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Attention turns to VIG as smallpox immunization plan is announced

Expectation for IV formulation is high, but questions remain

Now that the initial phase of President Bush's smallpox vaccination plan is scheduled to be under way, public health officials are scrambling to make sure they have enough supply of vaccinia immune globulin (VIG), the primary product available to treat complications of the smallpox vaccinia vaccination. **(For more information about the secondary treatment, see story, p. 12.)** Here are some important facts to know about VIG:

Facts about VIG

VIG is an isotonic sterile solution of the immunoglobulin fraction of plasma from people vaccinated with vaccinia vaccine. It is available only from the Centers for Disease Control and Prevention (CDC) under Investigational New Drug protocols. **(For information about how VIG will be distributed, see story, p. 12.)**

VIG is effective for the treatment of eczema vaccinatum and some cases of progressive vaccinia. This information is the result of using historic controls and not a randomized controlled trial, says **Inger Damon**, MD, PhD, chief of the poxvirus section of the CDC in Atlanta. VIG also may be useful in the treatment of ocular vaccinia resulting from inadvertent implantation and for severe generalized vaccinia if the patient has a toxic condition or a serious underlying disease, according to the CDC. VIG is contraindicated for vaccinial keratitis because increased scarring can occur. VIG also is not recommended for mild instances of accidental implantation, mild or limited generalized vaccinia, erythema multiforme, or encephalitis post-vaccination.

In some instances, VIG has been given concomitantly with the vaccine to "prevent" complications in a susceptible person. VIG, however, cannot prevent a side effect, says **Marguerite Neill**, MD, associate professor of medicine at Brown University and chair of the bioterrorism work group at the Infectious Diseases Society of America. "You can't give it to a person with eczema before the person gets vaccinated," Neill explains. Instead, VIG halts the progression of the adverse event, unless the individual has an underlying immunodeficiency. The CDC says not enough is known about the efficacy of concomitant administration to recommend its use. Furthermore, there is currently an insufficient amount of intramuscular VIG (IM-VIG) to use prophylactically when the benefits are uncertain.

The plasma used for VIG in the past contained a high titer of anti-vaccinia neutralizing antibody. Because it contained a high proportion of aggregated protein, it was administered intramuscularly as soon as possible after the onset of symptoms in an initial dose of 0.6 mL/kg of body weight, the CDC says. As much as 1-10 mL/kg were used in severe cases of eczema vaccinatum and progressive vaccinia. Because the therapeutic doses of VIG could be large, the product was given in divided doses over a 24- to 36-hour period. Doses could be repeated, usually at intervals of every two to three days, until recovery began. Data from a CDC survey indicate that VIG has been administered at a rate of 47 uses per one million primary vaccinees and two uses per million revaccinees.

The main adverse events have been local pain and tenderness, and swelling and erythema because of the IM injection. "There have been a few allergic or anaphylactic-type reactions following administration of IM or IV human IG preparations," Damon says. "Those are the significant adverse events — which are seen with certain immune globulin injections — that you need to watch for."

Now new lots of intravenous VIG (IV-VIG) are being produced that conform to intravenous standards. The CDC expects that IV-VIG most likely will be administered at a lower dose than the intramuscular preparation. In preliminary studies, IV-VIG appears to be five to 10 times as potent as IM-VIG when tested in animal models.

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Editorial Questions

Questions or comments? Call **Lee Landenberger** at (404) 262-5483.

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In addition, IV-VIG has a low level of aggregated protein, allowing it to be used by either the IM or IV route.

The new formulation will be a significant improvement, Neill says. "By having an IV preparation available, we can give more. So not only is more available to give, but when it needs to be given, particularly for the conditions that take a lot, we can provide it."

The CDC says IV-VIG will require new recommendations for both dosage and preferred method of administration. Not knowing specifics about IV-VIG is a concern to some health care professionals. Of bigger concern, however, is the uncertainty of how people with weak immune systems will react to VIG. People whose immune systems have been weakened by cancer, AIDS, or other diseases are at risk for having complications from the smallpox vaccine and are supposed to be disqualified from the vaccination process.

"There are some good reasons to think that by extensively, systematically, and incredibly carefully screening people, you will weed out [the people with weakened immune systems]," Neill says. But is there a chance a totally healthy-looking person who is immunized might have a condition such as asymptomatic, undiagnosed Hodgkin's disease? "The possibility is there, but the probability is low."

If some of these people do end up being vaccinated and experiencing complications, no one knows for sure how they will react to VIG. This concerns **Jared N. Schwartz**, MD, PhD, FCAP, chair of the College of American Pathologists ad hoc committee on national preparedness. He also is director of pathology and laboratory medicine at Presbyterian Health Care in Charlotte, NC. "[The reaction] would probably depend upon the dose of drugs they were on. We don't know how effective the vaccinia immune globulin would be for these individuals. There are a lot of unknowns."

When routine smallpox vaccination among the American public stopped in 1972, not as many people were being treated with strong immunosuppressive drugs for diseases. The first AIDS cases in the United States had yet to be reported.

Schwartz says that is why a lot of health care experts are anxious about the ramifications of immunizing the general population for smallpox too quickly without a real threat. "There is no specific data for many of these questions," he notes.

The varying VIG stock

Another concern some health care professionals have, including Schwartz, is whether the CDC has a large enough stock of VIG to handle adverse effects of the smallpox vaccination. The CDC says it has sufficient IM-VIG to counter approximately 600-800 adverse events if appropriate recommendations are followed. This is enough VIG to treat the adverse reactions that would be expected to result from the vaccination of four to six million people.

"One of the real concerns relating to VIG right now is that historically, if individuals had reactions to the smallpox vaccinia vaccine, the only treatment at the time [from the 1950s through the 1970s] was to give them vaccinia immune globulin," Schwartz says. "There was a good supply then because the vast majority of the population had been vaccinated. You were able to get blood from individuals and then harvest the immune globulin."

The harvesting stopped, though, when smallpox vaccinations were discontinued. "As a result, the great concern is that if someone had a reaction right now to the vaccine, there are few doses that would be available to help decrease the symptoms," he says.

