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Hepatitis B

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Liver Transplants for Hepatitis B Improving

Antivirals and hepatitis B immune globulin (HBIG) have markedly improved the success of liver transplantation in hepatitis B patients, according to a report by Mayo Clinic researchers in the August 2004 issue of *Liver Transplantation*.

Before 1990, transplanted hepatitis B patients faced a high rate of recurring infection and liver failure following transplantation. However, after the introduction of HBIG in the early 1990s and of the antiviral lamivudine (Epivir-HBV) in the late 1990s, survival af-

ter liver transplantation improved.

Today, survival between hepatitis-B and non-hepatitis-B liver transplant patients is similar. The introduction of lamivudine increased the one-year and three-year survival in hepatitis-B patients above that of non-hepatitis-B patients (86.5% vs. 78.6% respectively).

“These data underscore the importance of therapeutic innovations that have occurred incrementally in the past two decades for hepatitis B virus and support orthotopic liver transplantation as an appropriate treatment for patients with acute and chronic hepatic insufficiency or hepatocellular carcinoma from hepatitis B virus,” the study’s authors wrote.

Interferon Alpha Ineffective against Lamivudine-Resistant Hepatitis B

Researchers from Istanbul University found interferon alpha to be of little help when administered to hepatitis B patients who had developed hepatitis B virus (HBV) resistant to the antiviral lamivudine.

The researchers followed six patients who had been treated long-term with lamivudine. While initially effective, over time some HBV with mutations were able to resist lamivudine’s antiviral

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effects and viral load (HBV DNA) and alanine aminotransferase (ALT) levels begin to rise again.

Writing in the July 2004 issue of the *International Journal of Clinical Practice*, researchers reported they continued to treat the patients with lamivudine, but also added standard alpha interferon-2b for six months.

Despite the combination treatment, only one patient experienced undetectable HBV DNA and normal ALTs by the end of the treatment.

Lamivudine Has Limited Success against HBeAg-Negative Hepatitis B

Researchers followed 94 HBeAg-negative patients in Italy who were treated with lamivudine over a four-year period to evaluate lamivudine’s effectiveness in this population.

Initially, about 90% of patients responded to lamivudine with lowered viral load and ALT levels during the first 12 months of treatment. However, patients quickly developed viral resistance to lamivudine. By the fourth year, only 39% were experiencing any response to lamivudine, wrote researchers in the August 2004 issue of *Alimentary Pharmacology & Therapeutics*.

YMDD mutations in HBV, which are able to replicate despite lamivudine, occurred quickly in this group. However, researchers were surprised to find that 17.5% of patients who stopped responding to lamivudine did not develop the YMDD mutation. There were other viral mutations that apparently allowed this population to resist lamivudine.

“Neither response nor resistance to lamivudine could be predicted at baseline from the virological structure of the precore/core-promoter regions (of the virus), which were not different in patients who responded, did not respond or experienced a viral breakthrough,” researchers wrote.

While lamivudine

proved to have only short-lived success against HBeAg-negative hepatitis B, no patient experienced any severe or life-threatening ALT flares from lamivudine’s diminishing treatment impact over the four-year study. However, 7.4% of patients developed liver cancer.

No New Viral Strains Appear to Occur During Hepatitis B “Flares”

Taiwanese researchers compared the strains of HBV in the liver and in the bloodstream of people with chronic hepatitis B who developed increased HBV DNA and increases in ALTs before and during these “acute” exacerbations.

Writing in the August 2004 issue of *Hepatology*, they reported that they examined the HBV genome and looked for viral quasispecies in 11 patients with hepatitis B exacerbation.

They found the viral strain in the blood and

in the liver to be identical overall. “Random reactivation of the original HBV pool, rather than a sequential evolution of one strain, also contributes to the onset of repeated acute exacerbations,” they wrote.

One in 34,000 Tissue Donors Infected with Hepatitis B

Researchers, writing in the August 2004 issue of the *New England Journal of Medicine*, examined 11,391 samples at five tissue banks in the United States to find out what percentage of tissue donors carried undetected hepatitis B, hepatitis C, HIV and human T-lymphotropic (HTLV) viruses.

