often attributed to drug side effects," said Dr Meropol. "We compared risks of hospital admission for these diagnoses between people who received antibiotics to risks of hospital admission for people who did not receive them."

The adjusted risk difference for treated versus untreated patients per 100,000 visits was 1.07 fewer adverse events and 8.16 fewer pneumonia hospitalizations within 15 days following the visit.

"Comparing similar patients exposed versus not exposed to antibiotics, we did not find a significant risk of severe side effects," Dr Meropol said. "We did find a risk of less severe side effects that did not result in hospital admission."

Bacteria that cause diseases are becoming increasingly resistant to antibiotics, faster than the development of effective drugs to treat infections. "The more we use antibiotics, the faster bacteria in our environment become resistant to them, and the less well they work," Dr Meropol said.

URGENT PUBLIC HEALTH ISSUE

In the United States, almost half of patients diagnosed with common colds are prescribed antibiotics—"this is more harmful than helpful as almost all common colds are caused by viruses that don't respond to antibiotic treatment," she said. "Avoiding unnecessary antibiotic use, slowing the development of resistance, and preserving antibiotics' effectiveness as long as possible are urgent public health issues. Results of this study will help guide decision-making about antibiotic prescribing, reassuring us that we can safely avoid using antibiotics where they are unlikely to be of benefit, especially for the common cold, and help us target them to where they will be the most effective."

Although any drug can cause side effects, reports of a side effect after drug use should be considered carefully to assess whether it was actually caused by the drug, or if there is a different explanation, according to Dr Meropol.

"While any drug can have risks, it is best to use caution when attributing an adverse health event to a drug side effect, if that event could have instead been caused by chance alone or the patient's underlying medical condition," she said. "Comparison with an unexposed control group can help elucidate true drug risks." ■

VIDEO

Watch **Dr Meropol** talk to *Formulary* about how bacteria is becoming increasingly resistant to antibiotics.

Visit bit.ly/YoW9Pi

PEER-REVIEWED

Medication use in autism spectrum disorders: What is the evidence?

Jacintha S. Cauffield, PharmD, BCPS

Abstract

Autism spectrum disorders (ASD) are complex neurodevelopmental disorders that involve significant social functional impairment and behavioral inflexibility. Autism is the most severe form of ASD and includes significant impairment in communication skills. Treatment of ASD is complex and involves a comprehensive educational interventional plan. Medications are used only as adjuncts, and only in cases in which maladaptive behaviors are severe or life-threatening, or to enable a patient to participate in their behavioral therapies. The most commonly used medications include second-generation antipsychotics (SGAs), selective serotonin reuptake inhibitors (SSRIs), and psychostimulants. Risperidone and aripiprazole are the only medications to carry an FDA indication to treat ASD-related symptoms. There is interest in using newer agents, such as atomoxetine, galantamine, rivastigmine, and memantine, to treat ASD-associated symptoms, but data are lacking to support their use. (*Formulary*. 2013; 48:161-168.)

Autism spectrum disorders (ASD) are neurodevelopmental conditions that develop in early childhood that involve both impairment in social function and behavioral inflexibility. The class encompasses 3 disorders: "classic" autism, Asperger's disorder, and pervasive developmental disorder not otherwise specified (PDD NOS). The latter is given to patients whose symptoms do not meet the criteria for either autism or Asperger's disorder. Patients who have an intelligence quotient ≥70 and who began speaking at the expected age are diagnosed with Asperger's disorder.[1] Autism is the most severe form of the 3 and involves substantial deficits in 3 areas: 1) social interaction, 2) communication skills (including delay in speech development), and 3) behavioral and cognitive inflexibility. Patients with autism are unable to use nonverbal cues such as eye-to-eye contact or gestures to communicate and cannot "connect" socially with others. About half are nonverbal or have grossly impaired speech. Behavioral inflexibility manifests as repetitive and restricted behavior, activities, or interests. The presence of repetitive, nonfunctional, and atypical behaviors is known as "stereotypy." Examples of these activities include perseveration, rocking, hand flapping, finger movements, or hair twirling.[1,2]

No single pathognomonic feature identifies ASD in children. Social deficits occur early, but are subtle and can be difficult to recognize. The most distinguishing feature appears to be delayed or absent joint attention, a phenomenon in normal children in which they show enjoyment in sharing an object or experience with another by looking back and forth between the two. Delay in speech development is considered a hallmark, because this is the symptom that parents first recognize as abnormal. This usually occurs at age 15 to 18 months, although treatment is not usually sought until several months later.[2]

Patients with autism have a high incidence of comorbid conditions. Approximately 70% have comorbid mental retardation, and a third will have at least 2 seizures by the time they reach late adolescence. Sleep disturbances and gastrointestinal symptoms are also common. Patients with autism are not usually capable of living independently.[1]

EPIDEMIOLOGY

The wide variation in symptoms in a child can make diagnosis difficult. ASD is more prevalent than once believed. According to the Centers for Disease Control and Prevention, 1 in 88 children carried an ASD diagnosis in 2008. This represents a 78% increase since 2002. This increase may be due in part to heightened public awareness of the condition and the resulting increase in diagnosis. More cases are being diagnosed at an earlier age (before aged 3 years), but most are not diagnosed under after aged 4 years. Within the spectrum, autism is diagnosed in 44% of cases, ASD/PDD NOD in 47%, and Asperger's in 9%. Of the 3 diagnoses, Asperger's has the longest delay in diagnosis (75 months vs. 48 months for autism). ASD is 5 times more common in boys than girls.[3]

ETIOLOGY

The exact etiology of autism is unknown. ASD has a high degree of heritability that is complex and involves multiple genes. The phenotypic

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manifestation of these genes is highly variable, complicating the search for a cause. Although the majority of ASD cases result from genetics, environmental triggers may contribute. Many of the brain abnormalities associated with ASD occur during the first and second trimesters of pregnancy. Environmental factors may play a role, including exposure to teratogens. Although attempts have been made to link ASD to postnatal exposures to the measles, mumps, and rubella (MMR) vaccine and mercury-containing vaccines, no association has ever been proved. The original study attempting to link MMR to autism published by Wakefield in *The Lancet* in 1998 has been discredited, and the majority of the authors who published the study with Wakefield retracted their findings. Numerous reports published since the original proposals have refuted the link of autism with either MMR or mercury-containing vaccines.[2,4]

SCREENING AND DIAGNOSIS

The Diagnostic and Statistical Manual of Mental Disorders IV Text Revision (DSM-IV-TR) contains diagnostic criteria for autism, Asperger's disorder, and PDD NOS. Multiple tools exist for screening, diagnosing, and assessing ASD. A commonly used tool to monitor outcomes in clinical trials is the Aberrant Behavior Checklist (ABC). It was originally developed to measure problem behaviors in the developmentally delayed population but has also been validated for use in the ASD population. It contains 58 items and 5 subscales (Table 1). Each item is rated by the patient's caregiver (such as family or a teacher) on a 4-point scale, from 0 ("not at all a problem") to 3 ("the problem is severe in degree"). There is no composite ABC scale; each subscale is scored separately. Trial outcomes are designed around specific subscales.[5,6]

Table 1

Aberrant Behavior Checklist (ABC)*

Subscale	No. of items	Possible maximum score
Irritability, agitation, crying	15	45
Lethargy/social withdrawal	16	48
Stereotypic behavior	7	21
Hyperactivity/noncompliance	16	48
Inappropriate speech	4	12

* Please refer to the text for a description of the ABC.

Formulary/Source: Refs 5,6

TREATMENTS

ASD is not curable and thus must be managed as a chronic condition. The primary goals are to minimize the core deficits and maximize independent functioning and quality of life for both the patient and the family. Educational interventions are the cornerstones of treatment. These usually involve behavioral and rehabilitative components that address the complex deficits that exist with autism. The components can involve occupational therapies, behavior modification, and speech and language therapies.[7]

Patients with ASD experience a wide range of behavioral dysfunctions that influence their physical health and relationships. These dysfunctions can also interfere with educational interventions. Although usually harmless, stereotypy can prevent or distract a patient with autism from learning a new skill or accomplishing a task. It can also be self-injurious if it involves such activities as head banging or picking at skin. Attempts to distract the patient from stereotypical behaviors can cause distress that can escalate to aggression, self-injurious behaviors, and temper tantrums. If severe enough, these behaviors can be dangerous to patients or their caregivers. Because many comorbid psychiatric conditions, such as depression and anxiety, can contribute to these behaviors, they should be ruled out. Medical causes of pain or discomfort, such as otitis media or urinary tract infections, should also be ruled out as causes for escalation of maladaptive behaviors.[7]

Medication should be considered in the treatment of ASD only if nonpharmacologic interventions fail and the maladaptive behaviors are severe. Medications do not treat the core symptoms of ASD, nor can they cure it. Medications are adjuncts, only, that may be used to decrease the severity of symptoms, help patients participate more actively in educational interventions, or help them live outside of institutional settings. Patients with ASD are more sensitive to medication side effects, and so the benefits of use must always be weighed against the risk of developing adverse drug reactions (ADRs).