The CDC has ordered many more doses of IV-VIG and says the future supply should be more than sufficient to meet the need. Canadian drug manufacturer Cangene, for example, has contracted with the CDC to supply 100,000 doses of VIG.

"The VIG available now is adequate for the limited vaccination program presented by the president, which is a stage type of program," explains **John A. Becher**, RPh, chief of the CDC Drug Service. "The contract that we have with Cangene has adequate supplies of the VIG to cover any of the reactions that we statistically have put together and thought might be enough. The contract will be completed by the third quarter of 2003. Half should be done by the second quarter."

The United States may have enough supply for Americans, but what about other countries requesting our help? The *Washington Post* has reported that the Kuwaiti government asked the United States for the smallpox vaccine last summer "in readiness for any eventuality."

"The feeling is that if the United States is concerned enough to begin to immunize its own health care workers and military and within a year possibly make it available to the general

Another treatment option for smallpox reactions

Another drug besides vaccinia immune globulin (VIG) that may be used to treat certain serious smallpox vaccine reactions is the antiviral drug cidofovir (Vistide). Here are some of the facts about cidofovir, as provided by the Centers for Disease Control and Prevention in Atlanta:

- Cidofovir currently is licensed for the treatment of CMV retinitis and has demonstrated antiviral activity against poxviruses in vitro and against cowpox and vaccinia viruses in mice.
- However, its use for the treatment of vaccinia adverse reactions is restricted under an Investigational New Drug (IND) protocol. Under the IND, cidofovir would only be used when VIG was not efficacious.
- Renal toxicity is a known adverse reaction to cidofovir. ■

population, maybe the threat is more real than some people believe," Schwartz says. "Of course, [other countries] want to have access for their own population in case there truly is an outbreak."

One benefit of the new smallpox immunization plan is that public health officials will now have a significant pool of individuals from which to harvest immune globulin. Schwartz continues, "It could then be used when the vaccine might need to be given to a wider portion of the general population." ■

Pharmacists unsure of role in smallpox vaccination

CDC concerned about adverse reaction screening

President Bush has announced a plan to vaccinate millions of Americans against the threat of an attack with smallpox virus. Many pharmacists, however, are not sure of their role in the plan, especially concerning how they should handle any adverse effects from the vaccine.

The first phase of the president's plan includes vaccinating about 500,000 military and civilian personnel in late January who are or may be deployed in high-threat areas, as well as about 500,000 civilian health care and emergency workers. (These numbers may vary because some may choose not to be vaccinated.) In the second phase, up to 10 million "first responders," such as health care workers, police officers, firefighters, and emergency medical technicians, will be offered the vaccine. The government expects about half to end up being vaccinated. The public should be offered the vaccine at a later date on a volunteer basis.

This smallpox vaccination program is going to unfold under and through the authority of state health departments, explains **Marguerite Neill**, MD, associate professor of medicine at Brown University in Providence, RI, and chair of the bioterrorism work group at the Infectious Diseases Society of America in Alexandria, VA. State health departments must develop a vaccination plan that satisfies the framework of the Centers for Disease Control and Prevention (CDC) in Atlanta. For example, they must assure the CDC that the smallpox vaccine is locked up and secure, that the workers giving the vaccinations are trained, and that the health departments have around-the-clock medical coverage.

Once the CDC approves the states' plans, it will send the states a shipment of the vaccine through the national pharmaceutical stockpile. "[The CDC] has the expectation that this is not a plan that is on paper; it is a plan that is ready to go." The state health departments also have to tell the CDC that they are ready to start vaccinating within 30 days of receipt of the vaccine, Neill says.

An overall script has been written for this plan, she continues. The states are given leeway to allow for variances such as size, medical population, and relationships among the hospitals. One state, for example, may vaccinate in the state's clinic; another state may lease the space from an outpatient facility.

A major question about the smallpox vaccination plan is how state health departments will handle adverse events resulting from administration of the vaccine, which is made from a live virus. According to the CDC, historical data show that per million people vaccinated, there might be from 49 to more than 900 serious but not life-threatening events, 14-52 life-threatening adverse events, and one to two deaths.

The CDC promises to monitor the vaccination program closely, to accumulate information about the results, and to make this information available to clinicians and volunteers and then to the public. "We expect that the monitoring of the safety of this vaccine will be exemplary and that we will be taking measures far beyond those which would ordinarily be required for a vaccine program," says **Julie Gerberding**, MD, MPH, director of the CDC.

The CDC has developed software that states can use to keep track of the people they are vaccinating. "This software can be compiled centrally at the state or at the CDC, so that we can really do an overall job of comprehensively tracking people," Gerberding says.

If a serious adverse event occurs, the request for vaccinia immune globulin (VIG), the primary product available to treat complications of the smallpox vaccinia vaccination, must go through an undetermined triage screening process run by the states. VIG has previously only been available through the CDC under Investigational New Drug protocols. "As long as the patient met the criteria under its usage in the investigational new drug product form, the product would be released," says **Inger Damon**, MD, PhD, chief of the poxvirus section of the CDC. **(For more detailed information about VIG, see story, p. 9.)**

Mechanisms are being put into place by which VIG will be available through a particular network so it can get to each of the sites in a timely manner, Neill says. "[The CDC] is probably going to have some regional stockpiles. There will be a control mechanism built into place."

Pharmacists may play a role in requesting VIG, says **Mitchel C. Rothholz**, RPh, vice president for professional practice for the American Pharmaceutical Association in Washington, DC. "It hasn't been clearly stated how people will access it. Based on previous history, the pharmacies will probably be able to get it for physicians who need it."

This often has worked in the past, says **John A. Becher**, RPh, chief of the CDC Drug Service. "Requests for the vaccines and/or immune globulins and drugs have always come through the drug service, initiated by either the health care provider or by the pharmacist."

