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Hepatitis B

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Milk Thistle's Potent, Anti-cancer Powers Confirmed by New Research

In one of the first scientific studies of its kind, University of California Irvine Medical Center researchers have confirmed that silibinin, a highly purified extract from milk thistle, is effective in preventing or combating liver cancer.

Milk thistle, which has been used as an herbal supplement for decades to prevent liver damage, cirrhosis and cancer from viral hepatitis, alcohol abuse, and toxins, was found to signifi-

cantly reduce the growth of liver cancer cells by:

- Curbing cancer cell proliferation
- Altering the DNA structure of the cancer cells
- And enhancing the “programmed” death of cancer cells.

The research results, published in the October 2007 issue of the *World Journal of Gastroenterology*, indicate that silibinin can be used to prevent the development of liver cancer, one of the most common cancers worldwide that can result from long-term infection with the hepatitis B virus (HBV). Researchers encouraged more testing and research into

milk thistle's cancer preventive powers.

Primary Care Physicians Fail to Screen for and Treat Hepatitis B Properly

Two studies presented at the 58th annual meeting of the American Association for the Study of Liver Disease (AASLD) in Boston highlighted the failure of primary care physicians to adequately screen patients born in HBV-endemic regions, and to follow recommended clinical guidelines when treating HBV-infected patients.

In a study of New York City clinicians, researchers

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monitored how 18,457 patients (ages 19-49), who visited primary care clinics in the South Manhattan Network during 2005-2006, were screened for HBV infections. The patients included Asian/Pacific Islanders-APIs (26.1%), African-Americans (12.7%), Hispanics (42.3%), Native Americans (0.2%), and Caucasians (7%). About 70% of those screened were foreign-born.

Among the patients, 42.4% were screened for the hepatitis B surface antigen (HBsAg), which indicates an active infection, and 71.8% of people with elevated alanine transaminase (ALT) levels were screened for HBsAg compared to 49.6% of those with normal ALTs. Above normal ALT levels indicate liver damage.

The screening rate was greatest for those 19-29 years of age (48%) and lowest among the older ages 45-49 (34.4%). Women were slightly more likely to be tested than men (43.4% vs. 41.3%). A higher rate of APIs were screened (65.6%) than African-Americans (38.8%), Hispanics (33.4%), Caucasians (32.1%),

and Native Americans (28.3%).

Among patients born in regions with high HBV infection rates, those born in East Asian countries had the highest screening rate (63.6%) followed by Southeast Asia (50.3%), and Africa (44.1%). Patients born in regions of intermediate HBV infection rates (Eastern Europe, South Asia, Middle East, Central America, South America, and the Caribbean) had screening rates of 40.1%, similar to American-born patients (39.5%).

The screening rates varied greatly between clinics and were highest at clinics that served many APIs, and lowest (11.8%) at a clinic that served primarily Hispanics.

Screening occurred most frequently in younger patients of Asian birth who had elevated ALT levels. However, nearly half of patients from countries where HBV infection is high, and for whom screening is recommended by the U.S. Centers for Disease Control and Prevention, had not been tested.

“More rigorous efforts will be necessary to increase compliance

for HBV screening in this group of patients in order to decrease long-term morbidity and mortality,” researchers wrote.

In a second report that examined the same health network, researchers followed what happened to the 893 patients, mostly APIs (84%), who tested positive for HBsAg. About 98% of HBV-infected persons were tested for ALT, 71% for the hepatitis B “e” antigen (HBeAg), 68.2% for viral load (HBV DNA), and 63.6% for alpha fetoprotein (AFP), which can identify liver cancer. One-third of patients received an abdominal ultrasound exam, 9.9% had a CT scan, and 0.6% had a MRI.

Of the patients, 564 (63.2%) were tested for HBeAg, viral load, and had ALT measured, and 306 patients (34.3%) had all three measurements and an ultrasound exam. About 83% of those with abnormal ALTs had HBeAg and viral load tests, higher than 58.5% among those with normal ALTs.