Although most products are not FDA-approved, medication is used frequently in the treatment of ASD. In a recent survey of 2,853 children in the Autism Treatment Network, 27% were using at least 1 psychotropic medication. Use ranged from 11% in children aged 3 to 5 years to 66% in those aged

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Table 2

Medications used in the treatment of ASD-associated symptoms

	ADHD-like symptoms	Aggression/ irritability/self-injurious behaviors	Social behavior deficits	Stereotypy
SGAs (risperidone*, aripiprazole*, etc.)	X	X	X	X
SSRIs		X		X
Psychostimulants	X			
Atomoxetine	X			
Alpha-2 agonists (clonidine, guanfacine)	X	X		
Cholinesterase inhibitors			X	
Memantine			X	

* FDA-approved indication.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; SGAs, second-generation antipsychotics; SSRIs, selective serotonin reuptake inhibitors.

Formulary/Source:Refs 10,11,12, 13, 14, 15, 21,22,23,24,25,26,27,28,29,30

12 to 17. Much of the use was related to comorbid psychiatric diagnoses, including attention-deficit/hyperactivity disorder (ADHD)-like symptoms, bipolar disorder, obsessive-compulsive disorder, depression, and anxiety. Stimulants were used in 13% of patients, selective serotonin reuptake inhibitors (SSRIs) and second-generation antipsychotics (SGAs) were each used by 8%, and alpha-2 agonists in 7%.[8]

Despite the number of medications used to treat symptoms of ASD, very little evidence exists to support the use of most.[9] Studies of medications in ASD are sparse, have small sample sizes, and are often open-label. Trials are complicated by concomitant use of other medications to treat ASD-related symptoms. Often investigators have difficulty recruiting enough subjects. Children with ASD are also more sensitive to the side effects of medications. The medications used to treat ASD-related symptoms were chosen based upon their ability to treat similar symptoms in other psychiatric disorders. For example, SSRIs are used to treat stereotypical behavior based upon their use in the treatment of obsessive-compulsive disorder. Most medications used to treat ASD symptoms do not carry an FDA indication for this use. The following sections detail the medications most frequently used to treat ASD-related symptoms. These medications are also summarized in Table 2.

ANTIPSYCHOTICS

Antipsychotics are the most studied medications in the treatment of ASD. The main use is for associated aggression, irritability, and self-injurious behavior. Antipsychotics can, however, also be used to treat stereotypies and ADHD-like symptoms. Haloperidol is a first-generation antipsychotic that has been used and studied in ASD. An average dose of 1.12 mg/d decreased maladaptive behaviors in 2 clinical trials. Doses exceeding this had no additional effectiveness. Use was associated with a high incidence of side effects, including sedation, paradoxical increases in irritability, and dystonias. At doses of 1.75 mg/d, one-third of patients developed dyskinesias, mostly affecting the face and mouth.[10]

Of the antipsychotics prescribed to children, over 90% are SGAs. Risperidone is the most studied SGA in ASD, and the most commonly prescribed antipsychotic in pediatric patients. Risperidone and aripiprazole are the only 2 SGAs that carry FDA indications for treating irritability associated with autism in children.

Risperidone has reduced ASD-related maladaptive behaviors in multiple studies. The strongest evidence for the efficacy of risperidone derives from the Research Units on Pediatric Psychopharmacology (RUPP) Autism Network studies. In an 8-week randomized, double-blind, placebo-controlled (RDBPC) trial of 101 children aged 5 to 17 years, a mean risperidone dose of 1.8 mg/d resulted in a 14.9-point decrease in the ABC-irritability (ABC-I) subscale (versus -3.6 points for placebo, $P<0.001$). Significant decreases in the other 4 ABC subscales also occurred with risperidone treatment. Of the sub-

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jects receiving risperidone, 69% were labeled as responders (as defined by a ≥25% decrease in the ABC-I), versus 12% for placebo ($P<0.001$). Although 3 children withdrew from the risperidone group for lack of efficacy, none were withdrawn due to ADRs. Weight gain was higher in the risperidone group (2.7±2.9 kg vs 0.8±2.2 kg, $P<0.001$). The most common side effects were fatigue, drowsiness, and tremor. No other extrapyramidal symptoms (EPS) were reported.[11]

A 4-month open-label extension of the original 8-week trial enrolled 63 subjects who responded to risperidone during the original trial. The mean risperidone dose was approximately 2 mg/d. A 2.2-point increase in the ABC-I occurred ($P=.02$), but remained below pretreatment scores. Of the other subscales, only stereotypy showed a minor increase. ADRs were similar to the first trial. Total weight gain over the 6 months was 5.1 kg (±3.6 kg, $P<0.001$) and was greater than anticipated at the start of the trial. Of the study withdrawals, only 1 occurred due to side effects (constipation). A subsequent 8-week discontinuation phase resulted in a relapse rate of 62.5% in the placebo group. The National Institute of Mental Health (the sponsoring body) ruled that this phase be discontinued immediately.[12]

Aripiprazole reduced symptoms of irritability in patients with ASD in several small studies. The strongest the evidence for its utility comes from the 2 manufacturer-sponsored trials that led to its approval by the FDA for the treatment of ASD-associated symptoms of irritability. Both were RDBPC 8-week trials in children aged 6 to 17 years. In addition to a DSM-IV-TR ASD diagnosis, patients had to have ASD irritability-type behaviors such as tantrums, aggression, or self-injurious behavior. The first trial involved a flexible dosing schedule starting at 2 mg/d and increasing weekly to a maximum dose of 15 mg/d by 6 weeks at the latest. In 98 patients with a mean age of 9.3 years, the between-group change in ABC-I was -7.9 (CI, -11.7 to -4.1; $P<0.001$). Significant declines occurred in all other ABC subscales with the exception of lethargy/social withdrawal. Response (defined as a ≥25% reduction in the ABC-I scale) occurred in 52.2% of patients on aripiprazole (vs 14.3% placebo, $P<.001$). Side effects occurred in 91.5% of patients on aripiprazole (vs 72% on placebo). The most common side effects were fatigue, somnolence, sedation, drooling, vomiting, diarrhea, and tremor. EPS was reported in 7 cases of patients receiving aripiprazole versus 4 for placebo. None involved either acute dystonias or tardive dyskinesias.[13]

The second trial involved fixed-dose aripiprazole (5 mg, 10 mg, or 15 mg daily) in 218 patients with a mean age of 9.7 years. Decreases in ABC-I were statistically significant for all doses (vs placebo) in a dose-dependent fashion. In the 5-mg group, the total change was -4.0 ($P=.032$); for 10 mg, -4.8 ($P=.008$); and for 15 mg, -6.0 ($P=.001$). The 15-mg dose produced statistically significant decreases in all other subscales but lethargy/social withdrawal, and all doses produced statistically significant decreases in the stereotypy and hyperactivity subscales. Compared with a 72.5% incidence of side effects in placebo patients, side effects were experienced by 85.2% to 89.8% of patients on aripiprazole (not dose-dependent). ADRs resulted in 17 withdrawals (due to sedation, drooling, and tremor). EPS occurred in 22% to 23% of patients in each group of aripiprazole (vs. 11.8% on placebo), and was limited to tremor and extrapyramidal syndrome. Patients on aripiprazole gained 1.4 to 1.6 kg (vs 0.4 kg on placebo, $P< .05$).[14]

Evidence for the use of other SGAs is sparse. Olanzapine and ziprasidone each have 1 clinical trial demonstrating reduced maladaptive behaviors, but sample sizes in both cases were small (<20). In separate small trials, quetiapine has shown mixed results, mostly suboptimal.[10,15]

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Because the repetitive and maladaptive behaviors exhibited by patients with ASD resemble those of obsessive-compulsive disorder, treatment with SSRIs is common. Evidence from research has yielded mixed results. One trial of citalopram in 149 children failed to find any benefit.[15,16] In early trials, fluvoxamine improved repetitive behaviors and language usage in 8 of 15 adults, but a subsequent trial failed to find similar responses in children.[10] Similarly, a trial of paroxetine in 15 institutionalized patients initially showed benefit on aggression and self-injurious behavior, but the effect dampened after 4 weeks of treatment.[17] A small trial of escitalopram in 28 subjects demonstrated improvement in the ABC-irritability subscale.[10]

