

HCV ADVOCATE WEEKLY NEWS REVIEW

Review of HCV, HBV and HIV/HCV Coinfection Related News and Highlights

*Alan Franciscus
Editor-in-Chief*

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December 16th, 2007

San Francisco hospital to help sick in Vietnam

<http://www.mercurynews.com>

Bay City News

A San Francisco medical center is teaming up with a hospital in Ho Chi Minh City to help combat the deadly toll hepatitis B and other liver disorders and having in Vietnam.

The first fruit of the new partnership with California Pacific Medical Center will be to establish a center at Hoan My Hospital in Vietnam specializing in the care of patients suffering from liver and gastroenterology disorders.

The center will work to improve screening as well as managing patients with liver cancer and those in need of liver transplants. The center will also become home to a group specializing in diagnostic and therapeutic endoscopy.

"The goal of this partnership is to improve access to care," said Robert Gish, medical director of the Liver Disease & Transplant Program at California Pacific Medical Center. "By making our expertise and more resources available to our colleagues at Hoan My, we hope to be able to help them combat the devastating impact of hep B."

Hepatitis B is most commonly passed from mother to baby during childbirth, but it can also be transmitted through contact with infected blood or through unprotected sex. The disease carries few symptoms in its early stages, but left untreated it can lead to cirrhosis or scarring of the liver, liver cancer or death. It is the fourth leading cause of cancer death worldwide.

Update on Chronic Hepatitis B

www.medscape.com

Kris V. Kowdley, MD, FACP

Introduction

Hepatitis B virus (HBV) infection and its sequelae remain a major cause of chronic liver disease worldwide, with nearly 400 million persons infected. Although the majority of individuals with HBV infection will likely remain in an inactive phase associated with low viral replication and histologic remission, a significant proportion will develop chronic hepatitis B. Given the low rate of spontaneous remission as well as the increased risk for progression to cirrhosis and/or the development of hepatocellular carcinoma, there is a continued need for effective therapeutic intervention in chronic hepatitis B.

The drugs currently approved by the US Food and Drug Administration (FDA) for the treatment of chronic hepatitis B include interferon alfa-2b, pegylated interferon alfa-2a, and the oral nucleotide/nucleoside analogs lamivudine, adefovir, entecavir, and telbivudine, with other agents in development that demonstrate potent anti-HBV activity. This report explores some of the more clinically important HBV-related research presented during this year's meeting of the American Association for the Study of Liver Diseases (AASLD).

Tenofovir: The New Kid on the Block

Two large, pivotal trials were recently completed examining the efficacy of tenofovir compared with adefovir in hepatitis B e antigen (HBeAg)-negative and HBeAg-positive chronic hepatitis B. Tenofovir,* a nucleotide analog currently FDA-approved for the treatment of HIV, also has potent anti-HBV activity.

Marcellin and colleagues[1] reported the results of a phase 3, international, multicenter, randomized trial involving 375 patients with HBeAg-negative chronic hepatitis B. Subjects were randomized 2:1 to tenofovir 300 mg daily vs adefovir 10 mg daily for 48 weeks; liver biopsies were performed before and after therapy. Subjects ranged in age from 18 to 69 years; all had compensated liver disease, alanine aminotransferase (ALT) > upper limit of normal (ULN), HBV DNA > 105 copies/mL, and active necroinflammation on liver biopsy. Response was defined as serum HBV DNA < 400 copies/mL and at least a 2-point improvement in the Knodell activity index. The overall mean age was 44 years; 77% of subjects were male, 65% white, and 25% were Asian; 18% had been treated previously with lamivudine or emtricitabine.* Mean HBV DNA at baseline was 6.9 log₁₀ copies/mL; 64% of subjects had ALT > 2 x ULN; the majority were infected with HBV genotype D and 19% had cirrhosis. Safety and tolerability were comparable between the tenofovir and adefovir treatment groups, and no patient treated with tenofovir had an increase in serum creatinine > 0.5 mg/dL or a decrease in creatinine clearance value of < 50 mL. The primary efficacy endpoint, the proportion of randomized and treated subjects with complete response, was attained by 71% of patients in the tenofovir group compared with 49% in the adefovir group (P < .001). Serum HBV DNA was undetectable in 91% of patients in the tenofovir group and in 56% of patients in the adefovir group; HBV DNA was < 300 copies/mL in 92% and 59% of tenofovir vs adefovir treated patients, respectively (P < .001). There was no significant difference in histologic improvement or in normalization of serum ALT between the 2 groups. On the basis of these results, it is clear that tenofovir is safe and associated with a higher rate of HBV DNA suppression compared with adefovir. It will be informative to examine the efficacy of tenofovir in lamivudine-experienced patients as there is more experience with this oral antiviral agent in the treatment of chronic hepatitis B.

