DRUG FORMULARY REVIEW
Utilization, Criteria and Outcomes

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Protocol reduces anti-rejection medication for lung transplant patients

Rates of opportunistic infection have not increased

Surgeons at the University of Pittsburgh School of Medicine have reduced the number of anti-rejection pills that some lung transplant patients receive — and the patients seem to be tolerating the change well.

Standard treatment for lung transplant patients involves a three-drug combination given twice a day. The therapy is intended to ward off an immune system attack on the donor organ.

The new approach, however, focuses on pretreatment of the patient and the administration of as little immunosuppression as possible after transplantation. More specifically, the clinical protocol involves a one-time dose of a T-cell-depleting drug that is given just before transplantation. Following transplantation, patients are treated with just one anti-rejection drug, tacrolimus (Prograf), which is administered at reduced levels. Prednisone usually is continued after the transplant but at a negligible dose, 5 mg compared to 20 mg. Under the protocol, some lung transplant patients are taking just one anti-rejection pill daily and others just the one pill four or five times a week.

The results, so far, show that this has been a good approach, says **Kenneth R. McCurry**, MD, assistant professor of surgery at the school's division of cardiothoracic surgery, and director of the University of Pittsburgh Medical Center's Lung and Heart-Lung Transplantation Program. "Anecdotally, many of our patients have done extremely well and have a better quality of life than we would otherwise anticipate two-to-four months post-transplant. They are not taking high doses of prednisone and other types of agents that may impact their quality of life." He presented his results at the American Transplant Congress in Boston in May.

More than 80 patients have been treated under the protocol since June 2002. The first 38 patients were given anti-thymocyte globulin (rabbit) (Thymoglobulin) pre-transplant. The one-year survival for these patients is 87%. The other patients received alemtuzumab (CamPath),

which appeared to deplete T cells more broadly and for a longer period of time.

Acute rejection episodes have been fewer in the alemtuzumab patients reported in the presentation compared to those who received anti-thymocyte globulin. Twenty-five of the 38 anti-thymocyte globulin patients had rejection episodes greater or equal to Grade 2, compared to two of the first 10 alemtuzumab-treated patients.

Since alemtuzumab significantly depletes T cells, the physicians were concerned that they may be trading a greater incidence of bacterial infections on standard triple immunosuppression for a greater incidence of opportunistic infections such as viral infections.

That did not happen, although the physicians made rigorous attempts to identify them. For example, there were no opportunistic infections or related complications in the patients treated with alemtuzumab; a small percentage of the anti-thymocyte globulin patients developed cytomegalovirus (8%), the bacterial infection Nocardia (8%), or post-transplant lymphoproliferative disorder (3%), rates that were comparable to patients treated conventionally.

"We have not seen any increased incidence in infection in these patients and certainly no increased incidence of opportunistic infections compared to [those] utilizing standard triple immunosuppression," McCurry says. They attribute these in part to using prophylactic agents to prevent infection for several months post-transplant.

One-year follow-up results are not yet available to compare survival between the anti-thymocyte globulin-treated and alemtuzumab-treated groups. However, the overall patient survival for anti-thymocyte globulin-treated patients is 84%, compared to 98% in the alemtuzumab-treated patients.

Good record with other transplants

Some physicians have been reluctant to change the drug therapy for lung transplant patients since these donor organ recipients have the greatest incidence of immunosuppression-related complications. "The most common cause of death in the first three years after transplantation is infectious-related complications," McCurry says.

Instead, the fact that lung transplant recipients are plagued by poorer outcomes in general following transplantation was one reason for trying the approach, he explains. "Five-year survival is about 45%-50% and has remained that for the past 10 years of more. I thought that by altering our strategy to utilize agents that were more specific to the cells that cause rejection and utilizing less of nonspecific immunosuppressants, perhaps the result could be improved outcomes and fewer complications."

McCurry, however, also has seen the approach used with positive outcomes in kidney, liver, and intestinal transplant patients. "By the time I had initiated this in our lung transplant population, there was already substantial experience at this institution utilizing the strategy in numerous organs below the diaphragm, with a good safety record and good evidence for control of alloimmune responses," he says. "It appeared to be safe and efficacious. And you could run patients on lower-maintenance immunosuppression."

There had been no experience with thoracic

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organs, including lung transplants, but the basic way the immune system responds against an allograft, via any organ — the kidney, the liver, the intestine, the lung, the heart — is really no different, he says. "We felt that based on the efficacy and safety data in our organs that this was a reasonable approach in our lung transplant recipients."

Ultimately, McCurry doesn't think it is likely that patients using this approach are going to come off immunosuppressant medications altogether. Placing patients on lower doses of maintenance immunosuppression drugs may increase compliance, however, since patients will be taking fewer maintenance medications. "We hope we can decrease the morbidity associated with [the drugs] as well," he says.

The limitations of the approach have been that the study took place at a single center and that the results still are short term. "Our survival has been excellent, but we have yet to follow these patients for a long period of time to determine the impact of this on chronic rejection."