The president's plan, however, dictates a large number of vaccinations, and Becher fears that some health care providers may have difficulty deciding which adverse effects are really serious and need VIG. "Normally, there are a lot of reactions with this vaccine. If you have a severe or moderately robust reaction, it looks pretty nasty," he says. If these people have intact immune systems, they should survive without their clinicians having to administer VIG. "We have to make sure practitioners and whoever requests it understands that releasing VIG won't really be necessary [in those cases]."

Becher expects that his office will need some assistance in this process. "I have informed the Center that our office is limited and will probably be overwhelmed with the requests for immune globulin for just the screening."

As of late December, the screening process had yet to be set up. To find out the details as they become available, Rothholz advises pharmacists to be in contact with whoever is doing the planning for the smallpox administration clinics in their locality. "Talk to them about what the procedure is locally for getting the immune globulin. They may find that the CDC may be earmarking some for the coordinator." ■

Breast cancer survival improved by 'dense' dosing

Compressing chemotherapy into a two-week "dose-dense" schedule rather than the standard of dosing every three weeks leads to a significant improvement in survival with no increase in toxicity in women with node-positive breast cancer, according to new research.

The study, coordinated by Cancer and Leukemia Group B on behalf of the Breast Intergroup and sponsored by the National Cancer Institute, found a 31% decrease in the death rate with dose-dense chemotherapy administration. The first results of the study were announced at the annual San Antonio Breast Cancer Symposium in December.

"These findings are significant because all the women received the same individual and cumulative dosage of each drug — the only difference

was the interval between chemotherapy treatments — and that one difference is shown to have a positive impact on survival," says **Marc L. Citron**, MD, clinical professor of medicine at Albert Einstein College of Medicine in Bronx, NY, and principal investigator of the study.

The study enrolled 2,005 women with primary breast cancer that had spread to the lymph nodes, with no other metastases. They were randomized postoperatively to one of four treatments. Patients received either a biweekly dose-dense regimen of the adjuvant agent paclitaxel and the chemotherapeutic agents doxorubicin and cyclophosphamide in combination or sequentially, or they received a standard three-weekly moderate-dose regimen of the drugs in combination or sequentially. All patients received equal cumulative doses of the three agents. Tamoxifen was administered post-chemotherapy. Patients in the two-week arm also received filgrastim (Neupogen) to boost their production of infection-fighting white blood cells and combat neutropenia.

After follow-up, researchers found that the dose-dense regimens, either sequential or concurrent, were significantly better than the three-week regimens in improving both disease-free survival and overall survival. Researchers also found that side effects were no more severe among patients on dose-dense regimens than among those on the conventional treatments, and that patients on the dose-dense regimens suffered fewer cases of neutropenia. ▼

Adoption of medication-use technology slow

Adoption of technology into the medication-use system of hospitals and health systems has been slow, even though it could improve patient safety and free pharmacists for more clinical duties, according to the latest installment from the ASHP (American Society of Health-System Pharmacists) National Survey of Pharmacy Practice in Hospital Settings.

Only a small number of survey respondents report having proven safeguards available in their facilities, such as computerized prescriber order entry systems (7%) and bar code technology at the patient's beside (1.5%). Bar codes are used to a greater extent (10%) to verify doses before dispensing. Robotic distribution systems are used in only 8% of hospitals.

A majority of institutions report using point-of-use dispensing devices (58%) in decentralized distribution systems. More than 70% of those devices are linked to the pharmacy computer system.

The survey also found that pharmacists are required to review and approve all medication orders prior to administration in 79% of hospitals. One-fourth of hospitals require pharmacist review and approval of orders written for medical procedures in areas such as labor and delivery, surgery, and radiology.

This entire survey is available in the Jan. 1, 2003, issue of the *American Journal of Health-System Pharmacy*. A summary report containing graphs and charts of the survey data also may be obtained from Eli Lilly by calling (800) 874-2778. ▼

Bush will seek pediatric drug testing legislation

Health and Human Services (HHS) Secretary **Tommy G. Thompson** has announced that HHS will pursue rapid passage of legislation giving the Food and Drug Administration (FDA) authority to require pharmaceutical manufacturers to conduct appropriate pediatric clinical trials on drugs and biologics.

The announcement came as the federal government decided not to appeal an October decision in the U.S. District Court for the District of Columbia, which held that FDA lacks the legal authority to impose certain requirements for pediatric testing on drug manufacturers. That decision has prevented the FDA from enforcing such requirements, which were mandated in final regulations published in 1998 and known as the "pediatric rule." FDA Commissioner **Mark B. McClellan**, MD, says it is better to work with committees in Congress to enact new legislation than to continue with litigation that could take years to reach an uncertain outcome.

Thompson also announced further steps in the implementation of the Best Pharmaceuticals for Children Act (BPCA), which President Bush signed into law in early 2002, including an announcement of the first products to be named

for testing under this Act. The first two drugs to be studied in clinical trials under BPCA will be nitroprusside (Nipride), for the controlled reduction of blood pressure, and lorazepam (Ativan), for the treatment of status epilepticus and for sedation in the pediatric intensive care unit. ▼

FDA cracks down on drug importation

The Food and Drug Administration (FDA) has announced that it is strengthening the controls designed to protect patients by restricting imports of certain prescription drugs that can be used safely only with specified controls in place.

The FDA's action involves adding the drugs to an existing FDA Import Alert, which alerts FDA field personnel to the possible importation of these drugs, provides guidance regarding their detention and refusal of admission into the United States, and advises United States Customs personnel to refer any attempted importation to the local FDA field office.

The drugs added to the Import Alert are:

• **Isotretinoin (Accutane)** — indicated for the treatment of severe recalcitrant nodular acne.

• **Fentanyl citrate (Actiq)** — indicated for the management of severe cancer pain in patients who are tolerant to opioid therapy.

• **Clozapine (Clozaril)** — indicated for the management of severe schizophrenia in patients who fail to respond to standard drug treatments for schizophrenia.

• **Alosetron hydrochloride (Lotronex)** — indicated for the treatment of severe irritable bowel syndrome in women.

• **Mifepristone or RU-486 (Mifiprex)** — indicated for the medical termination of early intrauterine pregnancy.

