NEW DRUGS

Tablets for Hepatitis B

The Food and Drug Administration (FDA) has approved tenofovir alafenamide tablets (Hepsera™, Gilead Sciences) for patients with chronic hepatitis B, a serious infection that can cause cirrhosis, liver cancer, liver failure, and death. Hepsera™ slows the progression of the infection by interfering with viral replication and causing deoxyribonucleic acid (DNA) chain termination after its incorporation into viral DNA.

The FDA’s approval is based on two randomized, double-blind, placebo-controlled studies. At week 48, 53% of patients in one study and 64% in the other study showed significant improvement in liver inflammation caused by the hepatitis B virus (HBV), compared with 25% and 35% of patients receiving placebo. Patients taking Hepsera™ also showed statistically significant improvement in the degree of liver fibrosis. Hepsera™ has also been shown to be effective in treating patients with clinical evidence of HBV that is resistant to lamivudine, an antiviral agent.

The major adverse events included severe, acute exacerbation of hepatitis B after the drug regimen was discontinued; this result has also been seen with other hepatitis treatments.

Patients who stop taking Hepsera™ should be monitored for hepatic function at regular intervals over a period of time. Kidney toxicity was reported in patients who were at risk for or who had underlying kidney dysfunction. The FDA has noted a theoretical concern that resistance to HIV might emerge in patients who have chronic hepatitis B with unrecognized or untreated HIV infection.

(Source: FDA Talk Paper, September 20, 2002.)

DRUG NEWS

Alteplase: How Low Can a Dose Go?

Alteplase has replaced urokinase as the first choice in restoring blood flow through hemodialysis catheters, but the lowest effective dose has not been established. Reports have documented effectiveness with doses ranging from 2 to 45 mg.

In a retrospective study of 27 patients given alteplase and 10 given urokinase between June 1997 and December 2000, researchers from Grady Health System in Atlanta, found that 1 mg/ml per port of alteplase and 5,000 U per port of urokinase worked equally well. However, patients with alteplase-treated catheters were twice as likely to achieve hemodialysis blood flow rates of greater than 300 ml/minute and were more likely to complete hemodialysis during the session (90% compared with 70%). In addition to the effectiveness of alteplase, the researchers cite its potential cost savings. Using 1 mg rather than 2 mg per port saved approximately $2,000 for the 43 doses of alteplase administered in the study.

(Source: Am J Health Syst Pharm 2002; 59:1437–1440.)

New Weapon Against Bone Marrow Failure

Cytopenia related to bone marrow failure causes roughly 50% of the deaths in patients with myelodysplastic syndromes. Standard supportive care with transfusions and hematopoietic growth factors often fails. Some research has suggested that immune mechanisms might contribute to the cytopenia. That’s why researchers from the National Heart, Lung, and Blood Institute had hoped that its nonrandomized, single-treatment study would add to the data about the benefits of antithymocyte globulin (ATG), which had boosted blood cell counts in earlier, smaller studies.

Their hopes were rewarded when one-third of 61 patients in that study became transfusion-independent within eight months (median response, 10 weeks) after a four-day course of intravenous (IV) infusion. In addition, the treatment was associated with statistically significant longer survival and reduced time to disease progression. Seventeen of the patients who responded to the treatment needed no blood transfusions for a median of 36 months. Fifty percent of 21 patients with severe thrombocytopenia had sustained platelet count increases, and six of 11 patients with severe neutropenia had sustained neutrophil counts of greater than $1 \times 10^9$ cells per liter. Responding patients tended to be younger, with lower platelet counts.

Disease progressed in only one of the 21 responding patients but in 13 of 40 nonresponders. One responding patient, in contrast to 22 nonresponders, died before the end of the study.

(Source: Ann Intern Med 2002;137: 156–163.)

Botulinum Toxin after Stroke

When a stroke leaves a patient with disabling spasticity, botulinum toxin type A (Botox™, Allergan) may help restore enough muscle function to make life easier. In a multicenter trial of 126 patients, those who were given one-time intramuscular injections of botulinum toxin type A experienced greater improvement in flexor tone in the wrist and fingers at all follow-up visits through 12 weeks compared with patients who received placebo. Each patient (or caregiver) chose a principal target of treatment from four areas of disability: hygiene (e.g., ease of cleaning and nail trimming), dressing, limb position, and pain. At week six, 40 of 64 patients given botulinum toxin type A reported improvement in the individual principal target of treatment compared with 17 of 62 in the placebo...
group. No major adverse events were associated with the injection.