McCurry is interested in seeing the protocol tested in a large trial. "We have presented some of our preliminary work with the Campath population, and have received some interest from some other centers and colleagues. Certainly, a multicenter trail that would evaluate this in a prospective randomized fashion would provide stronger data," he says. ■

NovoSeven shows promise for hemorrhagic stroke

Drug given within four hours after onset

New research is showing that recombinant factor VIIa [rFVIIa] (NovoSeven) shows promise in the treatment of intracerebral hemorrhage (ICH). The Phase IIb study demonstrated that the use of the hemophilia drug in ICH patients led to a significant reduction in hematoma growth when given within four hours of onset.

ICH is the most deadly and least treatable form of stroke. Researchers say these are the first positive results seen in any ICH trial.

"There is no question that NovoSeven is a major advance in the field of ICH research," said **Stephan Mayer**, MD, associate professor of neurology and neurosurgery at Columbia University in New York City. Mayer, who presented the findings in June at the 5th World Stroke Congress in Vancouver, Canada, also is director of the Neurological Intensive Care Unit at the Columbia-Presbyterian Campus of New York Presbyterian Hospital. "These trial data, which suggest the historical lack of recognized treatment for ICH may soon be at an end, will be welcomed worldwide. This could benefit many thousands of lives a year."

The international ICH trial began in August 2002 and involved 400 patients in a multicenter, randomized, double-blind, placebo-controlled trial. Patients were divided into four groups of 100 patients, comparing three doses of rFVIIa (40, 80, and 160 µg/kg) with placebo. Patients all had spontaneous ICH confirmed by computed tomography (CT) scan within three hours of onset, and were treated within one hour of the admission CT scan. The outcome measures were change in ICH volume between admission and 24-hour CT scans, the proportion of patients who were dead or severely disabled at 90 days, and overall adverse effects over the study period.

Researchers say that rFVIIa travels to the ICH site through the circulatory system and accelerates the coagulation process from within. By doing this, rFVIIa can limit the hematoma size, which predicts the outcome for ICH patients. In the study, the patients treated with rFVIIa had significantly improved neurological and functional outcome after treatment. The treatment was associated with a minor, nonsignificant increase in thromboembolic events, but researchers say this is outweighed by highly significant clinical benefits across the trial. ■

Researchers examine the issue of patient compliance

Ways to document compliance will be one result

Researchers who recently studied the working memory of pharmacists are now turning to the issue of patient compliance. Indicators show that pharmacists who make medication errors and patients who do not adhere to their medication regimens may share several individual characteristics, such as a lack of organizational skills and working memory.

As described in last month's *Drug Formulary*

Review cover story, a study showed that some pharmacists are predisposed to medical errors due to individual factors, such as a lack of working memory. The study compared the pharmacists mandated by a state board of pharmacy for misfill errors to a control group of pharmacists on computerized neuropsychological tasks and personality tests, offered by ExamCorp (www.examcorp.com). The three-year results found no differences in personality, but highly significant decrements for the medical error group for working memory, attentional control, and verbal organization when compared with the controls.

The 90-minute battery of tests is now being adapted to evaluate patients and their adherence to medication regimens. Not only should the tests indicate which patients are more likely to be noncompliant with their medications, the results also should provide pharmacists with a tool to document compliance, as well as give them ways to encourage these patients to take their medication as directed.

"There are a number of strategies to develop increased compliance," explains **Robert O. Pihl**, PhD, professor of psychology and psychiatry at McGill University in Montreal. Pihl, president of ExamCorp, helped develop the battery of tests.

"The majority of [these strategies] rely on gadgets or contracts or what is called education," he says. "These kinds of things can work if a particular relationship is developed between the provider and the patient. But unfortunately, the type of relationship that needs to be developed is not typical in any medical setting other than the psychotherapeutic setting. It takes a great deal of time, a great deal of listening, and a great deal of empathy, skills that are not necessarily inherent to professionals in our business."

Can you predict noncompliance?

To increase medication compliance, the researchers believe that there must be a procedure, such as a prospective screening test, that can determine important individual characteristics of patients who are likely to comply or not comply. The next step is to develop relatively automated interventions that will increase compliant behavior.

The types of measures that the researchers are suggesting are the same that they used successfully to discriminate pharmacists who made the medication errors. "We looked in particular at the functioning of the pre-frontal cortex," Pihl says. The measures evaluate how well people can plan and organize, and the degree of their working memory and attentional control.

We know that kind of functioning is important to compliance because the literature shows that noncompliant individuals tend to be less well educated and tend to have particular deficits in this area," he says. "For example, if you look at the problem with compliance in HIV patients, it's really the difficulty of adjusting to the pill regimen. The major reason people don't comply is that they forget. It takes a great deal of planning and organization."

The researchers then want to look at certain personality characteristics that have been used to some degree in this area, but without much success. The problem is that the personality characteristics, such as conscientiousness, have to be addressed in terms of both the patient and the provider, Pihl says.