They compared this data to infection rates among first-time blood donors in order to estimate infection rates among tissue donors.

The prevalence of confirmed positive tests among tissue donors was 0.229 % for

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the hepatitis B surface antigen (HBsAg). The incidence rate for hepatitis B was estimated to be 18.325 per 100,000 person-years. The estimated probability of hepatitis B infection at the time of tissue donation was one in 34,000. In contrast, the probability of HIV infection was one in 55,000 donors and for hepatitis C it was one in 42,000 donors.

Researchers concluded that the prevalence rates of hepatitis B, hepatitis C, HIV, and HTLV infections are lower among tissue donors than in the general population. “However,” they added, “the estimated probability of undetected viremia at the time of tissue donation is higher among tissue donors than among first-time blood donors.”

Researchers recommend the addition of highly refined nucleic acid–amplification testing to the screening of tissue donors to reduce the risk of these infections among recipients of donated tissues.

No Link Found Between Hepatitis B Vaccine at Birth and Neonatal Death Rate

Researchers, writing in the July 2004 issue of the *Pediatric Infectious Disease Journal*, found no increased death rate among newborns immunized against hepatitis B, compared to those who were not vaccinated.

There have been unsubstantiated reports of increased death rates among vaccinated newborns, which has fueled the anti-vaccine movement in the United States and abroad.

Researchers tracked 350,000 live births in California between 1993 and 1998 and identified any infant deaths that occurred within 29 days after birth. They compared the proportions of deaths among birth HBV-vaccinated and unvaccinated newborns and reviewed the causes and circumstances of their deaths.

There were 1,363 neo-

natal deaths during the study period. While 67% of the 350,000 received HBV at birth, only 5% of the neonates who died were HBV-vaccinated at birth.

“We found no significant difference in the proportion of HBV-vaccinated (31%) and unvaccinated (35%) neonates dying of unexpected causes,” they wrote. “Further we could not identify a plausible causal or temporal relationship between HBV vaccine administration and death for the 22 vaccinated neonates who died unexpectedly.”

Lymphocytes Blamed when HBV Vaccine Isn’t Effective

Venezuelan researchers, writing in the August 2004 issue of *Virology*, say impaired lymphocytes may be the culprit in the 4 to 10% of people who do not develop immunity following hepatitis B immunization.

Lymphocytes are white blood cells that play an important role in the immune system’s production of antibodies. Researchers found that lymphocytes that lacked cytokines, which helped them identify antigens, were common among people who did not develop adequate immunity to hepatitis B after immunization.

How Long Are Children Protected when Vaccinated at Birth?

Researchers, writing in the July 2004 issue of the *Pediatric Infectious Disease Journal*, investigated how long children, who were immunized at birth against hepatitis B, remained immune. They discovered many lose immunity and may require an HBV booster during adolescence when sexual activity increases infection risk.

Researchers found hepatitis B antibodies

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disappeared by age 5 in most children who were vaccinated from birth. Although most children showed immunologic memory (the ability to quickly create antibodies to stave off infection), one-third of them failed to demonstrate an adequate antibody response to a booster dose.

“Our data suggest that one-fourth of children who responded to a plasma-derived hepatitis B vaccine in infancy lost protective antibody by early adolescence and did not show evidence of anamnestic response to a booster dose,” they wrote, “although the small number of participants makes it difficult to draw precise conclusions.”

The lack of an antibody response does not necessarily mean the children are not protected against HBV. The long incubation period of four to eight weeks for HBV could allow time for immune memory to prevent acute illness or chronic carriage while not preventing active infection.

“It will be very important to follow children into adolescence and early adulthood for evidence of clinically significant breakthrough infections indicating a possible need for routine booster doses,” they concluded. “Also additional long term follow-up studies at school entry and adolescence, including ones evaluating the effects of a booster dose at these times, will be necessary for low risk children initially vaccinated for hepatitis B starting at birth.”