Although the total number of patients treated with either is small, both sertraline and fluoxetine have shown the most promise. Sertraline improved aggression and self-injurious behavior in 8 of 9 patients in 1 open-label trial (dosing 25–150 mg/d). A separate open-label trial showed improved response to environmental change in 8 of 9 children (aged 6–12) at doses of 25 to 50 mg/d.[10]

In an open-label trial, 57% of patients with ASD (n=42) responded to a mean sertraline dose of 122 mg/d with significant decreases in aggressive and repetitive behaviors. Of note, those with Asperger's disorder had no response (n=6).[18]

In an 8-week DBPC crossover study in 34 children aged 5 to 17 years, fluoxetine at mean doses of 0.38 mg/kg/d decreased the 20-point compulsion subscale of the Yale-Brown Obsessive-Compulsive Scale

(Y-BOCSc) by 1.55 points (vs 0.25 for placebo; *P*=.004 to .038 depending on analysis type) with evidence of progressive treatment effects over the treatment period.[19] Similarly, a mean fluoxetine dose of 64.75 mg/d decreased the Y-BOCSc by 3.7 points (*P*=.005) in over 12 weeks in a RDBPC trial involving 37 adult patients with ASD. Fluoxetine was well-tolerated in both trials. Side effects were mild, not statistically different from placebo, and included nightmares or vivid dreams, mild insomnia, dry mouth, and headaches.[16]

STIMULANTS AND ATOMOXETINE

The DSM-IV-TR essentially precludes a diagnosis of ADHD if a patient has ASD. However, patients with autism frequently have ADHD-like symptoms, including distractibility, hyperactivity, excitability, and difficulty concentrating. As with ADHD, psychostimulants are considered first-line to treat these symptoms. Unlike children with ADHD, children with ASD are not as responsive to stimulants and have increased sensitivity to side effects such as agitation and emotionality. Methylphenidate is the preferred agent, because it has been used in the bulk of clinical experience and research. Short-acting formulations should be used first in order to gauge tolerability.[20]

Although a number of trials demonstrated efficacy of methylphenidate in treating ADHD-like symptoms in children with ASD, the strongest evidence to date comes from the RUPP trials. In a 4-week RDBPC crossover trial, 72 children aged 5 to 14 were treated with low-dose (0.125 mg/kg/d), medium-dose (0.25 mg/kg/d), and high-dose (0.5 mg/kg/d) methylphenidate, given in 3 divided doses. During this phase, 49% were found to be responders, and 18% stopped the medication due to intolerance. This phase was also used to find the patient's "best dose" for response (as measured by the ABC-I) with minimal side effects. During the crossover phase, the ABC-I decreased from 30.9–33.2 to 17.2–20.1 (depending on the evaluator; vs 26 for placebo, *P*<.001).[21] In the second phase, which was an 8-week "open-label" trial of responders (n=34) on their "best dose," response was maintained. The treatment failed to show benefit on the other ABC subscales. Indeed, the most common side effects included irritability, lethargy, sadness, dullness, and social withdrawal. In a subsequent subanalysis of 33 patients from this study, significant improvement in joint attention, self-regulation, and ability to regulate emotions was detected.[22]

Two small RDBPC suggest potential minor benefits of atomoxetine in children with ASD with ADHD symptoms. The first trial was a crossover trial that included 16 patients aged 5 to 15 years. Over 6 weeks, 16 patients taking a mean atomoxetine dose of 44.2 $\pm$ 21.9 mg/d experienced a mean drop of 5 points on the ABC-hyperactivity scale (vs. 0.1 point for placebo, *P*=.043). There was no correlation between dose and either severity of symptoms or degree of improvement.[23] In the second trial, 97 subjects aged 6 to 17 years were randomly assigned to either fixed-dose atomoxetine (1.2 mg/kg/d) or placebo. After 8 weeks, subjects taking atomoxetine experienced an 8.2-point drop in the 54-point ADHD Rating Scale (ADHD-RS) score (vs 1.2 on placebo, *P*<.001). Atomoxetine was well tolerated in both trials. Compared with placebo, the most common side effects were nausea, decreased appetite, fatigue, and early morning awakening.[24] Both trials were sponsored by the drug manufacturer. Although these trials suggest possible benefit of atomoxetine in the treatment of ASD-associated ADHD-like symptoms, further research is needed before it can be considered as first-line therapy.

Although clonidine and guanfacine have been used to treat symptoms of ADHD, data on their use in ASD is sparse. Both risperidone and aripiprazole have demonstrated a decrease in ADHD-like symptoms in children with ASD. However, because of the risk for weight gain and movement disorders, they are not recommended for use unless the degree of impulsivity threatens the child's life (eg, dangerous or impulsive running or jumping), or in those children with comorbid irritability or aggression.[20]

MEDICATIONS USED TO TREAT ALZHEIMER'S DISEASE

There has been interest in the use of both cholinesterase inhibitors and the glutamatergic antagonist memantine for improving executive level functional deficits, such as problem-solving, decision-making and social skills, in patients with ASD. The interest stems from autopsy findings that show a deficit of cholinergic receptors and abnormal functioning of those receptors in the cerebral cortex and prefrontal regions of the brain. Trials of these agents have been small and often open-label.[25] One RDBPC 10-week trial of 34 patients on donepezil 10 mg/d failed to show any difference in performance on a battery of tests designed to measure cognitive function, including verbal ability and problem-solving.[26] Rivastigmine 0.8 mg twice daily improved expressive speech and autistic behaviors (as a 3-point drop in the Childhood Autism Rating Scale score) in one open-label 12-week trial in 32 patients aged 2 to 12 years.[25] Galantamine has demonstrated mild improvements in hyperactivity, eye contact, and inappropriate speech, but results are limited to a total of 23 patients.[27,28]

Additional autopsy findings demonstrate decreased neuronal size in the highly interconnected structures of the limbic system. These findings suggest neuronal immaturity, which affects the ability to form memories.

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An "excitotoxicity" state may also exist in which persistent activation of *N*-methyl-D-aspartate (NMDA) receptors leads to high levels of the activating neurotransmitter glutamate and subsequent neuronal death. Small trials of both amantadine, which is structurally related to memantine, and D-cycloserine, which acts as partial agonist at the NMDA receptor, showed positive effects on ASD. These findings led to interest in memantine for treating ASD.[29] In 1 8-week open-label trial in 14 subjects aged 3 to 12 years, memantine 0.4 mg/kg (up to 20 mg/d) led to a small improvement in a simple memory test (*P*=.021) but not other cognitive measures. Subjects additionally showed improvements on all 5 ABC subscales (*P*=.001 to 0.027 depending on the scale).[29] In a second retrospective trial of 18 patients aged 6 to 19 years, a mean dose of memantine 10.1 mg/d over an average treatment period of 19.3 weeks were "much improved" or "very much improved" on the Clinical Global Impression, with decreases of 6.84 on the ABC-hyperactivity (*P*=.03) and 9 on the ABC-social withdrawal (*P*=NS) scales.[30] An increase in autistic behaviors, including hyperactivity, lethargy, and irritability was seen in several patients in these studies. The results of studies using galantamine, rivastigmine, and memantine show promise, but should be confirmed in larger RDBPC clinical trials before routine use in treatment of ASD can be recommended.

CONCLUSION

Medications are frequently used to treat ASD-related symptoms, even though most lack evidence to support use and do not carry an FDA indication for their use. Treatment focus in patients with ASD must remain on nonpharmacologic interventions. Medication use should be considered adjunctive only. Pharmacists play a crucial role in reviewing medication use to ensure it is appropriate in this population. This includes application of measuring scales such as the ABC to determine efficacy and assuring that appropriate measures are being followed to minimize or prevent ADRs. Medication use in ASD should be approached as short-term therapy with a plan to closely monitor and discontinue the medication if it is not of benefit to the patient. ■

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Ponatinib: An oral tyrosine kinase inhibitor for treatment of CML and Ph+ALL

Brett Feret, PharmD

Abstract

Ponatinib is an oral tyrosine kinase inhibitor (TKI) that was approved by FDA on December 14, 2012, for the treatment of adult patients with chronic-phase, accelerated-phase, or blast-phase chronic myelogenous leukemia (CML) that is resistant or intolerant to previous TKI therapy, and for Philadelphia chromosome (Ph)–positive acute lymphoblastic leukemia (Ph+ALL). CML accounts for a little over 10% of adult leukemias. In 2013, an estimated 5,920 cases will be diagnosed in the United States. Many patients are now showing resistance to standard TKI therapy. A major mechanism of resistance is mutation of the BCR-ABL kinase domain. One of the most common mutations (up to 20% of patients) is the T315I substitution, which leads to resistance to all the current TKIs. Ponatinib has demonstrated significant cytogenic and hematologic responses in patients with either CML or Ph+ ALL, including those with the T315I mutation in both phase 1 and 2 clinical trials. Ponatinib is given orally once daily and has significant adverse effects, including boxed warnings for both hepatotoxicity and arterial thrombosis. (*Formulary*. 2013; 48:169-170.)