Heathcote and colleagues[2] presented the results of a similar phase 3 multicenter, international study involving 266 patients with HBeAg-positive chronic hepatitis B randomized to receive tenofovir 300 mg daily (n = 176) vs adefovir 10 mg daily (n = 90) for 48 weeks. Entry criteria included serum ALT > 2 x ULN, active necroinflammation on liver biopsy, and serum HBV DNA titer > 106 copies/mL. The primary efficacy endpoint included improvement in histology and HBV DNA < 400 copies/mL. It is interesting to note that just over half of the patients were white, whereas slightly over one third were Asian. HBV genotype D was present in 33% of patients and genotype C in 26%. The safety of tenofovir was comparable to that of adefovir, and no patients developed evidence of nephrotoxicity. Flares in liver enzymes associated with steep reduction in HBV DNA level were observed in 19% of tenofovir-treated patients and 10% of adefovir-treated patients. The primary endpoint was attained in 67% of tenofovir-treated patients and 12% of adefovir-treated patients (P < .001). Serum HBV DNA became undetectable in 69% of tenofovir-treated patients vs only 9% of adefovir-treated patients (P < .001). Of interest, there was no difference in HBeAg seroconversion between tenofovir and adefovir-treated patients (21% vs 18%, respectively), although hepatitis B surface antigen (HBsAg) loss was more common among tenofovir-treated patients compared with adefovir-treated patients (3% vs 0%, respectively; P = .018). These data suggest that tenofovir has superior potency compared with adefovir, and once again highlight the fact that HBeAg seroconversion appears to be a distinct process that is only partially related to HBV DNA suppression, given the finding of strong differences between adefovir and tenofovir in potency but only marginal differences in HBeAg seroconversion rates.

In a multicenter observational study, van Bömmel and colleagues[3] described the effectiveness

of tenofovir monotherapy in 121 patients with chronic HBV infection who had previously been treated with lamivudine and/or adefovir. The majority were HBeAg-positive and all had serum HBV DNA levels > 105 copies/mL. Most patients (105 of 121) had been treated previously with lamivudine and over half (75 of 121) had been treated with adefovir. Subjects with adefovir resistance mutations were excluded. In the remaining 101 patients, there was a reduction in mean HBV DNA level after a mean duration of therapy of 14.8±12 months (range, 6-63 months) from a mean baseline level of 6.7±1.3 (range, 4.9-9.7) by a mean of 4.1±1.2 (range, 1.4-6.7) log₁₀ copies/mL at week 48. The majority (91%) of patients had HBV DNA < 400 copies/mL after 48 weeks of therapy. Rebound of HBV DNA >1 log was not observed. HBeAg seroconversion was documented in 23% of the patients after a mean tenofovir treatment duration of 9±3 (range, 2-33) months, and HBsAg loss was seen in 4% after 13±6 (range, 9-18) months; the presence of lamivudine resistance did not affect response to tenofovir. The study authors concluded that tenofovir is effective in lamivudine-resistant patients and has a low rate of resistance. These data are interesting; although they suggest a potential role for tenofovir in lamivudine-experienced patients, they are somewhat difficult to interpret because data for lamivudine-resistant patients were not shown separately nor was the proportion of patients with lamivudine resistance provided. Nevertheless, this study represents one of the larger cohorts describing tenofovir therapy in lamivudine-experienced patients.