• **Thalidomide (Thalomid)** — indicated for the acute treatment of the cutaneous manifestations of moderate-to-severe erythema nodosum leprosum.

• **Dofetilide (Tikosyn)** — indicated for the maintenance of normal sinus rhythm in patients with certain cardiac arrhythmias.

• **Bosentan (Tracleer)** — indicated for the treatment of severe pulmonary arterial hypertension.

• **Trovafloxacin mesylate or alatrofloxacin mesylate injection (Trovan)** — an antibiotic administered in inpatient health care settings for the treatment of severe, life-threatening infections.

• **Sodium oxybate (Xyrem)** — indicated for the treatment of cataplexy in patients with narcolepsy.

The FDA also alerted consumers not to buy these drugs over the Internet, because drugs obtained via web sites usually are not accompanied by these safety controls.

Because of the higher risk of these drugs to patients, the FDA took action to curtail further the products' availability from foreign sources, which generally are not FDA-approved. Controls on these drugs include limiting their distribution to specific facilities (such as hospitals), limiting their distribution to physicians with special training or expertise, or requiring certain medical procedures (such as pregnancy testing or blood testing) with their use. ■

IN THE PIPELINE

• AnorMED has initiated a Phase II clinical trial to evaluate the potential of AMD-3100 as a new agent for stem cell transplantation in cancer patients. In this study, AMD-3100 will be given in combination with the standard agent, G-CSF or Neupogen, to patients with **multiple myeloma** and **non-Hodgkin's lymphoma**.

• OncoGenex Technologies and Isis Pharmaceuticals have announced the initiation of a Phase I clinical trial of OGX-011 in patients with **prostate cancer**. OGX-011 is an antisense drug

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being developed to sensitize tumors resistant to existing treatments such as chemotherapy, hormone ablation therapy, and radiation therapy.

• VaxGen has announced that the U.S. Food and Drug Administration (FDA) has designated the company's HIV/AIDS vaccine candidates, AIDSVAX B/B and AIDSVAX B/E (rgp120), fast-track products for prevention of **HIV infection**.

• Millennium Pharmaceuticals has initiated a Phase I clinical trial of MLN1202, a humanized monoclonal antibody that blocks the chemokine receptor CCR2. MLN1202 is being developed as a potential treatment for patients with **rheumatoid arthritis** and possibly other inflammatory diseases.

• Pain Therapeutics has initiated a pilot clinical study of a proprietary drug in patients who suffer from **irritable bowel syndrome**.

• Acologix has initiated a Phase I clinical study of its lead compound AC-100 (Dentonin) to support its primary indication, **osteoporosis**.

• DOV Pharmaceutical has initiated a Phase III clinical trial investigating bicifadine, the company's non-narcotic analgesic, in the treatment of moderate-to-severe **post-surgical dental pain**. ■

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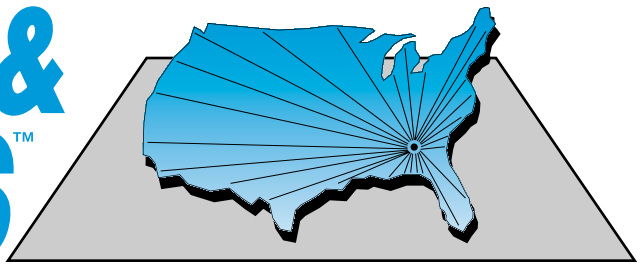

Pulmonary arterial hypertension treatment update: Bosentan (Tracleer) and treprostinil (Remodulin)

By **Abby Guest**, PharmD candidate
Harrison School of Pharmacy
Auburn (AL) University

Pulmonary hypertension is a disease characterized by an increase in blood pressure in the pulmonary artery. High pressure can be defined in one of two ways: pulmonary artery systolic pressure higher than 30 mmHg or pulmonary artery mean pressure higher than 20 mmHg.[1] Pulmonary arterial hypertension (PAH) is a commonly used term that includes both primary pulmonary hypertension (etiology is unknown) and secondary pulmonary hypertension (associated with an etiology such as hypertension secondary to HIV, congenital heart disease, use of appetite suppressants, systemic disease, or connective tissue disorders).

PAH is a progressive disease that with time will lead to higher pulmonary pressure and vascular resistance.[2] PAH very commonly leads to right-sided heart failure and can be fatal within five years of diagnosis.[3] Knowing the fatality of this disease, one can see how important pharmacotherapy becomes with regard to treating PAH. The purpose of this article is to review the standard therapy for PAH as well as to discuss the new therapies that recently have been approved by the U.S. Food and Drug Administration (FDA) for managing this disease state.

Standard therapy for pulmonary arterial hypertension

• **Calcium channel blockers** (CCBs) and anticoagulants are considered a standard of therapy for patients with PAH. Unfortunately, only about 20% of patients respond to vasodilator therapy with calcium channel blockers. To determine who should receive CCBs, patients are exposed to inhaled nitric oxide during a procedure known as the short-acting vasodilator test. If a patient shows a significant response, determined by a decrease in pulmonary artery pressure, calcium channel blockers remain first-line therapy.[4] Long-acting CCBs such as amlodipine (Norvasc), nifedipine (Procardia XL), and diltiazem (Cardia XT) are used most commonly.[5]

• **Anticoagulant therapy** becomes important in patients with PAH due to an increased risk of thromboembolism. Poor pulmonary blood flow, dilated right heart chambers, venous insufficiency, and low physical activity are all risk factors for thromboembolism. Warfarin is used in two-thirds of PAH patients, and has been shown in both retrospective and uncontrolled studies to prolong life when the international normalized ratio is kept between 1.5-2.0.[1]

Because PAH can lead to right-sided heart failure, fluid retention is a common problem seen in these patients, and can be managed with diuretic therapy with an agent such as furosemide (Lasix).[1,6]

New therapies for pulmonary hypertension

Because only about 20% of patients respond to calcium channel blockers, there is a need for alternative therapy in the other 80%. Also, of the original 20% of patients who initially respond to CCBs, the efficacy is maintained in about 75% of patients over five to 10 years.[7] Thus, the majority of patients (80%) used to have no drug therapy options available to manage their PAH. This led to the development of two classes of agents, prostacyclin analogues and endothelin-receptor antagonists, that have revolutionized the treatment of PAH.