Vaccine Booster Needed after Chemotherapy in Children

Children who have undergone chemotherapy may lose their antibody protection acquired from past immunizations. Italian researchers, reporting in the August issue of *Cancer*, suggest these childhood cancer survivors may need a hepatitis B booster.

Researchers from the University of Padua assessed the persistence

of vaccine-acquired immunity to hepatitis B, measles, mumps, rubella, tetanus, and polio in 192 children following chemotherapy for malignancies including acute lymphoblastic leukemia and Hodgkin's lymphoma.

About 46% of children lacked antibody protection for hepatitis B. Corresponding proportions for measles, mumps, and rubella were 25%, 28%, and 24%. About 14% of the children also lacked protective antibodies to tetanus and 7% lacked polio antibodies.

Among children who had immunity before chemotherapy, 52% lost immunity to hepatitis B. However, protection was regained when the children were given hepatitis B boosters.

Researchers recommend administering an HBV vaccine booster dose 12 months after chemotherapy as a simple and cost-effective way to restore immunity.

Hepatitis B Cited in Children's High Liver Cancer Rate in South Africa

Researchers, studying the unusually high rate of liver cancer and tumors in South African children, found two-thirds of children with liver cancer (hepatocellular carcinoma or HCC) tested positive for the hepatitis B surface antigen (HBsAg).

Writing in the June 2004 issue of *Cancer*, the team of South African researchers screened 194 children, up to age 14, who had malignant liver cancer and tumors. One hundred twelve tumors (57%) were hepatoblastoma, and 68 tumors (35%) were HCC.

Two-thirds of patients with HCC tested positive for the hepatitis B surface antigen (HBsAg). The mean age of onset was 1.47 years for hepatitis B and 10.48 years for

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liver cancer.

The researchers recommend a comprehensive effort to diagnosis and treat children at risk of liver cancer.

Hepatitis B Reactivates in Influximab-Treated Crohn's Disease Patients

Patients with Crohn's disease who also have hepatitis B experience an exacerbation of hepatitis B, including increased viral load and liver damage, when treated with the immunosuppressant drug infliximab. Currently, there are no guidelines that recommend screening or special care for hepatitis B-infected patients treated for Crohn's disease.

A team of Spanish researchers evaluated 80 Crohn's disease patients treated with infliximab, three of whom had chronic hepatitis B. Two of the patients experienced severe reactivation of hepatitis B after withdrawal of infliximab

therapy, and one died.

A third patient, who was treated with lamivudine at the time of infliximab therapy, had no clinical or biochemical worsening of liver disease during or after therapy.

The researchers, writing in the September 2004 issue of *Gut*, recommend that Crohn's disease patients who are candidates for infliximab therapy should be tested for hepatitis B before treatment and considered for antiviral therapy if they test positive.

HBV-Infected Patients with Liver Iron Deposits Fare Worse

Researchers in Brazil studied 81 hepatitis B-infected men who had no signs of cirrhosis to see what impact elevated iron levels had on their livers. Researchers have suspected that high iron levels accelerate liver disease in those infected with hepatitis B.

Writing in the Septem-

ber 2004 issue of the *Journal of Gastroenterology and Hepatology*, the researchers reported that patients with liver iron deposits, who constituted about half of their HBV-infected study group, exhibited significantly higher rates of liver damage than those without iron deposits.

The researchers also looked for any unique mutations in the iron deposits, but they found no difference in the prevalence of these mutations in HBV-infected patients and the general population. They concluded that liver iron deposits were frequent in non-cirrhotic HBV patients and that they were associated with higher activity and severity of liver disease.

Chinese Researchers Find Biomarker for HBV-Related Cirrhosis

Researchers, looking for a simple way to diagnose cirrhosis without an invasive liver biopsy, may have

found a way to make a cirrhosis diagnosis possible through a simple blood test.

Writing in the August 2004 issue of the *World Journal of Gastroenterology*, the team reported using "surface enhanced laser desorption/ionization time-of-flight (SELDI-TOF) mass spectrometry" to discover biomarkers in 25 patients with hepatitis B-induced cirrhosis. The test found no cirrhosis in 25 uninfected, healthy patients.