Cross-resistance Between Tenofovir and Adefovir

Van Bömmel and colleagues[4] separately analyzed the efficacy of tenofovir in the subset of patients from the cohort described above who had adefovir resistance. Ten patients who were treated with adefovir monotherapy after the development of lamivudine resistance and who subsequently developed adefovir resistance were described. All subjects had the signature adefovir resistance mutations (rtN236T and/or rtA181V/T). The HBV polymerase gene was sequenced in 6 patients. The mean decrease in serum HBV DNA after 48 weeks of tenofovir treatment was 4.3 ±1.2 log₁₀ copies/mL, although HBV DNA was still detectable in 8 patients after 48 weeks of therapy. There was persistence and enrichment of adefovir resistance mutations during the treatment period. These data suggest that there is cross-resistance between adefovir and tenofovir even though switching from adefovir to tenofovir in adefovir-resistant patients results in a further decrease in serum HBV DNA. The study authors concluded that patients with evidence of adefovir resistance should receive combination therapy with lamivudine or entecavir in addition to adefovir or tenofovir.

Commentary

The completion of pivotal phase 3 trials of tenofovir will likely lead to the approval of this agent for the treatment of both HBeAg-negative and HBeAg-positive chronic hepatitis B. On the basis of data presented at AASLD 2007, it appears that tenofovir will become another useful addition to the therapeutic armamentarium of chronic hepatitis B for the treatment of nucleoside-naïve patients. Long-term follow-up studies will be necessary to determine the relative rates of emergence of resistance mutations and the durability of HBV DNA suppression on treatment, particularly in patients with genotype C infection and high viral load. The role of tenofovir in lamivudine-experienced patients is less clear, although one retrospective observational study suggested a high rate of HBV DNA suppression among patients who had been treated previously with lamivudine, many of whom had lamivudine-resistant mutations. It appears that cross-resistance with tenofovir and adefovir occurs, suggesting that tenofovir monotherapy is unlikely to be a desirable therapy for patients with adefovir resistance. What will be the role of adefovir in

the post-tenofovir era? The available data suggest that tenofovir will be a superior alternative to adefovir among patients with lamivudine resistance, although until long-term data regarding safety and efficacy have been established, adefovir may continue to have a role in the treatment of lamivudine-resistant patients given the track record of this agent in the lamivudine-experienced population, especially when used in combination with lamivudine. It is also increasingly likely that sequential monotherapy will be discarded in nucleoside-experienced patients who continue to demonstrate a lack of complete viral suppression or who have virologic rebound after initial antiviral response. Combination therapy using a nucleoside analog such as entecavir and a nucleotide analog such as tenofovir likely will be used, with individual combinations of nucleoside analogs and nucleotide analogs (such as entecavir/tenofovir, telbivudine/tenofovir, or lamivudine/adefov) selected by practitioners on the basis of treatment history of the patient, severity of liver disease, pregnancy status, and other considerations.

Entecavir: Continued Efficacy After 4 Years of Therapy

The initial pivotal trials with the nucleoside analog entecavir compared the effectiveness of this agent with that of lamivudine in nucleoside-naive patients with HBeAg-positive and HBeAg-negative chronic hepatitis B. HBeAg-positive patients who demonstrated evidence of continued viral replication after completing the pivotal trial with entecavir 0.5 mg daily were enrolled in a long-term open-label treatment study using 1.0 mg of entecavir. One hundred eighty-three patients were rolled over into this long-term treatment study. Han and colleagues[5] presented data from 146 patients in this cohort after 4 years of entecavir therapy. Rates of HBeAg seroconversion, HBeAg loss, and on-treatment HBV DNA suppression were described. At week 192, 91% of nucleoside-naive patients did not have detectable HBV DNA in serum (< 300 copies/mL); continued HBeAg seroconversion (16%) and HBeAg loss (41%) were observed among those who continued on therapy up to week 192.