Prostacyclin analogues

• **Epoprostenol (Flolan)** is a prostacyclin I_2 analogue that was approved by the Food and Drug Administration (FDA) in 1995 after it was shown to improve patients both clinically and hemodynamically as well as to prolong survival.[8] Epoprostenol stimulates vasodilation of all vascular beds and inhibits platelet aggregation by increasing the level of cyclic adenosine monophosphate, but it is thought that epoprostenol may possess an additional mechanism of action.[9]

Chronically, epoprostenol may provide antiproliferative properties, which would benefit patients by preventing remodeling of the pulmonary artery.[7] Epoprostenol is given as a continuous intravenous infusion starting at 2 ng/kg/min via a central venous catheter, and is titrated in increments of 2 ng/kg until an effective dose is achieved. The dosage range is typically 20-40 ng/kg/min.[6] Once the drug is initiated, it will be infused continuously 24 hr/day for the remainder of the patient's life through a programmable ambulatory pump. This portable pump should be small and light to allow patients to continue with their daily activities. Patients should keep a backup infusion pump and IV infusion set to avoid potential interruptions in drug therapy.

Epoprostenol is temperature-sensitive, so cold gel packs must be replaced next to the infusion pump in the bag every eight to 12 hours to provide constant cooling. It also is light-sensitive, so the drug must be protected from light.[10] Adverse events that occur with more than 10% incidence include flushing, tachycardia, syncope, fever, chills, anxiety, dizziness, headache, nausea, vomiting, jaw pain, tremor, paresthesias, and flu-like symptoms. Other less common adverse events include hypotension, edema, palpitations, insomnia, depression, abdominal pain, constipation, and rash.[9] The annual cost of the drug is estimated to be $60,000-$120,000.[11]

• **Treprostinil (Remodulin)**, another prostacyclin analogue, recently received FDA approval for use in patients with Class II-IV symptoms **(see table, p. 3)** and acts by the same mechanism described above. This agent allows for both symptomatic and hemodynamic improvement, although the results of the six-minute walk test in the study were not statistically significant when compared to placebo.[6] Treprostinil is given as a continuous subcutaneous infusion, with the initial dose starting at 1.25 ng/kg/min. The drug typically is titrated to 20 ng/kg/min. Once treprostinil is initiated, it should be infused without interruption for the remainder of the patient's life via a microinfusion pump. This is a lightweight pump that can be placed in a bag to allow for easy mobilization. Like epoprostonol, patients should keep a backup pump to avoid interruptions in drug therapy. The most common adverse effects include infusion site pain and infusion site reactions, which were experienced by 80% of patients in clinical trials. Other adverse effects include headache, diarrhea, nausea, rash, jaw pain, vasodilation, dizziness, edema, pruritis, and hypotension.[12] The annual estimated cost is $50,000-$90,000.[11]

Endothelin-receptor antagonists

Bosentan (Tracleer) is a dual endothelin-receptor antagonist that is FDA-approved for the treatment of patients with Class III-IV symptoms **(see table, p. 3)** to increase exercise capacity and decrease the rate of clinical deterioration.[10,11] Endothelin recently has been discovered to play a role in the pathogenesis of PAH. Endothelin-1 (ET-1) is a substance that becomes elevated in the plasma and lung tissue in patients with PAH. ET-1 has four main pharmacological actions — vasoconstriction, smooth muscle mitogen, profibrotic effects, and proinflammatory effects — which are mediated through the stimulation of ET_A and ET_B receptors.[4]

Bosentan inhibits the effects of ET-1 by blocking both ET_A and ET_B receptors on the vascular smooth muscle and endothelium. The dose is 62.5 mg PO BID for the first four weeks. If tolerated, the dose should be increased to 125 mg PO BID as a maintenance dose. Bosentan has an 11% incidence of significant elevations in liver transaminases and therefore can be hepatotoxic. Liver function tests should be monitored on a monthly basis. Hemoglobin should be monitored during the first six weeks of therapy due to a possible dose-related decrease. Bosentan is contraindicated in pregnancy, with concurrent glyburide or cyclosporin therapy, and with serum transaminase levels elevated to more than three times the upper limit of normal. Headache is one of the most common side effects and occurs in 16-22% of the population. Other adverse events include nasopharyngitis, flushing, edema, hypotension, palpitations, pruritus, and anemia.[13,14] The cost of bosentan is $2,970 for a one-month supply of either dose ($30,000-$36,000/yr).[11]

Therapy undergoing clinical trials

With the approval of the therapeutic agents already discussed above, more therapeutic

Functional assessment of patients with pulmonary hypertension*	
Class I:	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II:	Patients with pulmonary hypertension resulting in slight limitation of physical activity. These patients are comfortable at rest, but ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III:	Patients with pulmonary hypertension resulting in marked limitation of physical activity. These patients are comfortable at rest, but less than ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV:	Patients with pulmonary hypertension resulting in inability to perform any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may be present at rest, and discomfort is increased by any physical activity

*Executive summary from the World Symposium of Primary Pulmonary Hypertension. Evian, France, Sept. 6-10, 1998.

opportunities are available for PAH patients. Over the past several years, much research has been aimed at developing newer and better agents for management of this disease state. Due to this research, there are numerous ongoing clinical studies involving new therapies for treatment of PAH. Below is a brief summary of several agents currently being investigated.