"There are studies that show you can increase compliance if, for example, the pharmacist looks his or her patients in the eyes when explaining something. Compliant behavior can be doubled."

Pihl contends that the issue of compliance is the No. 1 medication error that exists. "Medicines won't work if people don't take them." Research shows, he says, that only one-third of patients comply with the medication regimen. One-third is partially compliant. One-third doesn't even fill the prescriptions. "There are multiple reasons for this. It has to be an extreme dilemma to practitioners."

The ExamCorp research team recently received a grant to develop a compliance program suitable for all practitioners. The compliance program would include the testing procedure, the documentation processes of patient evaluation and education, as well as the reimbursement for services component. The team has partnered with several health care facilities for the research, but would be willing to work with others that are interested. ■

Be aware of common food-drug interactions

Interactions may affect effectiveness of therapy

Various food-drug interactions can result in an increase or decrease in the effectiveness of the object drug. That's why pharmacists need to know the most potentially important food-drug

interactions and the appropriate way to manage the interaction.

Here is a list of some of the most common interactions, compiled by **Melinda Spray**, PharmD, a student at the Harrison School of Pharmacy in Auburn, AL. She gathered this information while on clinical rotation at Huntsville (AL) Hospital.

• **Warfarin (Coumadin) and vitamin K-containing foods —** Vitamin K antagonizes the effects of warfarin, resulting in a decrease in therapeutic response to the drug. Patients taking warfarin should be advised to maintain a consistent intake of vitamin K, and consume vitamin K-containing foods in moderation. Each patient should decide approximately how many servings of vitamin K-containing foods they will eat per week, and then continue to maintain this amount. Some vitamin K-containing foods include cauliflower, broccoli, cabbage, spinach, kale, lettuce, other dark green leafy vegetables, liver, soybeans, and egg yolks.

• **Grapefruit juice —** There are several known drug interactions with grapefruit juice. Some of these drugs include felodipine, nifedipine, nimodipine, amlodipine, verapamil, cyclosporin, alprazolam, midazolam, triazolam, amiodarone, estrogens, and caffeine. Grapefruit juice is a CYP3A4 inhibitor; this can result in decreased gut wall metabolism of certain drugs. Consumption of grapefruit juice with these drugs causes increased bioavailability of the drug. An interaction can be observed with as little as four ounces of grapefruit juice. The risk of an interaction with grapefruit juice can last for up to three days after ingestion. To avoid this interaction, the food and nutrition services at some hospitals do not serve grapefruit juice or sections. Patients on these medications or other medications affected by grapefruit juice should be educated of this interaction.

• **Lithium and sodium —** Lithium has an interaction with sodium; therefore, patients should keep their consumption of sodium consistent. Low or restricted sodium intake can result in increased serum concentration of lithium, and high sodium concentration can result in increased clearance of lithium. Lithium should be avoided or used with caution in patients on sodium-restricted diets. Patients should be educated on the signs and symptoms of lithium toxicity such as muscle twitching, tremor, mild ataxia, drowsiness, muscle weakness, diarrhea, and vomiting.

• **Tetracycline and divalent cations** — Tetracycline should not be taken with food sources containing divalent and trivalent cations (including calcium, aluminum, and magnesium). This combination leads to decreased absorption of the drug, and this could potentially lead to a decrease in efficacy of the drug. Tetracycline should be taken two hours before or six hours after the consumption of products containing these ions. Foods to avoid include: milk, cheese, yogurt, iron-fortified foods, and iron supplements. Many over-the-counter antacids contain these cations.

• **MAOIs and tyramine —** Patients taking monoamine oxidase inhibitors (MAOI) should be educated on the interaction between these drugs and tyramine-containing foods and beverages. Phenelzine (Nardil), tranylcypromine (Parnate), and isocarboxazid (Marplan) are some drugs in the MAOI class of drugs. The combination of MAOI and tyramine-containing foods or beverages could result in severe hypertension. Some tyramine-containing foods and beverages include wine, beer, alcohol-free beer, cheeses, bananas, raisins, sour cream, yogurt, and pickled herring. The tyramine content of foods and beverages usually increases as the ripening process occurs. Patients on these drugs should be advised to avoid alcoholic beverage. This interaction may persist for up to two weeks after the discontinuation of the MAOI.

• **Antidiabetic agents —** Many patients contend that oral antidiabetic agents are a substitute for following the appropriate diet. Patients on these agents should be educated on the importance of a low-carbohydrate diet. Patients also should be educated on the importance of taking these medications as prescribed, adhering to a regular meal schedule, and recognizing the signs and symptoms of hypoglycemia such as sweating, tachycardia, palpitations, and tremor.

• **Spironolactone (aldactone) and potassium** — Patients should be advised to monitor their potassium consumption. Spironolactone, a potassium-sparing diuretic, in combination with foods high in potassium, could result in hyperkalemia. Some foods high in potassium are bananas, apricots, coconut, dates, prunes, peaches, grapefruit, tomatoes, and oranges. Many salt substitutes are also high in potassium.