The researchers point out that botulinum toxin type A has a localized effect, which minimizes the risk of systemic adverse events.


**Methadone Link to Torsades de Pointes?**

There is some concern that methadone, used in very high doses, might be linked to torsades de pointes, an atypical form of ventricular tachycardia (rapid heartbeat) that can lead to ventricular fibrillation. Methadone is used in the treatment of opioid dependency and pain.

Researchers at Denver Health Medical Center performed a retrospective study of patients in methadone treatment programs in the U.S. and in a pain management center in Canada. The mean daily methadone dose was 397 ± 283 mg. The mean corrected QT interval (QTc) was 615 ± 77 msec. Of the 17 patients who developed torsades de pointes, 14 had a predisposing risk factor for arrhythmia. A pacemaker or cardiac defibrillator was placed in 14 patients; all 17 survived.

A methadone derivative, levacetylmethadol, was withdrawn from the European market after being associated with torsades de pointes, the researchers say, but to date no association has been reported between methadone and the arrhythmia. The investigators have called for further research into their findings, given that methadone treatment is likely to expand into primary care.

(Source: *Ann Intern Med* 2002;137:501-504.)

**Bone Loss with Depo-Provera Is Reversible**

Medroxyprogesterone acetate (Depo-Provera®, Pharmacia), an injectable contraceptive, has been strongly associated with loss of bone density. A study funded by the National Institute of Child Health and Human Development (NICHD), however, has found that the bone loss appears to be largely reversible when the injections are stopped.

Although earlier trials had produced conflicting data on Depo-Provera® and bone density, in many studies bone density had been measured at only one point in time, and only one study examined the effects on bone density when Depo-Provera® therapy was discontinued. In the NICHD study, hip bone and spine bone density measurements of 182 women of reproductive age receiving Depo-Provera® injections were compared with those of 258 women who were not receiving injections. The measurements were taken every six months for up to three years.

The contraceptive users lost 1.12% of hip bone density per year and 0.87% of spine bone density, compared with 0.05% loss and 0.40% gain among nonusers. The researchers estimated that women who use Depo-Provera® continuously for four years would experience bone loss comparable to losses during lactation or menopause.

Women who stopped using Depo-Provera® during the study dramatically gained in bone density, although more slowly at the hip than at the spine. Two-and-one-half years after the injections were discontinued, the average bone density values in previous users were similar to those in nonusers. The only exception was among 18- to 21-year-olds, whose density values continued to lag. The researchers attributed this lag to large deficits in that age group at the beginning of the study.

(Source: National Institutes of Health news release September 6, 2002; *Epidemiology* 2002;13:581-587.)

**Transplantation Safe for Patients with HIV Infection**

Organ transplantation is a safe treatment option for patients with human immunodeficiency virus (HIV) infection who need the operation, conclude researchers who reported their findings at the International Congress of the Transplantation Society. More important, they add, the immunosuppressive drugs used to control organ rejection seem to have little effect on HIV progression.

The advent of new treatments, such as highly active antiretroviral therapies (HAARTs), has meant that HIV patients who have liver disease are living longer—and thus are at risk for end-stage liver failure as a result of the infection or as a result of nephrotoxic drugs. The challenge, the researchers say, lies in finding the right balance between the antirejection drugs and the antiretroviral therapies. Oversuppression of the immune system might allow the HIV infection to worsen, but too low a dose puts the patient at risk for organ rejection.

Researchers at Hahnemann University Hospital in Philadelphia reported that 17 of 20 kidney transplant patients with HIV infection are alive one year after their study, with a very low to undetectable viral load. In one of the 20 patients, graft rejection developed because of an interaction with HAARTs.

In a French study, presented by a researcher from Paul Brousse Hospital in Villejuif, six patients with HIV infection and hepatitis C underwent liver transplantation. One died of liver failure, but the rest are alive more than a year later, with negligible levels of HIV viral load. However, interactions between the antirejection drug tacrolimus and protease inhibitors caused an acute rejection in one patient and toxic levels of tacrolimus in another.