Other prostacyclin analogues

Iloprost currently is being studied in the AIR study involving patients in class III and IV **(see table, above)**. This is an aerosolized dosage form requiring six to 12 puffs per day.[7]

Beraprost is being evaluated in the ALPHABET study, including patients in class II. This is an oral dosage form that will require QID dosing if approved.[7]

Other endothelin-receptor antagonists

Sitaxsentan currently is being investigated to determine its efficacy in patients with PAH. This agent is different from bosentan in that it is ET_A receptor-specific. Sitaxsentan also is available as an oral dosage form.[4]

BREATHE-2 is investigating the use of combination therapy with epoprostenol and bosentan vs. epoprostenol alone.[4]

BREATHE-3 is another clinical trial involving the use of bosentan in pediatric patients.[4]

Conclusions

From the above updated information, it is evident that much progress is being made with the management of this disease state. Several agents are being studied with the hopes of providing not only more convenient dosage forms but also more efficacious therapeutic agents that are likely to become available in the near future. The introduction of the new therapeutic class of endothelin-receptor antagonists may serve as a cornerstone for the development of other new therapies for PAH. With the approval of bosentan and treprostinil as well as ongoing research for other drugs, new therapies may offer PAH patients hope for having better control of symptoms, decreased morbidity and mortality, and an improved quality of life.

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Sustained-release morphine: An evaluation of three products

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Morphine sulfate is the most widely used opioid analgesic for the treatment of moderate to severe pain. The U.S. market for sustained-release opioids has shown an annual growth of 46% since 1996. However, nearly 85% of patients suffering from chronic pain may still be undertreated. There are various morphine products available to treat moderate-to-severe chronic pain. The following facts are provided to differentiate among three sustained-release products that are currently available.

MS Contin

MS Contin is Huntsville (AL) Hospital's current formulary agent. It is available as 15, 30, 60, 100, and 200 mg tablets. In addition, MS Contin:

- is dosed every 8-12 hours. The 200 mg tablets are reserved for patients who are opioid-tolerant.
- can be titrated to provide appropriate doses for optimum pain control.
- can have decreased peak plasma concentration if administered with a high-fat meal.
- has a CYP2D6 enzyme substrate; half-life of 2-4 hours.
- is associated with adverse reactions, including palpitations, hypotension, bradycardia, nausea/vomiting, constipation, restlessness, and headache.

Kadian

Kadian is a sustained-release morphine formulation for the treatment of moderate-to-severe chronic pain. It is available as 20, 30, 50, 60, and 100 mg capsules. In addition, Kadian:

- is designed for BID to QD dosing, but most often is administered once daily.
- is not bioequivalent to other controlled-release formulations. Conversion from Kadian to the same total daily dose of another product may lead to excess sedation at peak or inadequate analgesia at trough.
- releases morphine significantly more slowly than sustained-release tablets.

Note: Do not chew, crush, or dissolve pellets in the capsules. The contents may be sprinkled on a small amount of applesauce prior to ingestion. Also, do not attempt to administer the pellets through a nasogastric tube.

Avinza

Avinza is the newest sustained-release morphine formulation. It is made of two components: The IR component (10%) rapidly achieves plateau morphine concentrations in plasma, and the ER component (90%) maintains plasma concentrations throughout a 24-hour period. Avinza is available as 30, 60, 90, and 120 mg capsules. The 60, 90, and 120 mg capsules are for use in opioid-tolerant patients. In addition, Avinza:

- is administered once daily, with a maximum daily dose of 1,600 mg.
- is not intended for use as a PRN analgesic.
- is not easily titrated due to IR and ER components.
- has plasma concentrations not affected by food.

The pharmacokinetics of Avinza have not been studied in patients younger than 18 years of age or older than 65 years of age. The capsules should be swallowed whole; the contents should not be chewed, crushed, or dissolved. The contents may be sprinkled on applesauce prior to ingestion.

Conversion from immediate-release morphine to sustained-release morphine:

- Give half the total daily oral morphine dose

every 12 hours.

• Give one-third the total daily oral morphine dose every 8 hours.

• Give the full daily oral morphine dose every 24 hours (for Kadian and Avinza only).

There are no differences in the adverse reaction or drug interaction profiles of MS Contin, Kadian, and Avinza. A randomized, open-label, multicenter, cross-over study comparing Kadian (administered once daily) and MS Contin (administered twice daily) was conducted in cancer patients. Primary efficacy measures that were analyzed were pain scores and patient preference. One hundred thirty-four of 178 patients were randomized to receive at least one dose of study drug and were included in the tolerability analysis. One hundred fourteen patients were randomized to receive at least one dose of Kadian and one dose of MS Contin. These patients were included in the efficacy analysis.

At day one of the study, the median total daily doses were Kadian 100 mg and MS Contin 90 mg. Daily doses at day 10 were Kadian 120 mg and MS Contin 100 mg. The study indicated that Kadian and MS Contin were equally effective in achieving pain control. However, 55% of patients preferred Kadian because it was dosed once daily. Because pain control and patient preference were analyzed at the end of 10 days, the long-term outcomes cannot be assessed. Two other double-blind studies comparing Kadian and MS Contin recently have been conducted. Both medications in these studies were administered twice daily to maintain blinding. Kadian and MS Contin exhibited similar pain control and adverse reaction profiles.

A double-blind, placebo-controlled trial of patients receiving doses of Avinza, MS Contin, or placebo was conducted in 295 patients with osteoarthritis. A total of 184 patients completed the four-week study. Physical functioning was measured weekly during the double-blind portion. An additional open-label portion of this study was conducted for 26 weeks. Eighty-six of 181 patients completed the open-label portion of the study.

At the end of 30 weeks, the study results indicated that there were statistically significant improvements in physical function for patients in the Avinza group. However, Avinza is not easily titrated, and initial effective doses would be difficult to achieve. MS Contin administered in the hospital environment can be titrated to provide optimum pain control. Although the first four weeks of the study were double-blinded and placebo-controlled, the 26-week portion can create open-label associated biases. Another note of interest is that this trial studied the use of Avinza in patients with osteoarthritis. This is a potential weakness because morphine products generally are reserved for patients with more severe pain, such as that experienced by cancer patients.