This list details just a few of the important drug-food interactions, Spray says. "There are numerous other drug-food interactions that deal with absorption, metabolism, and elimination. It is important, therefore, for health care providers to be aware of significant drug-food interactions so they can prevent possible adverse outcomes and maximize therapeutic benefits of drug therapy."

Resources

• Hansten P, Horn J. Drug Interactions: Analysis and Management. St Louis: *Facts and Comparisons*; January 2002.
• Jellin, JM. Migraines. *Pharmacist's Letter* 2002; September. ■

NEWS BRIEFS

Cost-related underuse of heart meds may have adverse outcomes

Middle-aged and older Americans with heart disease who cut back on their prescribed medications because of cost were 50% more likely to suffer heart attacks, strokes, or angina than those who did not report cost-related medication underuse, according to a new study funded in part by the National Institute on Aging (NIA), which is part of the National Institutes of Health.

This is the first nationally representative longitudinal study to demonstrate that patients with serious chronic illnesses experience adverse health events when they restrict their use of prescription drugs due to cost.

The downturns in patients' health were observed over a relatively brief (two- to three-year) period, suggesting that cost barriers to prescription drug use may have important short-term effects on older patients' health and well-being, says **Michele Heisler**, MD, MPA, one of the researchers at the Veterans Affairs Ann Arbor (MI) Healthcare System, who conducted the study. The findings appeared in the July 2004 issue of *Medical Care*.

The study included 7,991 middle-aged and older Americans who participated in a survey conducted between 1995 and 1996 as part of the Health and Retirement Study, a NIA-supported survey of adults ages 51-61, or the Asset and Health Dynamics Among the Oldest Old Study, a national survey of adults age 70 or older.

All participants reported using prescription medication, and 546 reported that they had taken less medication than prescribed because of cost. Heisler and colleagues assessed a range of important health outcomes reported in participants' subsequent surveys, conducted in 1998.

After controlling for risk factors for poor health outcomes, 32% of adults who had restricted medication use because of cost pressures reported a significant decline in their self-reported health status during their follow-up interviews compared to 21% of adults with no cost-related underuse. Self-reports of health have been found to strongly predict other serious life events, including mortality, according to the study.

In addition to cardiovascular declines, older individuals who restricted medication use because of cost had increased rates of depression, according to the study.

Researchers found no health differences among people with arthritis and diabetes who said they had restricted drug use due to cost. Community-dwelling people older than 65 paid an average of $410 for their drugs in 1999, and adults with multiple, chronic diseases paid twice as much, according to a cited study. ▼

Many consumers do not favor off-label drug use

Many consumers say they don't want physicians to prescribe drugs for off-label use, but a recent survey shows they are confused about the issue. For example, more than half of Americans (51%) in a recent poll wrongly believe that a physician can only prescribe drugs for their approved indications. In addition, only half of the respondents think that this practice actually happens very often (23%) or often (33%).

The findings were published from a Harris Interactive poll of 2,148 U.S. adults conducted online May 25-27, 2004, for *The Wall Street Journal* Online's Health Industry Edition. Other findings from the poll include:

• A 48% to 31% plurality contends that doctors should not be allowed to prescribe a drug for diseases for which that drug has not been approved by the FDA.

• Pharmaceutical companies should not be allowed to encourage doctors to prescribe a drug for diseases for which that drug has not been FDA-approved (by 73% to 12%).

"There is a massive public ignorance of off-label prescribing," says **Humphrey Taylor**, chairman of The Harris Poll at Harris Interactive. "There are several strong arguments in favor of off-label prescribing, but these data suggest that it is a potentially risky issue for both physicians and the pharmaceutical industry." ▼

Medicare extends access to self-administered drugs

The Department of Health and Human Services has announced a new Medicare demonstration program that will save seniors and people with disabilities substantial money on medicines they take for serious and chronic diseases.

The demonstration program, created as part of the Medicare Modernization Act, will extend Medicare coverage to prescription medicines that can be self-administered rather than administered by a health care provider. The demonstration will help up to 50,000 beneficiaries with serious illnesses who do not have comprehensive prescription drug coverage today.

The initiative, known as the Medicare Replacement Drug Demonstration, was mandated under Section 641 of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003. As set by Congress, enrollment in the demonstration will be open to 50,000 people and total spending on the covered drugs will be up to $500 million.

Program limits drugs covered

Under this initiative, Medicare will pay for certain drugs and biologicals that can be taken by the patient at home and that replace drugs that currently are covered under Medicare Part B when given in a physician's office. In addition, newer, more effective medications that replace some currently covered oral anticancer drugs also will be covered.

Drugs for treatment of such diseases as rheumatoid arthritis, multiple sclerosis, pulmonary hypertension, and a variety of cancers will be included in the demonstration.