Ponatinib is an oral tyrosine kinase inhibitor (TKI) that was approved by FDA on December 14, 2012, for the treatment of adult patients with chronic-phase, accelerated-phase, or blast-phase chronic myelogenous leukemia (CML) that is resistant or intolerant to previous TKI therapy, and for Philadelphia chromosome (Ph)–positive acute lymphoblastic leukemia (Ph+ALL).[1]

CML accounts for a little more than 10% of adult leukemias. In 2013, an estimated 5,920 cases will be diagnosed in the United States.[2] CML is a hematopoietic stem cell disease that is characterized by the Ph, which is formed from the translocation of chromosomes 9 and 22. A fusion protein product of Ph, BCR-ABL, is believed to give rise to CML and a subset of acute lymphoblastic leukemias that are positive for Ph (Ph+ALL). This BCR-ABL contains an activated tyrosine kinase domain that promotes cell growth. Current treatment for both CML and Ph+ALL includes TKIs such as imatinib, nilotinib, dasatinib, and bosutinib.[3]

Many patients are now showing resistance to standard TKI therapy. A major mechanism of resistance is mutation of the BCR-ABL kinase domain. One of the most common mutations (up to 20% of patients) is the T315I substitution, which leads to resistance to all the current TKIs.[3] Specifically, the isoleucine side chain of the T315I mutation does not form a hydrogen bond with the TKI, which then prevents the binding of the drug to BCR-ABL. Ponatinib has a unique scaffold chemical structure unlike other current TKIs. Due to its structure, ponatinib does not form a hydrogen bond with the T315 mutation, but is still able to link to the isoleucine side chain of the T315 mutation of the BCR-ABL through a novel triple bond linkage.[4]

EFFICACY

Cortes et al conducted a phase 1 dose-escalation clinical trial in 81 patients with resistant hematologic cancer including 60 with CML and 5 with Ph+ALL to determine the recommended dosage for ponatinib.[3] Patients were eligible if they had relapsed or were resistant to standard care. In addition, they had to be older than aged 18 years and to have an Eastern Cooperative Oncology Group performance status of 2 or lower (range 0–5, with 0 being fully active). Ponatinib was administered once daily at a dose ranging from 2 mg to 60 mg. The median follow-up was 56 weeks.

Ninety-eight percent of patients with chronic-phase CML (CP-CML; n=43) had a complete hematologic response, 72% had a major cytogenic response, and 44% had a major molecular response. In the subset of patients with CP-CML who had the T315I mutation (n=12), all had a complete hematologic response and 92% had a major cytogenic response. All 13 patients with CP-CML without detectable mutations had a complete hematologic response, and 62% had a major cytogenic

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In each issue, the "Focus on" feature reviews a newly approved or investigational drug of interest to pharmacy and therapeutics committee members.

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response. In addition, in patients with accelerated-phase (AP) or blast-phase (BP) CML or Ph+ALL (N=22), 36% had a major hematologic response and 32% had a major cytogenic response.

This phase 1 trial led to a recommended dosage of 45 mg daily and showed that ponatinib was effective and had activity in patients in whom previous therapy had failed with multiple TKIs, including patients with the T315I mutation.[3]

> In the subset of patients with CP-CML who had the T315I mutation, all had a complete hematological response and 92% had a major cytogenic response.

The phase 1 trial was followed by the phase 2 PACE (Ponatinib Ph+ALL and CML Evaluation) trial, which led to the approval of ponatinib.[1,5] Patients with refractory CML or Ph+ALL resistant or intolerant to dasatinib or nilotinib or with the T315I mutation were enrolled in a single-arm, open-label, international multicenter trial. All patients were administered 45 mg ponatinib daily. The trial enrolled 449 patients—267 patients with CP-CML, 83 patients with AP-CML, 62 patients with BP-CML, and 32 patients with Ph+ALL. The median time from diagnosis to the ponatinib trial was 6 years, and the majority of patients had been treated with multiple TKIs. Prior treatment included imatinib (96%), dasatinib (85%), nilotinib (66%), and bosutinib (7%). It should also be noted that 94% of patients had failed ≥2 TKIs and 59% had failed ≥3 TKIs. Almost one-third of patients (29%) had the T315I mutation. The primary efficacy end point in the CP-CML cohort was major cytogenic response within 12 months, which was defined as 65% normal cells, or major hematologic response in the AP-CML, BP-CML, and Ph+ALL cohort within 6 months of treatment, defined as normal white blood cell counts.[5,6]

A major cytogenic response was achieved in 54% of patients with CP-CML, including 49% who had been resistant or intolerant to previous TKI therapy and 70% with the T315I mutation. A complete cytogenic response defined as no measurable Ph-positive cells was achieved in 44% of patients. Major hematologic responses were seen in 52% of patients with AP-CML, 31% with BP-CML, and 41% with Ph+ALL.[6] There are no current data showing improvement in progression-free or overall survival.

Ponatinib is also currently being evaluated against imatinib for treatment-naïve CP-CML patients in an international, multicenter randomized trial.[7]

ADVERSE EVENTS

The most frequent adverse events during the PACE trial were hypertension (68%), rash (54%), abdominal pain (49%), fatigue (39%), headache (39%), dry skin (39%), constipation (37%), arthralgia (26%), nausea (23%), and pyrexia (23%). Myelosuppression also occurred in 48% of patients, with the incidence being higher in patients with AP-CML, BP-CML, and Ph+ALL. There were also cases of pancreatitis (6%), and it is recommended that serum lipase levels are checked every 2 weeks for the first 2 months of treatment and then monthly.[6]

The labeling for ponatinib also includes a boxed warning for both arterial thrombosis and hepatotoxicity. Serious arterial thrombotic events occurred in 8% of patients, with myocardial infarction or worsening coronary artery disease being the most common. Peripheral arterial events, deep vein thrombosis, pulmonary embolism, and congestive heart failure were also reported. Aspartate aminotransferase or alanine aminotransferase elevation was seen in 56% of patients, and 3 cases of acute liver failure resulting in death did occur.[6]

DRUG INTERACTIONS

Ponatinib is a substrate of CYP3A4 and is expected to interact with both inducers and inhibitors of the enzyme. Coadministration with a strong inducer such as carbamazepine or phenytoin is not recommended, and a dosage adjustment is recommended in patients taking a concurrent CYP 3A4 inhibitor such as clarithromycin or ketoconazole. Medications that elevate the gastric pH, such as antacid H-2 blockers and proton pump inhibitors, should also be avoided due to the reduction in bioavailability of ponatinib.[6]

DOSING AND ADMINISTRATION

Ponatinib will be available in both 15- and 45-mg tablets. The usual dose will be 45 mg once daily with or without food. A dosage reduction to 30 mg once daily is recommended in patients being treated with a strong CYP 3A4 inhibitor. Dosage adjustments are also recommended for patients experiencing myelosuppression, elevations in liver enzymes, or elevations in serum lipase and/or a diagnosis of pancreatitis.[6] ■

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Pipeline preview

Complete response

■ Elvitegravir and cobicistat for use as part of HIV treatment regimens (Gilead Sciences). In its communications, FDA states that it cannot approve the applications in their current forms. The letters state that during recent inspections, deficiencies in documentation and validation of certain quality testing procedures and methods were observed. Gilead is working with FDA to address the questions raised in the complete response letters and move the applications forward.

■ Dihydroergotamine (**Levadex**, Allergan) inhalation aerosol for the acute treatment of migraines in adults. In addition to the response, the company has already received draft labeling from FDA. Allergan anticipates minimal revisions to this labeling. The main issues cited in the complete response letter (CRL) were already identified by FDA in prior discussions with Allergan. The company has already taken the following actions to address these concerns: (1) Per FDA's comments in the CRL, during a previous inspection, the agency noted concerns with Exemplar Pharma, LLC, the canister filling unit manufacturer. In accordance with Allergan's overall manufacturing strategy to secure its supply chain, Allergan completed the acquisition of Exemplar on April 12, 2013, for less than $20 million. Allergan has appointed senior members of Allergan's Global Technical Operations to oversee the facility. Allergan anticipates that FDA will require a re-inspection of the Exemplar facility prior to approval; (2) FDA also noted concerns regarding the manufacturing process for the final filled canisters. Allergan has already responded to this concern. As FDA indicated in the CRL, the

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New molecular entity

Xeljanz

Tofacitinib

PFIZER

An oral non-biologic disease-modifying antirheumatic drug (DMARD) to be used as monotherapy or in combination with methotrexate or other non-biologic DMARDs for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have not had an adequate response to methotrexate or are intolerant to methotrexate.