Monitoring did not differ by patient gender, race, age or country of birth. Patients at hospital facilities were

more likely to receive the minimum adequate valuation (68.6%), compared to patients at community clinics (45.5%).

Researchers concluded that, “...management of patients with chronic HBV infection by primary care physicians in this study was suboptimal according to practice guidelines established by the AASLD. Additional education and training of primary care physicians in the proper management of these patients needs to be implemented and evaluated in order to decrease the long-term morbidity and mortality of persons chronically infected with HBV.”

Entecavir Produces Dramatic Drop in HBV DNA and Remains Effective, with Little Viral Resistance, for Years

A four-year study of the antiviral entecavir (Baraclude) found that the drug remained effective in suppressing viral replication over four years, and eventually even proved effective for patients who

did not respond well during the first year of treatment, according to two studies presented at the AASLD conference.

During the first year of the study, fewer than 5% (30 of 679) of patients did not respond, but continued to take the antiviral. Researchers continued to monitor 21 of the nonresponders over four years and found that eventually 15 of the 21 initial nonresponders achieved low to undetectable HBV DNA and 86 percent achieved normal ALT levels.

Four patients from the larger group who experienced resurgence of HBV DNA and elevated ALT levels over time did not have an HBV rebound because of viral resistance to entecavir.

The second study focused on HBeAg-positive patients who had never been treated. In this study, 91% of patients who received entecavir over four years achieved undetectable HBV-DNA levels, and 95% had normal ALT levels. Patients continued to lose HBeAg and develop antibodies to HBeAg (seroconversion) dur-

ing the study's third and fourth year.

The study is important in that many patients may require years of antiviral treatment. For physicians worried about resistance, this research puts entecavir at the top of the list of U.S. Food and Drug Administration-approved antivirals.

Tenofovir Significantly More Effective Than Adefovir

Two head-to-head studies found that the antiviral drug tenofovir is significantly more effective than adefovir (Hepsera) against hepatitis B after 48 weeks of treatment, which may lead the antiviral to become the first-line of treatment for hepatitis B.

In one study of HBeAg-negative patients with elevated ALT levels, 92% experienced declines in HBV DNA to low or undetectable levels, compared to 59% of adefovir-treated patients.

A second study of HBeAg-positive patients with elevated ALT levels, 74% of participants in the teno-

fovir group achieved undetectable HBV DNA compared to just 23% of adefovir-treated patients.

While participants in the two tenofovir groups had significant reductions in HBV DNA, their improvements in liver health and ALT levels were not statistically significant from the adefovir groups.

The results of the two studies have been included in Gilead's application in Europe and the U.S. FDA to market tenofovir as an HBV treatment. Currently, the FDA has approved tenofovir for HIV treatment only.

Hepatitis B Expert Reviews the Latest Treatment and Antiviral Developments

Emmet B. Keeffe, MD, MACP, a professor at Stanford University School of Medicine and co-director of the Liver Transplant Program at Stanford University Medical Center, reviewed the latest insights about antiviral treatment of hepatitis B derived from the AASLD conference, in an interview

published recently in *Medscape Gastroenterology*. Below are his insights into recent hepatitis B treatment developments.

Who needs treatment: HBeAg-positive and HBeAg-negative patients are both candidates for therapy if their ALT levels exceed 19 U/L in women and 30 U/L in men. Patients with HBeAg-positive chronic hepatitis B should receive treatment when HBV DNA levels are greater than or equal to 20,000 IU/mL and ALT levels are elevated, especially if they are twice normal.

Patients with HBeAg-negative chronic hepatitis B should receive treatment when HBV DNA levels are greater than or equal to 2,000 IU/mL and ALT levels are elevated. Some patients with borderline serum HBV DNA and ALT levels may be difficult to categorize and sequential and frequent laboratory testing or a liver biopsy may be necessary to properly classify them.