The drugs were selected based on criteria developed after extensive input from physicians and other experts. For a complete list of the drugs covered, see www.hhs.gov/news/press/2004pres/20040624.html. ▼

Pfizer expands access to its prescription medications

Pfizer has announced that it will launch a comprehensive initiative to significantly expand access to its prescription medicines across the United States, with a specific focus on enabling America's 43 million uninsured to obtain Pfizer medicines at significant savings.

Key elements of the new Pfizer initiative, "Helpful Answers," include:

• Savings on Pfizer medicines for America's uninsured, regardless of age or income, through "Pfizer Pfriends."

— Families making less than $45,000 per year (less than $31,000 for individuals) will receive average savings of 37%, and up to 50% off the average cash price at retail pharmacies for most Pfizer medicines.

— Families making more than $45,000 per year (more than $31,000 for individuals) will receive average savings of 15%, and up to 25% off the average cash price at retail pharmacies for most Pfizer medicines.

• Expanded eligibility for existing Pfizer programs that provide free medicines.

— Connection to Care: Families making less than $31,000 per year (less than $19,000 for individuals) can receive free Pfizer medicines from their physicians' offices.

— Sharing the Care and Hospital Partnership Program: Families making less than $31,000 (less than $19,000 for individuals) can receive free Pfizer medicines from eligible federally qualified community health centers and hospitals.

• Extending Pfizer's $15 flat fee for qualified Medicare beneficiaries.

— Low-income Medicare beneficiaries on all Medicare-approved drug discount cards will have access to many Pfizer medicines for a flat fee of $15 per prescription after they have exhausted the $600 credit. (Adjustments to income eligibility may be made at participating community health centers and hospitals based on family size.)

• Creation of a consumer-friendly, single entry

COMING IN FUTURE MONTHS

- Trending of adverse drug reactions related to analgesic use
- Cholesterol guidelines change
- A look at food and drug allergies
- How have new OTC drugs changed prescribing patterns?
- Rosuvastatin (Crestor) drug evaluation

point navigation component for all uninsured patients.

— This month, Pfizer will launch a web site and a single toll-free number with live operators to help people without insurance, or their caregivers, find the program that best meets their needs.

— The web site and the toll-free number will inform patients of both public and Pfizer programs.

Enrollment for initiative begins this month. ▼

Pharmacists are critical link to people with pain

Pain is the No. 1 cause of adult disability in the United States. Each year, 50 million people suffer from severe chronic pain, and another 25 million experience acute pain from injuries or surgeries. Yet despite important scientific advances in the management of pain, it continues to be vastly undertreated, resulting in needless patient suffering and complications.

Because of their knowledge about disease states and treatment options and their unique accessibility to patients, pharmacists play a critical role in providing pain management. They are in an ideal position to assist patients and ensure that their pain is treated properly.

Partners for Understanding Pain (PUP) is a consortium of more than 70 organizations, including patient advocacy groups, health care professional groups, and pain associations that have declared September as Pain Awareness Month. The mission of the coalition is to increase awareness and understanding of assessment, treatment, and management of pain among health care professionals and staff, patients, and the public.

This September, to support pharmacists' efforts in pain management across the nation, PUP has created the Pharmacists' Tool Kit. The kit offers:

• education in the full array of pain management strategies;

• outreach to the community and new ways to educate consumers about taking medications;

• ideas for bridging the gap between patients and health care providers;

• resources available from the PUP organizations.

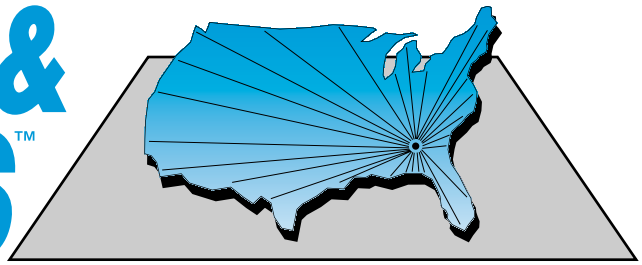
The tool kits will be distributed in August. To request a free tool kit, visit the PUP web site at www.understandingpain.org or e-mail ACPA@pacbell.net or call (800) 533-3231. ■

DFR now offers free CE

Thomson American Health Consultants is pleased to announce its accreditation by the Accreditation Council for Pharmacy Education to provide continuing pharmacy education. With this accreditation status, *Drug Formulary Review* is offering continuing education credits for the monthly *Drug Criteria & Outcomes* supplement.

Readers can earn up to 6 credit hours annually by participating in this education activity. The continuing education test questions and instructions can be found on page 4 of the supplement. If you have any questions about this program, please contact Managing Editor Paula Cousins at (816) 960-3730 or paula.cousins@thomson.com. ■

DRUG CRITERIA & OUTCOMES™



Telithromycin (Ketek) Formulary Evaluation

Part 1: Mechanism of Action, In Vitro Activity, Resistance Profile, Pharmacokinetics, Indication, and Dosage

By **Jennifer Herring**, PharmD Candidate
Harrison School of Pharmacy
Auburn (AL) University

Telithromycin is the first of the ketolides, a new class of antibacterial drugs that are derived from macrolide antibiotics.