Although Avinza has proven effective in clinical trials, it is significantly more expensive than MS Contin. Kadian is dosed less frequently than MS Contin, but it is no more effective. Kadian also carries a higher price tag. Because the disadvantages of these two drugs outweigh their advantages, MS Contin should remain on the formulary as the drug of choice in this category. Physician orders for Kadian or Avinza should be interchanged to MS Contin according to the values in the **table, below.**

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Morphine product	Interchange to MS Contin
Kadian 20 mg QD	MS Contin 15 mg BID
Kadian 30 mg QD	MS Contin 15 mg BID
Kadian 50 mg QD	MS Contin 30 mg BID
Kadian 100 mg QD	MS Contin 30 mg TID
Kadian 20 mg BID	MS Contin 15 mg TID
Kadian 30 mg BID	MS Contin 30 mg BID
Kadian 50 mg BID	MS Contin 30 mg TID
Kadian 100 mg BID	MS Contin 100 mg BID
Avinza 30 mg QD	MS Contin 15 mg BID
Avinza 60 mg QD	MS Contin 30 mg BID
Avinza 90 mg QD	MS Contin 30 mg TID
Avinza 120 mg QD	MS Contin 60 mg BID

	Loratadine (Claritin)	Desloratadine (Clarinex)
Mechanism of action	Non-sedating, selective H1-receptor histamine antagonist.	Non-sedating, selective H1-receptor histamine antagonist.
Indications and usage	• Indicated for the relief of symptoms associated with seasonal allergic rhinitis and chronic idiopathic urticaria. • Can be used in patients age 2 years and older.	• Indicated for the relief of seasonal and perennial allergic rhinitis and chronic idiopathic urticaria. • Can be used in patients age 12 years and older.
Available dosage forms	• Tablets: 10 mg • Syrup: 1 mg/mL • Reditabs: 10 mg	• Tablets: 5 mg • Reditabs: 5 mg
Dosage and administration	• ≥ 6 years of age: Recommended starting dose is 10 mg QD. (Children age 2-5 years should take 1 teaspoonful of loratadine syrup QD.) • ≥ 6 years of age with renal or liver impairment: Recommended starting dose of 10 mg QOD. (Children age 2-5 years with renal or liver impairment should take 1 teaspoonful QOD.)	• ≥ 12 years of age: Recommended starting dose is 5 mg QD. • Liver or renal impairment: Recommended starting dose is 5 mg QOD.
Pharmacokinetics	• Rapidly absorbed following oral administration. • Antihistamine effects begin within one to three hours, lasting ≥ 24 hours. • Food increases bioavailability by 40%. • Metabolized to des-carboethoxyloratadine by CYP3A4 and CYP2D6. • Mean half-life of loratadine is 8.4 hours; metabolite half-life is 28 hours. • Eliminated equally in urine and feces.	• Rapidly absorbed following oral administration. • Antihistamine effects within one hour, lasting ≥ 24 hours. • Bioavailability not affected by food or grapefruit juice • Metabolized to 3-hydroxydesloratadine in the liver. • Mean half-life of 27 hours. • Eliminated equally in urine and feces.
Special populations	• Geriatrics (≥ 65 years): Peak plasma levels are 50% greater than in younger subjects. • Renal impairment (CrCl ≤ 30 mL/min): Dosage adjustment is necessary. • Hepatic impairment: Dosage adjustment is necessary.	• Geriatrics (≥ 65 years): Peak plasma levels are 20% greater than in younger subjects. • Renal impairment (CrCl < 70): Dosage adjustment is necessary. • Hepatic impairment: Dosage adjustment is necessary.
Adverse drug reactions (≥2%)	• Headache • Somnolence • Fatigue • Dry mouth	• Sore throat • Dry mouth • Myalgia • Fatigue • Somnolence • Dysmenorrhea
Drug interactions	• Erythromycin increases loratadine and its metabolite's plasma concentrations by 40% and 46%, respectively. • Cimetidine increases loratadine and its metabolite's concentrations by 103% and 6%, respectively. • Ketoconazole increases loratadine and its metabolite's concentrations by 307% and 73%, respectively.	• Erythromycin increases desloratadine and its metabolite's plasma concentrations by 14% and 40%, respectively. • Ketoconazole increases desloratadine and its metabolite's concentrations by 39% and 72%, respectively. • Azithromycin increases desloratadine and its metabolite's concentrations by 5% and 4%, respectively. • Cimetidine increases desloratadine concentration by 19%. • Fluoxetine increases desloratadine's metabolite concentration 13%.
Contraindications	• Contraindicated in patients with hypersensitivity to this medication or its ingredients.	• Contraindicated in patients with hypersensitivity to this medication, its ingredients, or loratadine.
Other information	• Pregnancy category B. • Excreted into breast milk in nursing mothers.	• Pregnancy category C. • Excreted into breast milk in nursing mothers.

Loratadine (Claritin) vs. desloratadine (Clarinex) formulary interchange

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Desloratadine (Clarinex), a major metabolite of loratadine (Claritin), is the newest medication indicated for the treatment of allergic rhinitis. It is often a misconception that new drugs are more beneficial than their predecessors. The information in the **table on p. 6** has been provided in order to clarify the similarities between these two antihistamines.

The safety and efficacy of desloratadine is virtually identical to that of loratadine, the current formulary agent. Although desloratadine is currently less expensive than loratadine, the patent on loratadine expired in December 2002. Therefore, a less expensive, equally effective generic will be available soon. This will likely decrease loratadine's price by 50% or more. It is recommended that loratadine continue as the formulary representative for this drug class. Desloratadine should be interchanged automatically to loratadine as follows: Clarinex 5 mg QD and Clarinex Reditabs 5 mg QD interchanged to Claritin 10 mg QD.

New FDA Approvals

These drugs recently received final approval from the U.S. Food and Drug Administration (FDA):

• *A combination vaccine by SmithKline Beecham Pharmaceuticals that protects against* ***diphtheria***, ***tetanus***, ***pertussis***, ***polio***, *and disease due to the* ***hepatitis B virus*** *(Pediarix).* The FDA has approved this combination vaccine for children. The vaccine (Pediarix) is the only vaccine marketed in the United States that contains DTaP (diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed), hepatitis B vaccine (recombinant), and inactivated poliovirus vaccine (IPV) for administration as one intramuscular injection.