Sherman and colleagues[6] described the efficacy of entecavir therapy among patients with chronic hepatitis B who were classified as "nonresponders" in the initial entecavir pivotal trials. These were patients who did not achieve a serum HBV DNA titer < 0.7 MEq/mL using a bDNA assay after 48 weeks of therapy or during year 2 of entecavir therapy at a dose of 0.5 mg daily (protocol-defined criteria of "nonresponse"). The authors identified 30 patients (27 HBeAg-positive, 3 HBeAg-negative) from the original 679 nucleoside-naive subjects in the 2 pivotal trials who were classified as "nonresponders" (22 during the first 48 weeks of therapy and 8 during the second year of therapy). Twenty-one HBeAg-positive subjects classified as "nonresponders" were enrolled into an open-label study of entecavir given at 1.0 mg per day. After 1 year of therapy, 71% achieved undetectable serum HBV DNA, with 57% maintaining this endpoint at the end of the follow-up. Four patients experienced virologic breakthrough; however, these patients did not have any evidence of resistance mutations. Approximately one third of patients had HBeAg seroconversion.

Commentary

On the basis of these data, it appears that most nucleoside-naive patients treated with entecavir will respond to continued therapy when given at a higher dose if they fail to achieve a serum HBV DNA < 0.7 MEq/mL after the initial 1-2 years of treatment. Although virologic rebound occurs in a subset of these patients, entecavir resistance mutations have not emerged. Continued follow-up of these patients will be useful and will clarify whether late resistance may arise in this subset of patients. From a practical standpoint, it seems reasonable to consider using a higher

dose of entecavir (1.0 mg daily) for patients who do not respond after 1 year if resistance has not emerged.

Immune-Tolerant Chronic Hepatitis B: Not Necessarily a "Benign" Condition?

It has been assumed that patients in the immune-tolerant phase of chronic hepatitis B, which is characterized by positive HBeAg-status, relatively high levels of HBV DNA in the serum, and normal or near-normal serum liver enzyme levels, have relatively little liver damage, a benign course, and do not require therapy.[7] However, we have recently shown that a significant proportion of patients with "immune-tolerant" chronic hepatitis B have significant hepatic fibrosis and many have necroinflammatory changes on biopsy. The issue of whether such patients should be treated with antiviral agents to reduce the level of viremia has become more relevant with the publication of the REVEAL (Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-HBV) study data, which demonstrated that serum HBV DNA levels $> 10^5$ or even $> 10^4$ copies/mL may be an independent risk factor for development of cirrhosis and/or hepatocellular carcinoma.[8,9]

Nguyen and colleagues[10] described the prevalence of significant liver disease among patients with chronic hepatitis B from northern California who had normal serum ALT and $> 10^4$ copies/mL of HBV DNA in the serum. Significant histopathology was found in more than 40% of patients; among patients with persistently normal liver enzymes, 31% had significant hepatic histopathology. Older age (starting at 35 years) was the best predictor of abnormal liver histology. The study authors concluded that a high proportion of patients with normal serum liver enzymes but evidence of ongoing hepatitis B replication have active disease on liver histology.