In November 2012, FDA approved tofacitinib (Xeljanz, Pfizer) 5-mg tablets for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have not had an adequate response to methotrexate or are intolerant to methotrexate. Tofacitinib, an oral non-biologic disease-modifying antirheumatic drug (DMARD) can be used as monotherapy or in combination with methotrexate or other non-biologic DMARDs. It is contraindicated for use with biologic DMARDs or with immunosuppressive agents, such as azathioprine and cyclosporine.

Tofacitinib is the first treatment for RA with a new class of drugs, Janus kinase (JAK) inhibitors. JAKs are enzymes that transmit signaling from cytokines and growth-factor receptors involved in hematopoiesis and immune function. Tofacitinib inhibits JAKs which in turn blocks the signaling of several cytokines and interleukins involved in lymphocyte function. Tofacitinib is the first new oral non-biologic DMARD for RA in more than a decade.

Tofacitinib was approved with a Risk Evaluation and Mitigation Strategy (REMS), including a Medication Guide for patients, a communication plan for healthcare providers and pharmacists, and periodic submissions of assessments of the REMS. The manufacturer will also be conducting post-marketing clinical trials to evaluate long-term safety of tofacitinib and to determine its efficacy and safety in children with polyarticular juvenile idiopathic arthritis.

Efficacy. Tofacitinib was FDA approved based on two 6-month dose-ranging studies and 5 confirmatory studies, evaluating approximately 5,000 patients with RA. Based on 2 dose findings studies, tofacitinib 5 mg and 10 mg twice daily were evaluated in five confirmatory trials. Trials evaluated patients with moderate to severe RA in addition to 1 of the following characteristics: inadequate DMARD response, inadequate non-biologic DMARD response, inadequate methotrexate response, or inadequate tumor necrosis factor inhibitor response. Tofacitinib was either used alone or in addition to a non-biologic DMARD, often times methotrexate. In the trial evaluating patients with inadequate response to methotrexate, adalimumab was also used as a comparator. Primary end points of the trials included the American College of Rheumatology 20 (ACR20), change in Health Assessment Questionnaire-Disability Index (HAQ-DI), and rates of Disease Activity Score DAS28-4 (ESR) less than 2.6.

In all of the studies, patients treated with tofacitinib at either 5 mg or 10 mg twice daily had higher ACR20 response rates compared to the placebo, regardless of background DMARD therapy. In patients with inadequate response to methotrexate, addition of tofacitinib 5 mg or 10 mg twice daily increases achievement of a Disease Activity Score DAS28-4 (ESR) less than 2.6 (1% in methotrexate plus placebo, 6% in methotrexate plus tofacitinib 5mg, and 13% in methotrexate plus tofacitinib 10-mg groups).

Physical function as measured by the HAQ-DI improved from baseline to 3 months in patients who inadequately responded to methotrexate when tofacitinib 5mg or 10mg twice daily was added to methotrexate. The mean differences in both tofacitinib groups were significant [-0.22 (-0.35 to -0.10) in tofacitinib 5-mg and -0.32 (-0.44 to -0.19) in tofacitinib 10-mg groups]. The manufacturer reports that similar findings were noted in the other trials as well.

Safety. Tofacitinib carries a boxed warning of risk for serious infections, lymphoma and other malignancies. The most common adverse event observed in the clinical trial program was serious infection, although the difference in risk was not significant when tofacitinib was compared to placebo, using data at 3 months [risk difference 1.1 (-0.4 to 2.5) events per 100 patient years]. Longer-term data compared to placebo is not yet available. The most common serious infections were pneumonia, cellulitis, herpes zoster, and urinary tract infections. Although no cases of tuberculosis (TB) were reported at 3 months,

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Agency has not yet reviewed Allergan's response under the current PDUFA timeline.

■ Treprostinil diolamine extended-release tablets (oral treprostinil) (United Therapeutics) received a second complete response letter (CRL) for the treatment of pulmonary arterial hypertension. United Therapeutics is requesting an end-of-review meeting with FDA to discuss the CRL.

■ Pandemic Influenza A Virus Monovalent Adjuvanted candidate vaccine (Q-Pan H5N1, GlaxoSmithKline) for active immunization for the prevention of disease in adults aged 18 years and older who are at increased risk of exposure to the H5N1 influenza virus subtype contained in the vaccine. The complete response letter was triggered due to an administrative matter that has recently been rectified. GSK and FDA are working to complete the review.

Priority review

■ Riociguat (Bayer HealthCare) for the treatment of 2 distinct forms of pulmonary hypertension: inoperable chronic thromboembolic pulmonary hypertension and pulmonary arterial hypertension.

Fast-track designation

■ Daratumumab (Genmab A/S) for patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory (IMiD) agent, or are double refractory to a PI and an IMiD.

Orphan drug designation

■ ACE-536 (Celgene and Acceleron) for the treatment of 2 rare blood disorders: beta-thalassemia and myelodysplastic syndromes.

by 12 months 6 patients in tofacitinib 10-mg group had TB. Patients must be tested for latent TB prior to initiation of treatment with tofacitinib and if positive, should be treated for TB prior to tofacitinib therapy. All patients should be monitored for active TB as well as other infections during treatment since infections that have lead to hospitalization or death have been observed during tofacitinib therapy. Because of the lack of data, live vaccines should not be administered to patients taking tofacitinib and immunizations should be updated prior to initiation of therapy.

Patients who have had a malignancy prior to tofacitinib treatment or develop a malignancy during tofacitinib treatment need to consider the risk and benefits of tofacitinib. Of the 3,328 patients in the clinical trial program who have received tofacitinib with or without a DMARD, there have been 11 solid tumor and 1 lymphoma cases at 12 months. None have been reported in the 809 patients treated with placebo. In a small trial of renal transplant patients, 5 of 218 patients treated with tofacitinib developed Epstein Barr Virus-associated post-transplant lymphoproliferative disorder compared with none in the 11 cyclosporine-treated patients.

Other safety findings included gastrointestinal perforations, lymphocytosis, neutropenia, decreased hemoglobin, liver enzyme elevations, and lipid elevations. The most commonly reported side effects were upper respiratory tract infections, headache, diarrhea, hypertension, and nasopharyngitis.

Dosing. The recommended dose of tofacitinib is 5 mg twice daily. In the following patients, tofacitinib should not be initiated: those with severe hepatic impairment, a lymphocyte count less than 500 cells/mm3, an absolute neutrophil count less than 1,000 cells/mm3, or hemoglobin levels less than 9 g/dL. Tofacitinib should be interrupted for the management of lymphopenia, neutropenia, and anemia, either by reducing the dose to 5 mg daily or holding the dose until lab values have normalized. There are also recommendations to reduce the dose to 5 mg daily in patients with moderate to severe renal insufficiency, with moderate hepatic impairment, receiving potent inhibitors of cytochrome P450 3A4, such as ketoconazole, and receiving 1 or more concomitant medications that can result in moderate inhibition of CYP3A4 and potent inhibition of CYP2C19. Patients taking potent CYP3A4 inducers may have a reduced response to tofacitinib. ■

FDA actions *in brief*

Prothrombin Complex Concentrate [Human] (**Kcentra**, CSL Behring) the first non-activated 4-factor prothrombin complex concentrate, was approved for the urgent reversal of vitamin K antagonist anticoagulation in adults with acute major bleeding.

Updated labeling for reformulated oxycodone hydrochloride controlled-release (**OxyContin**, Purdue Pharma) tablets was approved. The new labeling indicates that the product has physical and chemical properties that are expected to make misuse and abuse via injection difficult and to reduce abuse via the intranasal route.

Supplemental new drug application (sNDA) for lubiprostone (**Amitiza,** Sucampo Pharmaceuticals and Takeda Pharmaceuticals) 24 µg twice daily was approved as the first oral medication for the treatment of opioid-induced constipation in adult patients with chronic, noncancer pain.

Brinzolamide 1.0% and brimonidine tartrate 0.2% (**Simbrinza Suspension**, Alcon, a division of Novartis) was approved for the reduction of intraocular pressure in patients with primary open-angle glaucoma or ocular hypertension.