Goal of therapy: The goal of treatment is long-term suppression of viral load, which is believed to slow liver

damage and prevent cancer. HBeAg-positive patients are also treated to increase chances of losing HBeAg and seroconverting. Patients with HBeAg-negative chronic hepatitis B are treated long-term with the goal of suppression of HBV DNA, as relapse is common if treatment is stopped after HBV DNA becomes undetectable.

Which medication should be used?

Pegylated interferon produces a higher rate of HBsAg loss, has a fixed treatment duration, and no drug resistance. The disadvantages are it must be injected and has side effects, including depression. Genotyping may be useful because this therapy has been shown to be more effective in patients with genotype A.

The preferred FDA-approved antivirals include adefovir, entecavir, and, potentially telbivudine (Tyzeka)—but only if HBV DNA is undetectable after 24 weeks of treatment, which predicts a low rate of viral resistance after two years of therapy. Lamivudine (Epivir-HBV) is not recommended because of its high rates of viral

resistance (70% after 5 years).

How to avoid drug resistance?

It is important that physicians and patients select antivirals that will quickly lower HBV DNA to undetectable levels without developing viral resistance. Viral resistance develops when the HBV that can continue to reproduce despite antiviral treatment over time become the “majority” virus and the infection rebounds with high ALT and viral load. Viral resistance develops quickly with lamivudine, for example, and less quickly with entecavir. A potential future strategy against viral resistance is to use a combination of antivirals that target different areas of the virus’s genetic material.

The various rates of resistance are:

- Adefovir—29% after 5 years.
- Entecavir—Less than 1% after 4 years.
- Telbivudine—21.6% in HBeAg-positive patients and 8.6% in HBeAg-negative patients after two years.
- For patients with lamivudine resis-

tance—Options include switching to or adding adefovir, with new research favoring the combination of lamivudine plus adefovir. Continuing lamivudine prevents adefovir resistance. Future treatment options for patients with lamivudine resistance may include tenofovir or the combination of tenofovir plus emtricitabine, neither of which is currently approved by FDA.

It is important to know the rates of resistance of each antiviral, Dr. Keeffe urged, because treatment can continue for several years, or in the case of HBeAg-negative hepatitis B, long-term. Given entecavir’s success in lowering viral load and spurring seroconversion after three or four years of treatment, it is important to note that it has a very low (1%) resistance rate after one year.

Of the four antivirals available, recent research suggests adefovir and entecavir are preferred, given their long-term efficacy and low rates of resistance. “There is agreement that lamivudine is no longer preferred due to the high rate of resistance associated with long-term therapy, and

telbivudine remains uncertain given its intermediate rate of viral resistance after two years of treatment,” Keeffe wrote.

“However, telbivudine may be an appropriate agent for the treatment of chronic hepatitis B when HBV DNA is undetectable after 24 weeks of therapy, which predicts a low rate of resistance at year 1 and year 2 of therapy.”

Tenofovir appears promising—Dr. Keeffe expressed optimism about the early reports about tenofovir’s quick effectiveness in dropping viral load and its lack of viral resistance in both HBeAg-positive and –negative hepatitis B. Tenofovir has been submitted to FDA for approval and will likely be approved in 2008.

The long-term safety of tenofovir has been demonstrated during its extensive use for treatment of HIV, but the ultimate rate of HBV antiviral drug resistance to tenofovir needs to be determined with longer-term follow-up. If tenofovir has a very low rate of resistance over several years of therapy, its high potency in combination with low rate of

resistance may make this drug, along with entecavir, the competitive first choices of oral antiviral agent for the treatment of chronic hepatitis B, Keeffe noted.

Sixty Months of Pegylated Interferon More Effective in HBeAg-negative Hepatitis B

Currently, 48 weeks of pegylated interferon, a once-weekly injection treatment that boosts the immune system to fight infection, is the recommended treatment period. However, conventional interferon, which requires three weekly injections, is more effective in HBeAg-negative hepatitis B when given for more than a year.