Chemical deviations from the macrolides

The only chemical modification necessary to classify a drug as a ketolide is replacement of the α-L-cladinose moiety at position 3 of the 14-membered erythronolide A ring of the macrolide with a keto function. This replacement is thought to increase the acid stability of this class of antibacterials, as well as overcome resistance.

Chemical changes specific to telithromycin are:

- cycling of the C11-12 positions to form a carbamate ring;
- imidazo-pyridyl group attachment to the carbamate ring;
- replacement of a hydroxyl group at position 6 of the erythronolide A ring with a methoxy group.

Mechanism of action

Similar to the macrolides, telithromycin binds to the 70S bacterial ribosome, specifically the 23S rRNA of the 50S ribosomal subunit. As a result, protein synthesis is prohibited secondary to inhibition of translation of the bacterial mRNA. Depending on the nature of the pathogen, this binding results in either bacteriostatic or bactericidal activity.

The primary binding site of the macrolides and ketolides is with domain V of the 23S rRNA, where binding is a result of interactions between the erythronolide A ring of the macrolide/ketolide and several nucleotides within the central loop.

Although their interaction is similar here, each antibacterial also interacts with the hairpin 35 region of domain II. This site, domain II, is where the ketolides differ from the macrolides. The L-cladinose structure of the macrolide does not sufficiently protect the N1 position of A752 nucleotide, thereby leaving it susceptible to chemical modification. Telithromycin, however, fully protects the N1 position of the A752 due to the extension of C11-12. This results in enhanced interaction and binding to domain II. Ultimately, telithromycin is able to maintain its position on the ribosome even after alterations of domain V significantly decrease binding of the erythronolide A ring. This dual binding also enables the drug to overcome resistance caused by modification to one of the sites due to methylation.

Improved resistance profile

Because telithromycin has been derived from the macrolides, it also is susceptible to some of the resistance mechanisms of bacteria, namely constitutive methylation on domain V of the 23S rRNA. This resistance is facilitated by *erm* genes found on plasmids or chromosomes of resistant bacteria. Unlike the macrolides, however, telithromycin does not induce methylase production. As a result, telithromycin remains effective vs. the inducible methylation. Telithromycin also is effective against *mef*-controlled efflux, which is the other main mechanism by which bacteria are resistant to macrolides.

In vitro activity

As most respiratory tract infections are caused by *Streptoccocus pneumoniae* and *Haemophillus influenzae*, it is pertinent to compare minimum inhibitory concentration (MIC) values of telithromycin **(see Table 1)** to other agents currently being used to treat them. The activity of telithromycin for *S. pneumoniae* is comparable to that of the other

Table 1: In vitro activity of telithromycin against pathogenic organisms

Organism	MIC_{90} (µg/mL)
Streptococcus pneumoniae	
Penicillin-sensitive	0.06
Penicillin-resistant	0.25
Erythromycin-sensitive	0.03
Erythromycin-resistant	0.25
Group A streptococci	0.03
Staphylococcus aureus	
MSSA	0.12
MRSA	> 16
Enterococcus faecalis	
Vancomycin-sensitive	0.25
Vancomycin-resistant	8
Moraxella catarrhalis	0.12
Haemophilus influenzae	4
Neisseria meningitidis	0.12
Neisseria gonorrhoeae	0.12
Legionella pneumophila	0.03
Chlamydia pneumoniae	0.06
Mycoplasma pneumoniae	0.00097
Bacteroides fragilis	4
Clostridium difficile	1
Mycobacterium avium	> 40

Key: MIC = minimum inhibitory concentration; MSSA = methicillin susceptible *S. aureus;* MRSA = methicillin-resistant *S. aureus*.

Source: Shain CS, Amsden GW. Telithromycin: The first of the ketolides. *Ann Pharmacother* 2002; 36:452-464.

first-line agents, including clarithromycin, amoxicillin/clavulanic acid, trovafloxa-cin, and amoxicillin. For penicillin-resistant *S. pneumoniae* (PRSP) and erythromycin-resistant *S. pneumoniae* (ERSP), telithromycin has been found to have superior in vitro activity vs. the macrolides/azalides. Against *H. influenzae*, however, telithromycin appears to have less optimal and more variable activity, especially compared to that of trovafloxacin.

Pharmacokinetics

Absorption:

• Oral bioavailability of telithromycin is 54% in both young and elderly subjects due to an extensive first-pass effect.

• Neither rate nor extent of absorption is affected by food; therefore, it may be taken without regard to food.

Distribution:

• Protein binding of telithromycin has been reported as 60-70%.

• Volume of distribution following intravenous infusion is 2.9 L/kg.