Norethindrone acetate and ethinyl estradiol capsules and ferrous fumarate (**Minastrin 24 FE**, Warner Chilcott) capsules were approved for the prevention of pregnancy.

Carbinoxamine maleate extended-release oral suspension (**Karbinal ER**, Tris Pharma), the first sustained-release histamine receptor blocking agent was approved for the treatment of seasonal and perennial allergic rhinitis in children aged 2 and up.

Levonorgestrel/ethinyl estradiol and ethinyl estradiol (**Quartette**, Teva) tablets were approved for the prevention of pregnancy.

Dimethyl fumarate (**Tecfidera**, Biogen Idec) capsules were approved for the treatment of adults with relapsing forms of multiple sclerosis.

Medication reconciliation efforts meeting needs and showing promise

by Christopher DiLascia, PharmD and F. Randy Vogenberg, PhD, RPh

Medication Reconciliation, "med rec" as it has come to be known, is recognized as an important part of the growing practice of medication management and a critical step in improving the care of patients in all settings. Despite the many challenges associated with implementation of a successful med rec program, the potential for significant value drives the ongoing effort to find scalable, cost-effective solutions.

Since the inclusion of medication self-management and dynamic patient-centered records by Eric Coleman, MD, MPH, in his Care Transitions Intervention process, recognition of the importance of accurate medication information transfer and its potential impact on patient outcomes has been increasing.[1]

BACKGROUND

Medication errors and the resulting adverse drug events (ADEs) have a major impact on patient outcomes and pose a significant financial burden, both to the patient and the healthcare system. According to the Agency for Healthcare Research and Quality, approximately 838,000 emergency department visits and 1.8 million hospitalizations annually are due to ADEs, with an estimated $2.6 billion in total mean hospital costs.[2] Medication reconciliation is now recognized as an important component of patient safety, as well as an important part of the strategy for reducing healthcare costs.

In 2005, medication reconciliation was included as a National Patient Safety Goal by the Joint Commission. From 2005 through 2008, the Joint Commission expected hospitals to reconcile a patient's medication from admission through discharge, documenting a complete list of the patient's current medications on admission and communicating a complete list of the patient's medications at discharge to the next provider.[3]

As hospitals began serious efforts to address the process of medication reconciliation, through paper-based methods and with technology, the difficulties of implementing an acceptable med rec process became evident. From 2009 through 2011, the Joint Commission suspended scoring of medication reconciliation during on-site accreditation surveys, in recognition of the lack of proven strategies for accomplishing the task.[3]

As of July 2011, medication reconciliation was reintroduced as part of the National Patient Safety Goal #3, "Improving the safety of using medications."[3] With this inclusion, the expectation for reconciliation of medication information was streamlined to place emphasis on critical risk points in medication reconciliation as part of the care transition process. The revised National Patient Safety Goal requires hospitals to record and pass along correct information about a patient's medication, find out what medicines the patient is taking, compare those medicines to any new ones intended to be or newly given to the patient, make sure the patient knows which medicines to take when he or she is at home, and to tell the patient it is important to bring his or her up-to-date list every time he or she visits a doctor.[4] The last 2 points highlight the importance of the patient or caregivers in closing the loop and ensuring provider efforts result in measurable improvements in care.

PROVIDER CHALLENGES TO EFFECTIVE MED REC

The Joint Commission listed the breakdown of provider-to-provider communication as the most frequently found cause in listed sentinel events.[5] In a study conducted at the Mayo Health System, poor communication of medical information at transition points was responsible for as many as 50% of all medication errors in the hospital and up to 20% of ADEs.[6] Pharmacist-provided medication therapy review and consultation in various settings resulted in reductions in physician visits, emergency department visits, hospital days, and overall healthcare costs.[7] While pharmacists have taken a key leadership role in successfully implementing the medication reconciliation process, pharmacists and their fellow healthcare team members continue to struggle with the challenges of scaling up a predominantly manual task. Pharmacists across various care settings have been evolving this capability and support systems to provide leadership in successful med rec implementation.

Medication reconciliation is only as accurate as the initial list of medications obtained. Med rec may be a function of a lack of proper

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staff training on how to obtain an accurate, detailed medication history. Data collection forms are often poorly designed and confusing, and sometimes more than one list may exist. Further, in a busy practice setting, staff members frequently fail to obtain an accurate history due to lack of time. There may be an emphasis on completing the requirement to acquire a list (any list) rather than ensuring the accuracy of such a list. The end result is an inaccurate medication list, despite being prepared by licensed medical professionals.[8]

Physicians may also fail to thoroughly review the medication list obtained on admission for accuracy and order medications as listed. There may be a lack of communication from a primary physician to the admitting physician on duty when a patient is admitted through the ED. In addition, the physician caring for the patient transitioning through the hospital frequently isn't the patient's primary physician, but may be a surgeon, hospitalist, and/or specialty physician.[8]

Hospital-based clinicians also may not be able to easily access patients' complete medication lists or may be unaware of recent medication changes made just prior to admission. As a result, the new medication regimen prescribed at the time of discharge may inadvertently omit needed medications, unnecessarily duplicate existing therapies, or contain incorrect dosages.

PATIENT'S ROLE IN MED REC

To streamline healthcare delivery and control costs, both market forces and government regulations are driving the formation of new outcomes-focused practice models, such as accountable care organizations (ACOs) and medical home model group practices. These new care delivery models are forcing the recognition of the critical role played by the patient in the healthcare equation. Patients are an important part of the medication reconciliation process.[6] However, they are not clinicians and do not consider themselves "patients" in their everyday lives, thus presenting a unique set of medication reconciliation challenges.

> Until more progress is made on an electronic database... med rec will rely on communication between providers and patients.

Patients admitted to a hospital are often unsure what medications they are taking and often fail to keep an accurate, updated record of their medications. Many lists provided by patients have wrong dosages and discontinued medications and are missing new prescriptions. They often do not mention medications like those not in pill form or non-prescription medications, both of which can have significant clinical consequences. The proverbial "brown bag" solution is also problematic, with patients mixing discontinued medications, their spouse's medications, and their current medications in the same bag.[8]

Ideally, a patient medication list would be created digitally, from a nationally standardized pharmacy database. The Meaningful Use guidelines call for the capability to perform medication reconciliation to be included in the certification standards for certified electronic health record (EHR) technology.[9] However, obtaining an accurate list of medications electronically faces its own challenges, such as patients obtaining medications from multiple pharmacies, hospitals, and physicians. In addition, the current state of electronic medical records (EMRs) and health information exchanges does not permit the exchange of data across systems, even within the same state.[10]

Until further progress toward regional, state, and/or a national electronic database linked to software that provides a timely and accurate record of a patient's medication, the process of med rec will continue to rely significantly on direct communication between healthcare providers and patients.

A growing area of concern is now known as "white bag." This situation arises when medications are shipped by mail directly to patients for use in an ambulatory, clinic, or in-hospital setting due to benefit coverage rules under both medical or pharmacy benefits. Health plans and other self-funded entities are tightening drug cost management at the same time physician practices are being consolidated under a hospital or health system umbrella. These coincidental events create an ever-growing number of patients with white bags entering a previously closed healthcare system.

EFFECTIVE MED REC

Effective medication reconciliation requires accurate and complete information collection, a standardized process for information hand-offs, and a multidisciplinary approach. When done right, medication reconciliation can be a cost-effective tool to reduce costs and improve patient care. For example, in a 2012 study of 563 patients admitted to Johns Hopkins Hospital, a collaborative nurse-pharmacist medication reconciliation effort, which included pharmacist review and identification of medication discrepancies, dramatically and cost-effectively decreased the risk of ADEs. The researchers found that, at a cost of $113.64 per potentially harmful discrepancy, the program would need to prevent one ADE per 290 patients to offset costs. In fact, the program prevented 81 potentially

harmful ADEs per 290 patients.[6]

Recognizing communication patterns and addressing breakdowns at critical points in the information transfer process is the first step in implementing an effective medication reconciliation process.[11] This requires a cross-functional approach with organizational support including leadership, physicians, nurses, pharmacists, and other stakeholders that play a role in the medication management process. Once mapped out and in place, the process requires qualified professionals trained in medication reconciliation, focused on obtaining a detailed medication history, and generating an accurate medication list.