U.S. researchers, from several medical centers, treated 13 patients with HBeAg-negative hepatitis B with 60 weeks of pegylated interferon, with or without the antiviral lamivudine, to see if the extended treatment would be more effective.

According to their report published in *The*

American Journal of Gastroenterology, 60 weeks of pegylated interferon with or without lamivudine resulted in a higher number of patients (4) who experienced a 100-fold drop in their viral load (HBV DNA), and a 90% decline in HBsAg, which indicates a decline in viral replication. This response rate was higher than when HBeAg-negative patients were treated for just 48 weeks. Researchers called for additional studies to confirm the success of the longer treatment duration.

HBV DNA Decline after Four Weeks of Lamivudine Indicates Success or Failure

While many doctors no longer use lamivudine as a first-choice antiviral because of its high rate of viral resistance, it remains the least expensive antiviral on the market and is used commonly in Asia. Researchers in Hong Kong followed HBV DNA levels over five years in 74 HBeAg-positive patients to see if they could predict early which patients would

respond to lamivudine, in order to avoid development of viral resistance.

At year five, 17 of the 74 patients had achieved success with undetectable HBV DNA, HBeAg seroconversion, and normal ALT levels without viral resistance. What the successful patients shared in common was at week four of treatment, all of their HBV DNA levels had fallen to less than 2,000 IU/mL.

The researchers, reporting in the November 2007 issue of *Hepatology*, recommend that HBV DNA be measured at week 4 and treatment should be continued only in patients whose HBV DNA levels have declined to 4 log copies/mL (2,000 IU/mL) or less.

Hepatitis B Virus Genotype C May Cause Most Perinatal Transmission Due to Delayed HBeAg Clearance

Researchers affiliated with the Arctic Investigations Program of the CDC followed 1,158 native Alaskan native

people infected with the hepatitis B virus over 20 years to see what impact HBV genotype, or viral strain, had on the age when people seroconverted and developed the “e” antibody.

If patients have HBeAg for many years, it means they have high viral load and are at higher risk of liver damage and cancer. Additionally, the many years of high viral load during adulthood means the person has more changes to infect others through exposure to body fluids, or by giving birth. Babies born to mothers with high viral loads are at higher risk of contracting the infection, despite preventive treatment with vaccination and hepatitis B antibodies (HBIG).

Researchers identified the peoples’ genotype, how many years they tested positive for HBeAg, and their age at HBeAg clearance in the study. Their results, published in the November 2007 issue of the journal *Gastroenterology*, found that people with genotype C had HBeAg much longer than other genotypes. After losing HBeAg, those with

genotypes C and F were more likely to revert to the HBeAg-positive state later on.

“Genotype may have a strong effect on mode of transmission and outcome,” the researchers wrote. “Genotype C may have been responsible for most perinatal (mother-to-infant) transmission (in this population), given that seroconversion from HBeAg occurs decades later than in other genotypes.”

In another report in the same issue, Taiwanese researchers followed 133 asymptomatic, people (75 men, 58 women, average age 28), who had undergone HBeAg seroconversion over five years to see if there was a common thread among those in whom HBeAg returned, resulting in a resurgence of viral load and ALT. Among the study group, 108 had genotype B and 25 had genotype C.

Reactivation of infection occurred in 26 patients at an annual rate of 3.3%. Those at highest risk of viral reactivation were men with genotype C. Researchers suggest HBV genotype C is harder to eliminate and the longer period of infectiousness may contrib-

ute to more perinatal infections.

Doctors Identify When HBIG Alone or with Antivirals Are Needed to Prevent HBV Re-infection after Liver Transplants

U.S. researchers studied what combination of HBIG and/or antivirals was most effective in preventing re-infection among liver transplant patients. Preventing HBV re-infection is vital for patient survival following a transplant.