The vaccine is recommended for administration as a three-dose primary series to infants at approximately 2, 4, and 6 months of age. Infants receive nine injections when DTaP, hepatitis B, and IPV vaccines are administered separately in the same time frame. The combination vaccine should not be administered to infants before the age of 6 weeks, and therefore is not indicated for infants born to mothers who are infected with hepatitis B or whose hepatitis B status is unknown. Such infants should receive hepatitis B vaccine shortly after birth and complete their immunization according to a particular schedule.

In clinical trials, the most frequently reported adverse reactions to the vaccine were local injection site reactions (pain, redness, swelling), fever, and fussiness. Fever occurred more frequently after administration of the vaccine than separately administered licensed vaccines.

• *New indication for docetaxel (Taxotere) by Aventis.* The FDA has approved docetaxel (Taxotere) for Injection Concentrate as first-line therapy in combination with cisplatin in patients with unresectable locally advanced or metastatic **non-small cell lung cancer** (NSCLC) who have not received prior chemotherapy. With this approval, docetaxel is the first new treatment option for the first-line treatment of NSCLC patients in more than four years.

Taxotere previously had been approved in the United States to treat patients with locally advanced or metastatic breast cancer after failure of prior chemotherapy, and patients with locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy.

• *New formulation for ciprofloxacin (Cipro) by Bayer Corp.* The FDA has approved ciprofloxacin extended-release tablets (Cipro XR), a new formulation of ciprofloxacin, given once a day over three days, for the treatment of uncomplicated **urinary tract infections** (UTIs) due to susceptible strains of indicated organisms. The new formulation will be marketed at a dosage strength of 500 mg.

Ciprofloxacin extended-release tablets were developed using a bilayer matrix of the active ingredient ciprofloxacin, and enables two different release mechanisms. The first is a rapid release of ciprofloxacin, which distributes to the serum and tissues within hours. This is followed

by a second extended release of the active ingredient to allow sustained levels over 24 hours.

• *New indication for clozapine (Clozaril) by Novartis Pharmaceuticals Corp.* The FDA has approved clozapine (Clozaril) for the treatment of recurrent **suicidal behavior** in patients with schizophrenia or schizoaffective disorder who are at chronic risk. This action by the FDA marks the first time that any medication has been approved for use in treatment of suicidal behavior. Although generic versions of Clozaril are available, FDA regulations provide Novartis with exclusive rights to market the new indication for a period of 36 months.

• *New indication for linezolid injection, tablets, and oral suspension (Zyvox) by Pharmacia Corp.* The FDA has approved the supplemental new drug application of linezolid injection, tablets, and oral suspension (Zyvox) for the treatment of **gram-positive infections** in infants and children, which include complicated skin and skin structure infections and nosocomial (hospital-acquired) pneumonia. The FDA approval also included the treatment of community-acquired pneumonia, uncomplicated skin and skin structure infections, and vancomycin-resistant *Enterococci faecium* in infants and children.

Zyvox was approved for use in adults in the United States in April 2000.

• *New indication for imatinib mesylate (Gleevec) by Novartis.* The FDA has approved imatinib mesylate (Gleevec) for first-line treatment of adult patients with newly diagnosed **Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML)**. Gleevec also is indicated for the treatment of patients with Ph+ CML in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy. In addition, Gleevec received FDA approval in February 2002 for the treatment of patients with Kit (CD 117) positive unresectable (inoperable) and/or metastatic malignant gastrointestinal stromal tumors.

• *New indication for clobetasol propionate (Olux) by Connetics.* The FDA has approved clobetasol propionate (Olux) Foam, 0.05%, to include the short-term topical treatment of mild-to-moderate **plaque-type psoriasis** of non-scalp regions excluding the face and intertriginous areas. Clobetasol propionate previously was approved for the short-term topical treatment of the inflammatory and pruritic manifestations of moderate-to-severe corticosteroid-responsive dermatoses of the scalp including psoriasis.

• *Approval for fluoxetine (Prozac) by Eli Lilly for children and adolescents.* The FDA has approved the antidepressant fluoxetine (Prozac) to treat children and adolescents 7-17 years of age for **depression** (major depressive disorder) and **obsessive-compulsive disorder**. This is the first approval of one of the newer types of antidepressants (selective serotonin reuptake inhibitors, or SSRIs) for treating depression in this population. (Fluoxetine also is approved for major depressive disorder in adults, bulimia, and panic disorder.)

Common side effects associated with use of fluoxetine in children and adolescents were similar to those experienced by adults and include nausea, tiredness, nervousness, dizziness, and difficulty concentrating. One clinical trial in children and adolescents 8-17 years of age showed a slight growth inhibition after 19 weeks of treatment with fluoxetine; Lilly has agreed to conduct a Phase IV postmarketing study to further evaluate any potential impact of fluoxetine on long-term growth in children.

• *Eletriptan hydrobromide (Relpax) by Pfizer. The FDA has approved eletriptan hydrobromide (Relpax) for the acute treatment of migraine.*

In clinical trials involving more than 9,000 patients and more than 70,000 migraine attacks, eletriptan hydrobromide was shown to relieve **migraine pain** and associated symptoms such as nausea and sensitivity to light and sound. Eletriptan hydrobromide was shown to be effective at doses of 20 mg, 40 mg, and 80 mg. The maximum recommended single dose of eletriptan hydrobromide is 40 mg.

The most common side effects reported in clinical trials included fatigue, somnolence, nausea, and dizziness. Eletriptan hydrobromide should not be used by patients with severe hepatic impairment, or those older than 65 years or younger than 18 years. Eletriptan hydrobromide tablets also should not be used within at least 72 hours of potent CYP3A4 inhibitors.

• *New indication for latanoprost ophthalmic solution (Xalatan) by Pharmacia Corp.* The FDA has approved the once-daily prescription eye drop latanoprost ophthalmic solution (Xalatan) as an initial treatment for **elevated eye pressure** associated with open-angle glaucoma or ocular hypertension. Latanoprost ophthalmic solution was introduced in the United States in 1996 as the first prostaglandin-based intraocular pressure-lowering medication. The FDA initially approved the medication for second-line use.