After the medication list has been obtained and reviewed by the pharmacist and/or his or her designated support person, the list needs to be effectively communicated to the physician responsible for the patient's care across each point of transition. The increasing use of hospitalists creates both challenges and opportunities in the med rec handoff process. Hospitalists have less involvement in the long-term care of a patient, but their focus on hospital care processes and patient outcomes affords them a key role in optimizing the med rec process.[12]

Development of multidisciplinary educational programs and ongoing program assessment are also key to a successful medication reconciliation process. Along with training on enhanced medication history-taking skills, education needs to recognize the important role patients and caregivers play in the success of the process. Training on how to educate patients and families about how to maintain accurate medication lists as part of an updated personal health record is critical to achieving measurable results. Following an in-depth education program, the medication reconciliation process should be audited, and healthcare providers should be given feedback on their performance.

THE FUTURE OF MED REC

The benefits of reduced healthcare costs and improved return on the healthcare dollars spent are driving the development of new processes and technologies designed to facilitate a scalable medication reconciliation process. In the absence of a centralized database, hospital software vendors offer software applications designed to be integrated into the hospital's CPOE system to maintain a digital medication reconciliation record. In some of these systems, a physician can be locked out of placing orders using CPOE unless the medication reconciliation record is updated to ensure that medication reconciliation is completed for all their patients.[13]

On the outpatient side, the movement to ACOs and medical home models is fostering the evolution of anticoagulation clinics and other medication-focused clinics into "medication management" clinics.[14] These clinics provide a resource for patients with conditions that place them at risk for hospitalization, such as congestive heart failure or chronic obstructive pulmonary disease, to proactively prepare accurate medication lists in a more relaxed setting. In some cases, the use of these pharmacist-run clinics is covered by insurance.

Along with the government regulation and financial incentives driving these market-based solutions, professional associations and healthcare quality organizations are also actively supporting efforts to improve medication reconciliation. For example, the American Society of Health System Pharmacists (ASHP) offers a medication reconciliation toolkit to provide ASHP members with tools, references, and recommendations as well as ideas and examples of success stories and lessons learned.[15] Alternatively, the Institute for Health Improvement (IHI) offers guidance for the development of a toolkit based on the MATCH medication reconciliation initiative at Northwestern Memorial Hospital.[16]

SUMMARY/CONCLUSION

The process of medication reconciliation while complex is very important in today's healthcare marketplace and continues to evolve. The reality of healthcare today presents a number of challenges, which hinder efficient as well as effective medication reconciliation, including the following:

- Patients who are unaware of current medications.
- The "brown bag" effect, where prescription medications of spouses and family members are mixed.
- The "white bag" effect, where medications are shipped by mail directly to patients for use in an ambulatory or hospital setting due to benefit coverage rules.
- Poor communication among providers on the care team.
- Poorly designed data collection forms.
- Inconsistent implementation of EMR and EHR in general.

All of these situations inhibit efforts aimed toward better medication reconciliation across the continuum of care settings. Pharmacists are stepping up to take a greater leadership role in the process of medication reconciliation, not only those who are hospital-based, but in the community, too.[17] Pharmacist-led medication reconciliation clinics are showing promise, especially for complex diseases such as chronic obstructive pulmonary disease. In addition, equally promising are new hospital-based technologies that connect to multiple provider systems and a wider range of care-related toolkits and electronic capabilities focused on providing solutions.

As healthcare becomes more complex as an industry—with more patients entering the system, more providers on the increasingly integrated care team, greater use of technology, and increasingly greater oversight—new strategies for medication reconciliation

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will continue to be needed. Current experiences are showing that when pharmacists take a leadership position in the process and reach out to deliver better coordinated education and inform patients and caregivers, the result will be enhanced collaborations to provide better outcomes and lower costs.[7] ■

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FROM THE 2013 GENITOURINARY CANCERS SYMPOSIUM

5-ARI does not affect prostate cancer mortality

by Alice Goodman

Eighteen years of follow-up from the Prostate Cancer Prevention Trial (PCPT) suggests that 7 years of treatment with the 5-alpha-reductase inhibitor finasteride (Proscar) for prostate cancer prevention does not appear to affect mortality but does reduce the risk of a prostate cancer diagnosis.

These findings, based on men randomized to the PCPT, were reported at the Genitourinary Cancers Symposium in Orlando.

Finasteride is the only method shown to be efficacious in the prevention of prostate cancer. In the PCPT, finasteride reduced the relative risk of prostate cancer by 24.8%. Of concern in that trial was an increased relative risk of 26.9% of developing high-grade disease. Subsequent analysis found that finasteride increased the detection of prostate cancer through improved sensitivity of PSA, biopsy, and digital rectal exam as well as improved sensitivity to PSA and digital rectal exam for high-grade disease.

"Despite these analyses, finasteride has been largely eliminated for prevention of prostate cancer," explained Phyllis J. Goodman, MS, lead author of the present study.

Because finasteride has the potential to substantially reduce the incidence of prostate cancer, Goodman and colleagues conducted an analysis of survival in the 2 study arms of the PCPT to seek evidence of increased risk of death in men randomly assigned to finasteride. An increased risk of death in this group would be a potential indicator of a "true" increased risk of high-grade prostate cancer with lethal potential, said Goodman, lead statistician at SWOG Statistical Center, Seattle, who worked on the study with Leslie G. Ford, MD, of the National Cancer Institute, and co-authors.

The authors used a Social Security Death Index search on all participants randomly assigned to finasteride and placebo to ascertain date of death. A total of 5,128 deaths have been reported: 2,584 in men on finasteride and 2,544 in men in the placebo group. The 15-year survival rate for all randomized men in each arm is 78%. The hazard ratio (HR) for overall survival on finasteride versus placebo is 1.04, which is not significantly different. Ten-year survival from diagnosis for men with prostate cancer was slightly higher in the finasteride group: 83% versus 81% for placebo, but again this was not significantly different.

There was no evidence for poorer survival for men with high-grade prostate cancer randomly assigned to finasteride, while those who were diagnosed with low-grade prostate cancer had superior survival (P=.01).

> Goodman suggested that the explanation for the phenomenon of superior survival in the low-grade prostate cancer group could be lead-time bias.

REASON FOR SURVIVAL DISCREPANCY UNCLEAR

Goodman suggested that the explanation for the phenomenon of superior survival in the low-grade prostate cancer group could be lead-time bias. However, the identical survival in both treatment arms in men with high-grade prostate cancer argues against a lead-time bias.

She offered another potential explanation: that men with low-grade prostate cancer in the placebo group included a greater number of men with undetected high-grade disease, while high-grade prostate cancer was more likely to be detected in those who received finasteride due to the improved sensitivity and performance of prostate biopsy.

"If finasteride truly affected the natural history of the cancer, then this should be reflected as a long-term reduction of survival in this group," said Bruce J. Roth, MD, professor of medicine at Washington University in St. Louis, who moderated a press presentation on the study findings but was not involved in the study. "In this report, with follow-up of 18 years, 7 years of finasteride does not decrease overall mortality from prostate cancer despite the diagnosis of higher grade tumors, but significantly reduces the risk of a prostate cancer diagnosis." ■

One of Goodman's co-authors has served as a consultant/adviser to the Cancer Prevention Research Institute of Texas; has received honoraria from the American Society of Clinical Oncology and the American Urological Association; and has received research funding from the National Cancer Institute and National Institutes of Health.

Meeting coverage continued on page 178

Ms Goodman is a freelance medical writer who lives in Bearsville, N.Y. She has written extensively about cancer over the last 2 decades.

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Meeting coverage continued from page 177

Little survival difference seen with kidney cancer agent

by Wayne Kuznar

Use of tivozanib, an experimental tyrosine kinase inhibitor (TKI) with increased specificity and potency for the vascular endothelial growth factor (VEGF) receptor, as initial targeted therapy for patients with advanced renal cell carcinoma did not translate into improved overall survival compared with sorafenib (Nexavar) in a phase 3 clinical trial.

However, allowance for use of next-line cancer therapies hindered the overall survival comparison, said first author Robert J. Motzer, MD.

TIVO-1 RESULTS

In TIVO-1, final overall survival results showed no significant difference between tivozanib and the first-generation TKI sorafenib in patients with renal cell carcinoma who received up to 1 prior line of therapy, excluding targeted agents, said Dr Motzer, attending physician in the genitourinary oncology service at Memorial Sloan-Kettering Cancer Center, New York.

As part of the design of the extension phase of TIVO-1, patients who experienced disease progression on sorafenib based on investigator assessment were eligible to receive tivozanib, and patients who progressed while on tivozanib received subsequent treatment according to regional standards of care. Of the 257 patients on sorafenib, 70% advanced to next-line VEGF therapy, including 155 who started next-line tivozanib at the time of the final analysis. Only 10% of patients in the tivozanib arm received next-line VEGF therapy.

No difference in overall survival between the 2 treatments emerged despite superior progression-free survival (PFS), the primary end point, with tivozanib, which targets all 3 VEGF receptors.