Grossman and colleagues[11] examined the prevalence of significant liver disease among patients with chronic hepatitis B who had HBV levels below the current thresholds for initiation of therapy ($< 100,000$ copies/mL in HBeAg-positive patients and $< 10,000$ copies/mL in HBeAg-negative patients as per AASLD guidelines), defined as "low-level viremia" (LLV). They identified 52 such patients, 64% of whom were HBeAg negative. Patients with other known causes of liver disease (other than nonalcoholic fatty liver disease) or HIV infection were excluded. Normal serum ALT was defined as ≤ 30 U/L in men and ≤ 19 U/L in women. Of these HBeAg-negative patients, 9 had LLV. Among the 9 patients who were HBeAg-negative and had LLV, 5 (56%) had at least stage 2 fibrosis (1 patient had evidence of cirrhosis), as compared with 52% (13/25) of HBeAg-negative patients with HBV DNA $\geq 10,000$ copies/mL and 53% (10/19) of HBeAg-positive patients. The study authors concluded that severe hepatic fibrosis and necroinflammation could be present despite low levels of HBV viremia and negative HBeAg status. They recommended that liver biopsy be considered in all patients with chronic hepatitis B regardless of serum ALT level or HBeAg status.

Gui and colleagues[12] reviewed the liver histology of 139 patients from Shanghai with chronic hepatitis B who had ongoing HBV replication ($> 10^3$ copies/mL) and normal serum ALT (measured on at least 3 occasions more than 2 months apart over a period of 12 or more months prior to biopsy). A comparison group of 135 patients with abnormal serum ALT during the same period was used as a control. The serum ALT values of the 139 patients had been normal from 1 to 30 years (median was 6 years). In this group with persistently normal ALT, 33 patients had evidence of significant hepatopathology (Histologic Activity Index ≥ 4 or Ishak fibrosis score \geq

3), including 13 with cirrhosis. Those older than 40 years of age and having serum ALT 0.75-1 x ULN were more likely to have abnormal liver histology (P = .005). HBV DNA level and HBeAg status were not associated with abnormal histology.

Commentary

These studies again demonstrate that significant hepatic pathology may be present among patients with chronic hepatitis B despite low levels of viremia and normal serum liver enzymes levels. It is reasonable that clinicians evaluate patients individually with regard to risk for chronic liver disease. Older age (> 35 to 40 years) should probably lower the threshold for additional diagnostic evaluation, particularly in patients with serum HBV DNA levels > 104 copies/mL.

Update on Telbivudine: Refining the Treatment Strategy

The nucleoside analog telbivudine was approved for the treatment of chronic hepatitis B approximately 1 year ago. This agent has high potency and is associated with impressive reduction in HBV DNA suppression in both HBeAg-positive and HBeAg-negative patients. Furthermore, telbivudine is the only category B drug (no known association with birth defects or other pregnancy-related complications) currently approved for the treatment of hepatitis B. The main limitations with the use of this agent have been the development of resistance, which, although less common than with lamivudine, may still result in diminished efficacy. In fact, on the basis of high rates of lamivudine resistance, which are associated with loss of biochemical and virologic response and result in lower efficacy with subsequent use of other nucleoside analogs, lamivudine is no longer considered an acceptable option as first-line monotherapy for the treatment of patients with chronic hepatitis B.[7] It was observed that patients with early and profound HBV DNA suppression induced by telbivudine treatment had a low likelihood of developing resistance and a high rate of durable HBV DNA suppression. Several studies presented at AASLD 2007 extended these observations and provided further useful information about the optimal use of this agent.

Zeuzem and colleagues[13] presented baseline data that predicted response to telbivudine at 24 weeks, which in turn predicted outcomes at 104 weeks, in patients from the pivotal GLOBE study. The GLOBE study, a 2-year phase 3 randomized trial of telbivudine vs lamivudine, enrolled 1367 patients with chronic hepatitis B from several countries worldwide. Pretreatment serum HBV DNA levels and ALT levels were significant predictors of virologic response at week 24 and of efficacy outcomes and virologic breakthrough at week 104. Optimal response was noted among HBeAg-positive subjects who had elevated serum ALT > 2 x ULN and HBV DNA levels < 109 copies/mL at baseline. In this subset of patients, 71% had undetectable HBV DNA at week 24, while 47% had evidence of HBeAg seroconversion and only 14% had virologic breakthrough at week 104, compared with an HBeAg seroconversion rate of 30% and virologic breakthrough of 29% in the overall cohort of HBeAg-positive patients. Similar relationships were observed in HBeAg-negative patients with baseline serum ALT > 2 x ULN and HBV DNA level < 107 copies/mL, although the higher rate of viral clearance in this group made this relationship less strong compared with the HBeAg-positive patients. Among patients who had a baseline HBV DNA < 109 copies/mL and elevated serum ALT at baseline, undetectable HBV DNA at week 24 resulted in 52% HBeAg seroconversion and only a 3.6% rate of virologic rebound at 2 years.