Two biomarkers were detected in blood of healthy men, but were absent in patients with HBV-induced cirrhosis. The test had a success rate of 80%. If found to be reliable, the tests would be a valuable tool for diagnosing cirrhosis and monitoring the progression of liver disease.

Multicenter Phase 2 Trial of Remofovir Begins

Metabasis Therapeutics Inc. has begun a multicenter, multinational

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Phase 2 study to evaluate the oral antiviral compound remofovir mesylate in patients with chronic hepatitis B.

Remofovir was developed using HepDirect technology, a liver-targeting drug technology that was recently described in a *Journal of the American Chemical Society* article. A prodrug is a drug that has been chemically modified to remain inactive until enzymes in the body convert it to its active form. In the case of a HepDirect prodrug, the enzyme that converts it to an active form is found primarily in the liver.

Remofovir is a HepDirect prodrug made of the antiviral adefovir (Hepsera). Hepsera is converted to the active form primarily in blood, while remofovir becomes active in the liver where HBV resides.

“We expect this new clinical trial to build on the pre-clinical and clinical results we have seen to date with remofovir,” said Dr. Paul Laikind, Metabasis’

chairman, president and CEO. “Valeant submitted an abstract to the American Association for the Study of Liver Diseases (AASLD) describing the safety, tolerance, pharmacokinetic and pharmacodynamic results from a recently completed clinical trial of remofovir in patients infected with hepatitis B virus. The findings from that trial led to the decision to proceed with the Phase 2 study.”

This new study is designed to assess the maximally effective dose of remofovir for the Phase 3 studies, which could begin next year. The Phase 2 study is an open-label, randomized, multiple oral dose study that will enroll 220 patients worldwide. The study consists of five groups treated with remofovir at 5, 10, 20 and 30 mg/day doses, and adefovir (Hepsera) at 10 mg/day. Treatment duration will be 48 weeks and an interim analysis will be conducted after 24 weeks of dosing to evaluate drug safety and efficacy.

Valtorcitabine (LdC) and Telbivudine May Be Potent Combo against HBV

Current treatments for chronic hepatitis B are able to lower serum HBV DNA levels by 1,000- to 10,000-fold and to normalize ALT in 60 to 70% of patients after one year of treatment. Idenix Pharmaceuticals is investigating using two of its antiviral drugs – telbivudine and valtorcitabine – to treat patients who require a more potent antiviral combination.

Telbivudine, in Phase III clinical trials, has demonstrated HBV DNA suppression greater than 1,000,000-fold and ALT normalization in 86% of patients after one year of treatment. Valtorcitabine is an HBV-specific L-nucleoside (val-LdC) that is similar to telbivudine and inhibits HBV replication.

Animal studies using the combination sug-

gest greater viral suppression compared to either agent alone, and further suggested that the combination of telbivudine and valtorcitabine was more active than the combination of telbivudine and lamivudine.

At four weeks, valtorcitabine resulted in an HBV DNA decrease of 100-fold copies/mL, compared to no change in the placebo group. This phase I/II dose-escalation trial is currently evaluating higher doses of valtorcitabine, up to 1,200 mg/day. Presentation of the final results of this trial are anticipated at the AASLD in November.

Physicians and Friends Play Key Roles in HBV Vaccine Decision

Researchers surveyed STD clients, who are at high risk of hepatitis B, to find out what motivated them to get vaccinated against this

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sexually-transmitted infection. Writing in the July 2004 issue of *Sexually Transmitted Diseases*, the researchers interviewed clients before they were treated for an STD and offered the vaccine, and after.

They found that half of the clients elected to receive an HBV vaccine during the visit. The factors that played a role in a client's acceptance of the vaccine included having a friend who had been vaccinated, the perceived health benefits of the vaccine, and the clinician's recommendation.

Knowledge about hepatitis B and its health risks did not affect the clients' decision to be vaccinated. Some patients expressed concern about vaccine safety and questioned why the doctor was promoting it.