"It's felt that inhibition of the VEGF receptor is the most important part of response to treatment, and so a drug that inhibits the receptor more strongly is believed to be potentially more effective," said Dr Motzer.

"Also, since it's more selective it has a better safety profile, and that's what we see in the trial," added Dr Motzer, who presented the findings at the Genitourinary Cancers Symposium in Orlando.

In TIVO-1, 517 patients with advanced renal cell carcinoma were randomly assigned to receive either 1.5 mg of tivozanib once daily for 3 weeks, followed by 1 week off the drug, or 400 mg of sorafenib twice daily continuously in a 4-week cycle. Although the study achieved its primary end point, the difference in PFS with tivozanib relative to sorafenib was relatively modest (11.9 vs 9.1 months, P=.042). In a pre-specified subgroup analysis of patients who were treatment-naïve, which accounted for approximately 70% of patients in each treatment arm, the PFS benefit of tivozanib was 12.7 months versus 9.1 months with sorafenib (HR=0.756; P=.037).

LITTLE DIFFERENCE IN OVERALL SURVIVAL

Median overall survival was 28.8 months for tivozanib and 29.3 months for sorafenib.

At final analysis, 27% of patients were alive and had not discontinued tivozanib versus 12% of patients who were alive and had not discontinued sorafenib.

"The anti-tumor activity of tivozanib may be contributing to the overall survival of patients randomized to sorafenib in TIVO-1," Dr Motzer said. Median PFS was 8.4 months after switching from sorafenib to tivozanib, and tumor shrinkage occurred in 74% after crossover to tivozanib.

Patients receiving sorafenib had higher overall rates of diarrhea (32% vs 22%), hand-foot syndrome (54% vs 13%), and alopecia (21% vs 2%) compared with the tivozanib arm.

"The one side effect that occurs most commonly with tivozanib is hypertension. It's believed that hypertension relates to the ability to inhibit the VEGF receptor. It's actually an on-target effect," Dr Motzer said. "The hypertension is something we can generally manage with antihypertensives."

PFS AS PRIMARY END POINT

Clinical trials in kidney cancer to date have used PFS as the primary end point, for 2 reasons, Dr Motzer said.

"Survival is improving, so PFS gives you an answer faster," he said. "Also, with multiple therapies that have become available in the last 5 years, it's hard to control what therapies the patients are going to get after they are on the study," confounding overall survival comparisons.

Tivozanib "should be an option for patients," he continued. "What I really would like to see is a head-to-head comparison between tivozanib and one of the drugs we commonly use as first-line in the United States, such as pazopanib [Votrient]." ■

Mr Kuznar is a medical journalist based in Cleveland.

Disclosure Information: The author reports no financial disclosures as related to products discussed in this article.

Dr Motzer is a consultant/adviser for Pfizer, and has received research funding from AVEO, GlaxoSmith-Kline, and Pfizer. Several of his co-authors are consultant/advisers; have employment/leadership positions in; and/or own stock in AVEO.

Efficacy of androgen receptor blockade in castration-resistant prostate cancer not dependent on age

by Wayne Kuznar

Older men with metastatic castration-resistant prostate cancer (mCRPC) derive a similar if not superior survival benefit from treatment with enzalutamide as do younger men, according to a post-hoc analysis of the phase 3 AFFIRM trial.

Relative to placebo, overall survival and progression-free survival improved equally in enzalutamide-treated men 75 years and older, who comprised about one-fourth of the AFFIRM study population, and men younger than 75 years, while tolerability was also comparable between the two groups, said Cora N. Sternberg, MD, at the Genitourinary Cancers Symposium in Orlando.

"We know that prostate cancer, even when it's considered castration-resistant (CRPC), is still responsive to hormonal manipulation" because prostate cancer remains driven by androgen receptor signalling and additionally there are also endogenous androgens that that can be activated, she said.

"Enzalutamide is an interesting drug that works specifically by blocking the androgen receptor, it also has multiple mechanisms of action which block the androgen receptor signaling pathway," Dr Sternberg said.

AFFIRM TRIAL RESULTS

The overall results of the AFFIRM trial demonstrated an improvement in median overall survival of 4.8 months in the patients randomly assigned to enzalutamide versus placebo, corresponding to a 37% reduction in the risk of death. The study enrolled patients with progressive mCRPC despite previous treatment with hormonal therapy and docetaxel chemotherapy. Patients were randomly assigned in a 2:1 ratio to enzalutamide, 160 mg/day, or placebo. They remained on treatment until disease progression or institution of new systemic antineoplastic treatment.

"These are patients in whom several lines of hormonal therapy, docetaxel chemotherapy and even a second line of chemotherapy had failed," said Dr Sternberg, chief, of the department of medical oncology, at the San Camillo & Forlanini Hospitals, Rome, Italy.

> Fatigue was slightly more common in the older men treated with enzalutamide compared with the younger men and the incidence of nausea was similar between the 2 age cohorts.

TREATING OLDER PATIENTS

"We thought it would be interesting to look at patients 75 years or older because we wanted to see if they tolerated the therapy as well as younger patients or if their outcome was worse. The study showed that they did as well or perhaps even better," Dr Sternberg said.

The median duration of enzalutamide treatment was 8.2 months in the patients younger than aged 75 years versus 10.3 months in those ≥75 years. About 44% of the younger cohort was treated with subsequent antineoplastic therapy compared with 33% of the patients ≥75 years.

The median overall survival in the younger men assigned to enzalutamide had not yet been reached compared with a median overall survival of 13.6 months in the younger men assigned to placebo, for a hazard ratio (HR) of 0.633 (P<.0001). In the older men, median overall survival was 18.2 months in those assigned to enzalutamide and 13.3 months in the placebo recipients, with a HR of 0.606 (P=.0044).

Radiographic progression-free survival was 8.3 months in the younger men randomly assigned to enzalutamide compared with 2.9 months in the younger men randomly assigned to placebo (HR=0.447; P<.0001), and 9.9 months in the older men treated with enzalutamide versus 2.8 months in the older placebo recipients (HR=0.271; P<.0001).

The HR for time to PSA progression, compared with placebo, was 0.290 in the younger men (P<.0001) and 0.135 in the older men (P<.0001).

Fatigue was slightly more common in the older men treated with enzalutamide compared with the younger men (40% vs 32%) and the incidence of nausea was similar between the 2 age cohorts (32% vs 33%).

"The AFFIRM trial was performed in patients with metastatic CRPC after failure of docetaxel. The PREVAIL study is looking at the use of enzalutamide before chemotherapy. If the results of PREVAIL are positive, it will definitely move the field toward earlier use of hormonal therapy—pre-chemotherapy," said Dr Sternberg. ■

Mr Kuznar is a medical journalist based in Cleveland.

Disclosure Information: The author reports no financial disclosures as related to products discussed in this article.

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Selected websites

http://www.idsociety.org/Index.aspx
Infectious Diseases Society of America

http://www.cdc.gov/oid/
Centers for Disease Control and Prevention
Office of Infectious Diseases

Infectious disease agents

New drugs	Product type/proposed indication	FDA status/notes
sofosbuvir Gilead Sciences	nucleotide analogue hepatitis C virus (HCV) NS5B polymerase inhibitor/for the treatment of HCV	phase 3/investigated as 2 coformulations, with ledipasvir and with simeprevir/NDA for the single drug entity has been filed with FDA
ledipasvir Gilead Sciences	an oral HCV NS5a protein inhibitor/for the treatment of HCV	phase 3
simeprevir Janssen Pharmaceuticals and Medivir AB	an oral NS3/4A protease inhibitor/for the treatment of genotype 1 chronic HCV in adult patients with compensated liver disease	phase 3/NDA for the single drug entity has been filed with FDA
oritavancin The Medicines Company	an injectable, second-generation lipoglycopeptide/for the treatment of acute bacterial skin and skin structure infections	phase 3
ceftolozane/tazobactam Cubist Pharmaceuticals	an intravenous cephalosporin and beta-lactamase inhibitor/for the treatment of complicated intra-abdominal infections and complicated urinary tract infections caused by Gram-negative bacteria, including those caused by multidrug-resistant *Pseudomonas aeruginosa*	phase 3
surotomycin Cubist Pharmaceuticals	an oral antibacterial lipopeptide/for the treatment of *Clostridium difficile*-associated diarrhea	phase 3

The purpose of Drug Watch is to keep drug decision-makers informed about pharmaceuticals in late-stage development. In each column, 1 or more disease areas or drug classes are presented. The column is researched and compiled by **Diana M. Sobieraj, PharmD,** assistant professor, University of Connecticut School of Pharmacy, in Hartford, Conn.

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