• Telithromycin concentrates in extracellular tissue, as well as in phagocytic cells, specifically bronchial mucosa, epithelial lining fluid, and alveolar macrophages.

• Uptake into extracellular tissue, like the macrolides, is enhanced by inflammation and blunted by the lack of it.

• Pregnancy category C.

Metabolism:

• Liver metabolizes 37% of dose.

• Metabolized to four major metabolites, of which RU 76363 retains antibacterial activity at a level four- to 16-fold less than the parent compound.

• Substrate and inhibitor of CYP3A4.

• Possible competitive inhibitor of CYP2D6.

• Possible interactions with drugs metabolized via CYP1A2.

Elimination:

• 75% feces (unchanged and metabolites).

• 13% excreted unchanged in urine.

• No dosage adjustment for hepatic insufficiency.

• No dosage adjustment for renal insufficiency, although no dose has been established for severe insufficiency (less than 30 mL/min).

• Effect of dialysis has not been studied.

Table 2: Pharmacokinetic profile for telithromycin

Parameter	Day 1 (single dose)	Day 10 (multidose)
A_e (% dose)	11.5 ± 2.7	13.7 ± 4.4
AUC_{0-24} (mg x hr/L)	7.25 ± 2.33	8.4 ± 2.59
Cl_{ren} (0-24 h, L/h)	13.07 ± 1.95	12.9 ± 3.2
C_{max} (mg/L)	1.99 ± 0.84	1.84 ± 1.14
C_{24h} (mg/L)	0.025 ± 0.007	0.046 ± 0.016
$t_{1/2}$ (h)	10.64 ± 2.53	13.4 ± 3.5
t_{max} (h, range)	1.0 (1-2)	2.0 (0.5-3)

Key: A_e = percentage of dose eliminated unchanged in urine; AUC_{0-24} = AUC from time 0-24 hours; Cl_{ren} = renal clearance; C_{max} = peak concentration; C_{24h} = concentration 24 hours post-dose; $t_{1/2}$ = half-life; t_{max} = time to peak concentration.

Source: Shain CS, Amsden GW. Telithromycin: The first of the ketolides. *Ann Pharmacother* 2002; 36:452-464.

Table 3: Dosage and administration of telithromycin

Infection	Daily dose and route of administration	Frequency of administration	Duration of treatment
Acute bacterial exacerbation of chronic bronchitis	800 mg orally	Once daily	5 days
Acute bacterial sinusitis	800 mg orally	Once daily	5 days
Community-acquired pneumonia	800 mg orally	Once daily	7-10 days

Source: Ketek package insert, Aventis Pharmaceuticals.

• Combined hepatic and renal disease likely would require adjustment.

• No dosage adjustment necessary based on age alone.

The pharmacokinetics of telithromycin allow for once-daily dosing due to a longer half-life **(see Table 2)**, which is similar to that of trovafloxacin. Telithromycin exhibits concentration-dependent killing, also more similar to trovafloxacin than the time-dependent killing of the beta-lactams and some macrolides.

Indication and dosage

Telithromycin is indicated for the treatment of the following infections in patients 18 years old and older:

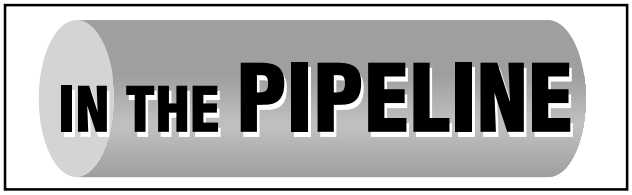
• **Acute bacterial exacerbation of chronic bronchitis (AECB)** due to *Streptococcus pneumoniae, Haemophilus influenzae,* or *Moraxella catarrhalis.*

• **Acute bacterial sinusitis (ABS)** due to *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* or *Staphylococcus aureus*.

• **Community-acquired pneumonia (CAP)** (of mild-to-moderate severity) due to *Streptococcus pneumoniae,* (including multidrug-resistant isolates [MDRSP]), *Haemophilus influenzae, Moraxella catarrhalis, Chlamydophila pneumoniae,* or *Mycoplasma pneumoniae.*

Decreased compliance with medication regimens often is cited as a factor responsible for increasing resistance to current antibiotic therapy.

Telithromycin offers distinct advantages over standard agents, in that the pharmacokinetic profile of telithromycin allows for once-daily dosing (compared to two and three times daily dosing with comparator agents), as well as a shorter duration of treatment (5 days vs. 7-10 days). **Table 3** summarizes the dosage and administration regimens for telithromycin's three indications. *(Editor's note: Part 2 of this evaluation will continue with a discussion of Clinical Trials, Adverse Events, Drug Interactions, Cost, and Recommendation in the September issue of* Drug Criteria & Outcomes.) ■



• Chiron Corp. has initiated a new Phase II study of aldesleukin (Proleukin) interleukin-2 (IL-2) plus rituximab in rituximab-naive patients with **low-grade non-Hodgkin's lymphoma** to determine the combination's potential in patients receiving rituximab for the first time.