The researchers concluded that friends and physicians play an important role in the decision to be vaccinated. They also noted that mistrust of the medical community and of vaccines remained barriers to acceptance.

Simultaneous HBV DNA and Genotype Test under Development

Thai researchers have developed a real-time method to simultaneously measure HBV DNA and identify the genotype of hepatitis B. Writing in the September 2004 issue of the *Journal of Virological Methods*, the researchers from Chulalongkorn University described their development of a rapid and sensitive method for simultaneous HBV DNA measurement as well as a test that would distinguish between HBV genotypes B and C, which are the predominant HBV genotypes in Southeast Asia. The test is a single-step reaction by real-time PCR and melting curve analysis using SYBR Green I fluorescent dye.

The genotypes were compared with those examined by PCR-RFLP and direct sequencing on 52 blood samples of patients with chronic hepatitis B. Using the results obtained by direct se-

quencing and phylogenetic analysis, the accuracy of their genotyping by PCR-RFLP and melting curve analysis was 90.38% and 92.31% respectively.

HBV DNA measurement levels were similarly accurate in hepatitis B patients with cirrhosis and liver cancer.

This method has the advantage of speed, reproducibility and accuracy, which is attractive for large-scale analysis in regions where HBV genotypes B and C predominate, researchers concluded.

HBV Genotype E Reported in India for First Time

Senior Lecturer of the Department of Biochemistry at Kurukshetra University, Dr Jasbir Singh reported finding HBV genotype E for the first time in India. Historically, genotype E has been documented primarily in the western region of Africa.

Previously, only geno-

types A, C and D were reported in India. About 387 million people worldwide are infected with HBV, of whom 42 million live in India.

T-Cell Response Critical when Hepatitis B Therapy Ends

Researchers, studying the immune response of hepatitis B patients treated with overlapping lamivudine and interferon alpha therapies, say it is what happens when treatment ends that dictates success or failure of treatment.

Writing in the August 2004 issue of *Liver International*, researchers reported that they studied the T-cell response in 16 hepatitis B patients treated with interferon and antiviral drugs. A short-lived hepatitis B core antigen (HBcAg)-specific immune response was detected in four of five patients who achieved undetectable HBV DNA at end of the combination therapy.

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However, these patients reverted to pre-treatment HBV DNA levels after treatment stopped.

In contrast, no significant T-cell response was detected in eight patients who failed to achieve notable HBV DNA suppression, as well as in three patients who experienced no HBV DNA rebound after therapy discontinuation.

The researchers suggest that a return of viral replication after treatment stops is driven by the patient's immune response to HBV. They encourage more study into what happens in the immune system when treatment stops to determine successful treatments.

Parents Discussing STDs with Kids, but Not Hepatitis B

A national survey conducted by the Society

for Adolescent Medicine (SAM) found 84% of parents of high school-bound teens did not believe their children were sexually active.

Meanwhile, a Centers for Disease Control and Prevention (CDC) study showed that almost half of high school students have had sex, suggesting that parents may be hesitant to acknowledge that their teen could be sexually active and exposed to harmful diseases.

To help raise awareness about the importance of adolescent sexual health, the society is launching a national campaign to educate parents on how to protect their teens from various health risks including hepatitis B.

“Hepatitis B, a highly contagious disease, is one of the diseases high schoolers could be exposed to through sexual contact, tattooing, body piercings, or contact sports,” said Dr. Leslie Walker, director of the Section for Adolescent Medicine at Georgetown University Hospital, Washington, D.C. “While routine vaccination for hepatitis B

for infants has occurred since 1991, many teens born prior to this date may have been missed. As such, SAM recommends that all teens be vaccinated against hepatitis B to catch up and ensure they are protected.”

The survey also found that three out of four parents reportedly had personally discussed sexually transmitted infections with their teens. Not surprisingly, HIV/AIDS was the most common theme in those discussions. While it is good news that parents discussed sexually transmitted infections with their adolescents, more than half did not talk about hepatitis B, a disease that can be 100 times more contagious than HIV.