The study looked at the treatments used in 41 transplant patients at a Virginia medical center since 1985 who received HBIG with or without an antiviral. The average age was 46 and 81% were male and 88% were white.

Eight out of 15 HBeAg-positive transplant patients who received only HBIG redeveloped infection after 17 months. In contrast, none of 10 HBeAg-negative patients who received HBIG alone and none of the 10 HBeAg-positive patients who received both HBIG

and either lamivudine or adefovir developed recurrence. In both groups, as long as hepatitis B surface antibodies remained detectable, re-infection did not recur.

The researchers, reporting in *Liver International*, say recurrence of HBV infection following a liver transplant can be prevented in HBeAg-positive patients with a combination of HBIG and an antiviral agent, and in HBeAg-negative patients it can be prevented with HBIG alone.

HBV Patients on U.S. Liver Transplant List Decline Dramatically

The number of U.S. patients registered for liver transplants for HBV-related liver disease has decreased by 37% since 2000, according to a study presented at the AASLD conference, probably due to effective use of antivirals that halt or prevent additional liver damage.

Researchers analyzed data from the Organ Procurement and Transplantation Network waitlist from

1994 through 2006. The 125,800 patients included 6,087 with HBV, 41,021 with hepatitis C, and 79,937 with other conditions.

The number of registrants with HBV peaked in 2000 at 586 and dropped 30% to 409 in the ensuing six years. There has been no parallel drop in transplant list registrants with hepatitis C since 2000.

The HBV registrants included patients with severe liver disease and cancer. From 2000 through 2006, the number of waitlist registrants with severe liver disease dropped 37% while the number with liver cancer increased 146%.

Even with Normal ALTs and Low Viral Loads, Liver Damage Can Occur, Requiring Treatment and Liver Biopsy

Several studies presented at the AASLD conference confirmed that can have liver damage and may require liver biopsies and treatment even if their viral loads are low and their ALT levels nor-

mal. Current medical guidelines call for treatment only when ALT and HBV DNA levels are elevated.

One study of patients with moderate HBV DNA levels and normal ALTs found liver damage (fibrosis and some scarring) in 43.4%. The risk of liver damage—despite normal ALT and low viral load—appears to increase with age.

Researchers concluded, “Only 62% of patients with normal ALT at evaluation have persistently normal levels on follow-up, a third of whom can still have significant histology (liver damage). Older age, starting at 35, is the strongest independent predictor of significant histology. Asian patients with normal ALT should be followed closely and histologic evaluation should be considered if patients are 35 or older or if ALT becomes elevated.”

In another study of 53 patients with normal ALTs and low to moderate viral loads, researchers found mild inflammation in 89% (8 of 9) of HBeAg-negative patients with low viral load, in 84% (21/25) of HBeAg-negative patients with

higher viral loads, and in 79% (15/19) of HBeAg-positive patients.

Of nine HBeAg-negative patients with low viral load, 56% (5) had more severe fibrosis, compared with 52% (13/25) of HBeAg-negative patients with lower viral load and 53% (10/19) of HBeAg-positive patients. Of the four patients with very low HBV DNA, two (50%) had serious fibrosis. Even among the five patients with low viral load and normal ALTs, two (40%) had serious (stage 2) fibrosis. Stage 2 fibrosis was as common among patients with elevated ALT and high viral load, for whom treatment is recommended, as in this group with normal ALTs and low HBV DNA levels.

Researchers found that neither HBeAg status nor viral load predicted who had severe fibrosis and should be treated.

In HBeAg-negative patients with low viral load, a significant proportion had serious fibrosis, including one with incomplete cirrhosis. “More data are needed on the natural history of chronic hepatitis B in patients

with low viral loads. For now, a liver biopsy should be considered in the evaluation of HBeAg-negative patients with low-level viremia including those with normal ALT,” they urged.



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