These data expand the set of tools we can use in selecting patients for treatment with telbivudine. The current data suggest that telbivudine has a favorable profile, with high efficacy and low resistance among patients who achieve undetectable HBV DNA in the serum after 24 weeks of therapy.

Pegylated Interferon: Durability of Response in Patients Who Achieve HBeAg Loss

A large multicenter study described by Buster and colleagues[14] enrolled 172 patients with chronic hepatitis B from 28 centers in a long-term follow-up study after pegylated interferon alfa-2b therapy; 91 patients (53%) received pegylated interferon alfa-2b alone and 81 (47%) received pegylated interferon alfa-2b as well as lamivudine. Data were collected in a follow-up visit 3±0.8 years after completion of the study (52 weeks of therapy and a follow-up at 78 weeks). At week 78, 39% of patients in the pegylated interferon alfa-2b monotherapy group were HBeAg negative and 36% in the pegylated interferon alfa-2b + lamivudine group were HBeAg negative. HBeAg loss was durable in 52 of 64 initial responders (81%); 67% had HBV DNA < 10,000 copies/mL and 65% had normal ALT. HBsAg became negative in 19 initial responders (30%). HBsAg became negative in 58% of genotype A infected initial responders compared with 14%, 0%, and 6% of patients with genotype B, C, or D, respectively (A vs C or D, P < .004). The study authors concluded that HBeAg response to pegylated interferon alfa-2b with or without lamivudine is durable in the majority of patients and is associated with loss of HBsAg, and that sustained virologic response is superior in patients with genotype A infection.

This study provides valuable information about the long-term responses in patients treated with pegylated interferon alfa and once again demonstrates the high rates of response in patients with genotype A as well as the unique ability of pegylated interferon alfa to achieve HBsAg loss among responders to this therapy.

*The US Food and Drug Administration has not approved this medication for this use.

References

Milk thistle, liver health

<http://seattletimes.nwsources.com>

By Astrid Pujari, M.D.

Special to *The Seattle Times*

Q: I have hepatitis C and my friend told me that milk thistle might help. What is your opinion? Is there any proof that it works?

A: Many people use milk thistle — usually the seeds — for chronic hepatitis B and C. It's actually a weed; I've seen it growing in parks around Seattle. As an aside, I must say that I admire the courageous people who collect those seeds. I found some growing in my compost pile one summer, and let me tell you, it is one very large, prickly plant.

Anyway, milk thistle has a component called "silymarin" which has anti-inflammatory and antioxidant properties. Silymarin also may protect liver cells from being damaged by toxic chemicals and help liver cells to regenerate if they are injured. So it makes sense that people

have been interested in using it medicinally for liver disease, including hepatitis.

The data is still controversial on how effective milk thistle is for hepatitis B and C. Many of the studies are small and not necessarily the best design. Keeping that in mind, however, some of the research is interesting. One short study found that a specific milk thistle product called Silipide improved liver tests in people with chronic active hepatitis.

Another found that after one year, people who took milk thistle felt better, though they didn't have any improvements on their liver tests. A review of 13 studies also found that milk thistle reduced the risk of dying from liver disease.

Milk thistle has a pretty good track record for safety. It has been used as a food for centuries by people around the Mediterranean. Some will notice a mild laxative effect. People with a history of ragweed, chrysanthemum and marigold allergies may also react to milk thistle. However, as always, talk to your doctor before trying anything new.