• Vertex Pharmaceuticals has initiated a Phase I clinical trial for VX-950, an investigational oral protease inhibitor for the treatment of **hepatitis C virus infection**.

• Aspreva Pharmaceuticals has initiated a global Phase III study of mycophenolate mofetil (CellCept) for **myasthenia gravis**.

• Peninsula Pharmaceuticals has announced that patient enrollment has begun in the fifth pivotal Phase III trial of its lead product candidate, doripenem for injection, in patients with **hospital-acquired pneumonia**.

• Medarex has announced that under the U.S. Orphan Drug Act, the U.S. Food and Drug Administration (FDA) has granted orphan drug designation to Medarex's fully human anti-CTLA-4 antibody, MDX-010, for the treatment of **high-risk Stage II, Stage III, and Stage IV melanoma**.

• Array BioPharma has initiated a Phase I clinical trial for its **small molecule anticancer compound, ARRY-142886 (AZD6244)**.

• Angstrom Pharmaceuticals has initiated a Phase II clinical trial of its proprietary lead product, A6, for the prevention of clinical relapse in patients with **ovarian cancer**.

• Alexion Pharmaceuticals has announced that it and its collaboration partner for pexelizumab,

Procter & Gamble Pharmaceuticals, have received written confirmation from the FDA indicating agreement with the protocols for two independent Phase III trials of the investigational drug. One Phase III protocol covers patients **undergoing coronary artery bypass graft surgery** and the second covers a separate program in patients experiencing **acute myocardial infarction treated with primary percutaneous intervention.**

• Valeant Pharmaceuticals has begun the second of two global Phase III clinical trials for its antiviral compound, Viramidine, a nucleoside (guanosine) analog. The compound is being studied in oral form for the treatment of **chronic hepatitis C in conjunction with a pegylated interferon**.

• CoTherix has begun a Phase II trial of iloprost inhalation solution (Ventavis) in combination with bosentan (Tracleer) in patients with **pulmonary arterial hypertension**.

• InterMune has initiated the DIRECT Trial, a Phase III clinical trial designed to evaluate the safety and efficacy of daily Interferon alfacon-1 (Infergen) in combination with ribavirin for the treatment of patients chronically infected with **hepatitis C virus** (HCV) who have failed to respond to a previous course of therapy with pegylated interferon alfa-2 plus ribavirin.

• Xanthus Life Sciences has initiated Phase I clinical trials for Symadex (formerly C-1311) in patients with **advanced solid tumors**.

• Advanced Magnetics has initiated a Phase III multicenter study for ferumoxytol, the company's investigational intravenous iron replacement therapeutic. The study is a Phase III clinical trial in **anemic chronic kidney disease patients who are on hemodialysis**.

• Pharmacyclics is enrolling patients in a multicenter Phase II clinical trial of motexafin gadolinium (Xcytrin) Injection, the company's lead cancer therapeutic candidate, for the treatment of patients with **recurrent low-grade non-Hodgkin's lymphoma.**

• deCODE genetics has completed enrollment for its 10-week Phase IIa clinical trial of DG031, its developmental compound for the **prevention of heart attack**. The trial is designed to examine the effect of various doses of DG031 on biomarkers such as C-reactive protein and myeloperoxidase and on the production of leukotrienes.

• Therion Biologics Corp. has initiated a Phase III clinical trial for Panvac-VF, Therion's lead vaccine candidate, for the treatment of **metastatic pancreatic cancer in patients who have not responded to treatment with gemcitabine**. ■

CE *Questions*

Pharmacists participate in this continuing education program by reading the article, using the provided references for further research, and studying the CE questions. Participants should select what they believe to be the correct answers.

Participants must complete a post-test and evaluation form provided at the end of each semester (June and December) and return them in the reply envelopes provided. A certificate of completion requires a passing score of 70% or higher. When a passing test and evaluation form are received, a certificate and answer guide will be mailed to the participant.

This CE program will improve participants' ability to:

- **Compare** the clinical efficacy and safety of one therapeutic agent over another used in the same setting.
- **Assess** clinical trial data and explain how the results influence formulary decision making.
- **Perform** cost-effectiveness analyses.

5. Telithromycin is the first of the ketolides, a new class of antibacterial drugs that are derived from macrolide antibiotics.
   A. True
   B. False

6. Compared to the macrolides/azalides, telithromycin appears to have less optimal and more variable activity against:
   A. Penicillin-resistant *S. pneumoniae.*
   B. Erythromycin-resistant *S. pneumoniae.*
   C. *H. influenzae.*
   D. All of the above

7. Telithromycin may interact with drugs metabolized by which of the following isoenzymes?
   A. CYP3A4
   B. CYP2D6
   C. CYP1A2
   D. All of the above

8. Dosage adjustment is necessary in which of the following situations?
   A. For patients with hepatic insufficiency
   B. For patients with renal insufficiency
   C. In elderly patients
   D. None of the above