In a study of seven liver and four kidney transplant patients at the University of
Pittsburgh, the researchers observed profound drug interactions between tacrolimus and HAART that included a protease inhibitor. In contrast, regimens that included nucleoside reverse transcriptase inhibitors or non-nucleoside reverse transcriptase inhibitors resulted in less significant effects.

A study conducted at the University of California, San Francisco, found that viral loads have remained undetectable in four liver and 10 kidney transplant recipients. One patient died as a result of a rapid recurrence of the hepatitis virus. The researchers reported no evidence of significant HIV progression and no adverse effects of the virus on organ function.


Shorter Course of Oral Amoxicillin for Childhood Pneumonia

Three days of oral amoxicillin therapy is as effective as five days for children with nonsevere pneumonia, according to the Pakistan Multicentre Amoxicillin Short Course Therapy (MASCOT) Pneumonia Study Group.

The researchers assigned 1,000 children aged two months to 59 months to three days of treatment and 1,000 children to five days of treatment. The therapy succeeded in 791 of the children in the three-day group and in 798 of those in the five-day group. The shorter course offers several advantages, the researchers point out: lower cost, better compliance, better tolerance, and wiser use of antibiotics.

(Source: Lancet 2002;360:835–841.)

Replacement Cells Fight Melanoma

A technique called adoptive transfer—replacing a patient’s immune system with cancer-fighting cells—has shown promise in a National Cancer Institute (NCI) study of 13 patients with metastatic melanoma. Tumors shrank at least 50% in six patients, with no growth or appearance of new tumors. Some cancer growth disappeared in four other patients.

A small fragment of each patient’s melanoma tumor is used to grow T cells in the laboratory. Improvements in the way immune cells are generated in the laboratory and in the way the patient’s body is prepared to receive the cells has led to dramatic results, says Steven A. Rosenberg, MD, PhD, the lead investigator of the NCI study.

“In the past, only a fraction of the cells we injected were able to survive, and they would persist for only a few days,” he explains.

Exposure to the tumor activates the immune cells so that they recognize and attack cells from each specific cancer. The patients were also given high-dose interleukin-2 to stimulate the growth of T cells in the body. Prior to the immunotherapy, chemotherapy was used to deplete the patients’ own immune cells in order to allow the new T cells to repopulate the immune system.

Analysis of the blood and tumor samples showed that the replacement cells could thrive, multiply rapidly, and attack tumor tissue, with T cells activated against the melanoma becoming the major component in the patient’s immune system. Over time, the patient’s old immune system recovered, with a restored ability to fight infections. Only occasional opportunistic infections developed during the treatment. Other side effects were mild, easily controlled autoimmune disorders.

(Source: National Institutes of Health news release, September 19, 2002.)

No Monitoring Needed for Warfarin Alternative

Ximelagatran (Exantra®, AstraZeneca), an oral direct thrombin inhibitor, is an effective change of pace from warfarin, a commonly used anticoagulant, according to a 74-hospital study of 680 patients who had undergone total knee arthroplasty.

After seven to 12 days of treatment, the incidence of venous thromboembolism (measured by central adjudication) was 19% in patients taking ximelagatran and 26% in those taking warfarin. On local assessment, the incidence was 25% with ximelagatran and 34% with warfarin. Major bleeding was rare, affecting only 1.7% of patients taking ximelagatran and 0.9% of those taking warfarin.

Unlike warfarin, ximelagatran does not call for monitoring or dose adjustment. Drug interactions, diet, concomitant disease, and varying metabolisms all influence the utilization of warfarin, the researchers explain. Warfarin also has a delayed onset and does not achieve the target anticoagulant level until at least the third postoperative day—a problem in orthopedic surgery, when thrombosis may start on the first day. Ximelagatran is rapidly absorbed and converted to its active form, melagatran, which acts directly on thrombin and is eliminated unmetabolized through the kidneys.

In fixed doses, ximelagatran produces predictable plasma melagatran concentrations and produces no known food or drug interactions, the researchers say, although plasma concentrations are influenced by renal function and the patient’s weight. Animal studies have indicated that ximelagatran has a wide therapeutic window and increases bleeding only slightly at therapeutic doses.

Because wound healing is a concern when antithrombotic therapy is used, the researchers also analyzed complications at the surgical site but observed no differences between the two groups.

(Source: Ann Intern Med 2002;137: 648–655.)