Dr. Astrid Pujari is a Seattle M.D. with an additional degree as a medical herbalist; she practices at the Pujari Center and teaches as part of the residency programs at Virginia Mason and Swedish/Cherry Hill hospitals. Send questions to apujari@seattletimes.com for possible use in future columns. All information is intended for education and not a substitute for medical advice. Consult your doctor before following any suggestions given here.

The public's right to know

<http://www.zwire.com>

By Scott Brinton

New York state Sen. Charles Fuschillo Jr. spoke about what his 8-year-old daughter's elementary school does when a student tests positive for a potentially contagious illness, such as strep throat.

The nurse, he said, immediately sends home warning letters to the parents of other children.

So why, Fuschillo wondered, did the state Department of Health wait 34 months to tell more than 800 patients, including a number of South Shore residents, that their Dix Hills doctor had put them at risk of contracting the HIV and hepatitis B and C viruses by reusing syringes in his practice?

Fuschillo, a Republican from Merrick, was speaking during a Senate hearing last Thursday at Farmingdale State College to gather ideas on how to upgrade the state's system of reporting medical mistakes and malfeasance to the public.

Sen. Kemp Hannon, a Republican from Garden City who is chairman of the Senate Health Committee, convened the forum. It came only a month after the state health department revealed that from January 2000 to January 2005, Dr. Harvey Finkelstein, an anesthesiologist and pain management specialist, reused plastic syringe barrels and drew medication from large, multi-use vials, rather than single-dose vials, at his Massapequa practice and possibly his Melville office.

After visiting Finkelstein's Island Orthopedic Sports Medicine and Physical Therapy Clinic in Massapequa in January 2005, state health officials warned the doctor to reform his injection practices, but allowed him to continue practicing medicine - and never informed the public about the possibility of infection. Health officials have since followed up to confirm that Finkelstein no longer reuses syringes. To date, the health department has not sanctioned him.

State investigators have confirmed one case of hepatitis C infection caused by the reuse of syringes at Finkelstein's practice. No patients were infected with HIV or, apparently, with hepatitis B. Officials note, however, that six of Finkelstein's patients have tested positive for hepatitis B and six more for hepatitis C, but authorities will likely be unable to prove that Finkelstein infected them.

If you need change, ask

Dr. Richard Daines, the state health commissioner, answered questions for nearly two hours at the Senate hearing. The panel of four senators and one assemblyman noted repeatedly that Daines was not commissioner when the health department began investigating the Finkelstein case in 2004, so Daines is not responsible for how the case was previously handled, but he would be held accountable for future cases.

Fuschillo told Daines, "If you need statutory changes, ask for it. If you need more staff, ask for it. We're dealing with human lives."

The senator said he believes the state should immediately notify the public about any doctor who has potentially infected multiple patients with life-threatening illnesses, such as hepatitis C in the Finkelstein case.

Eighty percent of people infected with the hepatitis C virus develop no symptoms, Daines said. Of the remaining 20 percent, roughly half to three-quarters suffer chronic liver infections and develop liver disease, usually over a period of decades, possibly leading to death. Roughly 1.6 percent of Americans carry the hepatitis C virus.

The state health department first learned of Finkelstein's syringe practices in 2004. In December that year, the Nassau County Department of Health identified two cases of acute hepatitis C infection through routine surveillance of laboratory reports. The county health department determined that both individuals had had spinal injections performed by Finkelstein.

The state health department dispatched a team of doctors to Finkelstein's Massapequa office to investigate in January 2005. Daines said that, in front of investigators, Finkelstein reused syringe barrels, with medication drawn more than once from large vials. "As the physician gave injections to patients," Daines said, "the investigators observed the physician, on several occasions, appropriately changing the needle tips between injections on the same patients, but reusing the same syringe barrel, which had been in contact with the hub of a needle placed in the patients."