NEW INDICATION

Irbesartan for Diabetes Complications

The FDA has approved irbesartan...
(Avapro®, Bristol-Myers Squibb and Sanofi-Synthelabo), an angiotensin II receptor blocker, for the treatment of diabetic nephropathy in patients with high blood pressure and type 2 diabetes. Research has shown that the hypertension drug helps to slow kidney disease in patients with diabetes and might be able to delay or prevent dialysis or the need for transplantation.

The Irbesartan Diabetic Nephropathy Trial included 1,715 hypertensive patients with type 2 diabetes and kidney disease. Patients who were given irbesartan had a 20% lower risk of progression of nephropathy or death, compared with patients given placebo, and a 23% lower risk than patients given amlodipine, a calcium channel blocker. Irbesartan therapy, compared with the other two treatments, was also associated with a 23% lower relative risk of end-stage renal disease.

Patients who received irbesartan were more likely to report orthostatic symptoms and to show increases in serum potassium levels more often than the control patients. However, no adverse effects were reported in the trial that had not already been reported with irbesartan in earlier hypertension studies. In the Irbesartan Microalbuminuria Type 2 Diabetes Mellitus in Hypertensive Patients (IRMA 2) trial, a two-year international study of 590 patients, severe adverse events were less frequent with irbesartan (15.4%) than with placebo in addition to other antihypertensive agents (22.8%).

Although the FDA’s Cardiovascular and Renal Drugs Advisory Committee voted 6 to 5 against expanding the drug’s indication to include renal disease, the American Diabetes Association has issued guidelines that recommend angiotensin II receptor blockers such as irbesartan as the initial agent of choice in treating high blood pressure in patients with type 2 diabetes and kidney disease.

(Case 1)

A woman with schizoaffective disorder started on ziprasidone therapy in place of risperidone. She was admitted for altered mental status with reduced level of consciousness, agitation, and disorientation. Her body temperature was 38.5°C (rising to 41.3°C on day three), her blood pressure was 160/100 mm Hg, and her pulse was 112 beats per minute.

Results of a physical examination revealed nothing else remarkable. Laboratory studies, however, told a different story. The patient’s white blood cell count was elevated; her creatinine level was high, peaking at 7 mg/dl on day seven; and her glucose level was 250 mg/dl, spiking to 980 mg/dl a day later. The creatinine kinase level was more than 64,000 U/L during the first week. The tests also showed a seven-fold increase in pancreatic amylase. An abdominal computed tomography (CT) scan revealed pancreatic inflammation.

Ziprasidone and lithium treatments were stopped. Clozapine was stopped and later restarted because of severe psychosis. The patient’s mental status returned to baseline values, and the pancreatitis resolved. After one week of hemodialysis, renal function returned. The severe hyperglycemia was managed with IV insulin; over three weeks, the hyperglycemia gradually improved.

Although the patient never had muscle rigidity, the clinicians say that the rhabdomyolysis, hypertension, and fever suggested neuroleptic malignant syndrome.

(Case 2)

An obese female patient with schizoaffective disorder was switched to ziprasidone in place of one of the older atypical antipsychotics, which are associated with weight gain. She was also taking citalopram for depression. Although the patient did begin to lose weight, however, acute trismus (lockjaw) and painful photophobia developed. The patient reported no headaches and had no history of migraine. The ziprasidone dose was lowered to 60 mg orally twice a day, and oral clonazepam was added. At follow-up a week later, the trismus and photophobia had resolved.

The patient was not taking a triptan, but the reporting physician stated that in vitro studies of ziprasidone have revealed strong antagonism at the serotonin 5-HT_{1D} receptor, which is acted upon by certain antimigraine drugs. Because of this, the physician suggests that it is important to be alert to a possible drug–drug interaction when ziprasidone is used with a triptan.

Case 3

Clinicians described a patient with bipolar disorder type I. After several months of stability as a result of taking a variety of drugs, the patient began to experience symptoms of tardive dyskinesia four months after ziprasidone was added to the regimen. He had had tardive dyskinesia years earlier after long-term treatment with traditional antipsychotics, but his symptoms had been latent, even during a period of treatment with risperidone.

His doctors suggested that ziprasadone might be associated with the re-emergence of tardive dyskinesia, particularly in a patient with several risk factors, such as long-term exposure to traditional neuroleptic agents.