The state then began an epidemiological investigation to determine if, in fact, Finkelstein had transmitted hepatitis C and other blood-borne viruses. That investigation lasted more than two years.

During that time, the state identified 98 of Finkelstein's patients who were at greatest risk of infection, and worked to track them down to notify and test them, but Finkelstein's other patients had no knowledge of his syringe practices.

On Jan. 7, 2005, state epidemiologists called the health department's Office of Professional Medical Conduct to ask whether Finkelstein had had any problems with "infection control" in the past. The answer was no. The state's epidemiological department and the OPMC then did not speak on the Finkelstein case for seven months.

"The first and primary lesson that emerges is that there must be an established system of communication between OPMC and whichever division in the vast [health] department is responsible for originating" an investigation of a physician, Daines said.

Why not notify?

When asked why the state did not notify all of Finkelstein's patients of possible infection at the outset through the media, Daines said the answer was "philosophical" in nature. Should the state health department have immediately notified every patient, potentially causing widespread panic, when it was unsure whether Finkelstein had spread hepatitis C or other viruses? Or should it have waited until it was relatively certain that he had infected a patient with a blood-borne disease? Ultimately, the state chose the latter course.

Universally, the lawmakers said the health department should have erred on the side of caution and immediately notified all patients of possible infection, which would have allowed them to act early to protect their health if necessary.

Daines, however, said the law did not allow the health department to do so. "The public health law sections creating the OPMC require that an investigation file be kept confidential, including the name of the doctor who is the subject of an investigation, unless and until there is a finding of misconduct by the Board of Professional Medical Conduct."

Sen. Eric Schneiderman, a Democrat from Manhattan, said he believes the system protects doctors, not patients, and that must change.

During his prepared testimony, Daines said the health department "continues to support greater transparency and will pursue the possibility of a statutory change."

When questioned by Schneiderman, though, Daines said he was "not sure" how the state Legislature could rewrite the law to require that all of a physician's patients be notified of a medical error leading to a possible infection.

Schneiderman retorted, "I'm happy to report that it's not that hard."

A 'failed' system

Assemblyman David McDonough, a Republican from North Merrick, said he had a hard time finding Finkelstein's 10 malpractice settlements on the state health department Web site, and had to call the department for assistance in navigating the site. "It's about impossible for the average consumer, or patient, to find this information," McDonough said.

Daines said the health department would look into streamlining the site to give the public better access to critical information, such as malpractice suits.

Sen. Carl Marcellino, a Republican from Syosset, said Finkelstein got off easy. "He doesn't even know he's doing the wrong procedure, and he keeps doing it, and all he gets is a slap on the wrist ...," Marcellino said. "I understand doctors have rights, and doctors are getting sued all over the place. Nothing happened to this man. You can only say that the system failed."

Hannon said the Senate would look into measures that the state could take to improve the health department's reporting practices when a physician is found to have made a mistake.

"We're in a whole different era," Hannon said.

What other states do to report medical errors

Arthur Levin, director of the non-profit Center for Medical Consumers in New York City, spoke at length during last week's state Senate hearing on reporting medical mistakes and malfeasance to the public. Levin said that New York's notification practices are geared toward protecting doctors.

"The trend in most states has been to make the [reporting] process more transparent and less opaque," but not in New York, Levin said.

Along with the New York Public Research Interest Group and the Citizen Advocacy Center, the Center for Medical Consumers recently sent surveys to medical review boards in all 50 states, asking when and how they report problems with physicians to the public.

Thirty-eight states responded. To the question of whether patient complaints are reported, 34 said no and four said yes.

When formal charges are brought against a physician, 33 said they report them to the public; five states do not, one of them being New York.

"The public wants - and deserves - a much more transparent system," Levin said.

Brinton@liherald.com or (516) 569-4000 ext. 203.

December 18th, 2007

Medivir and Tibotec collaborate for hepatitis C treatment

<http://www.pharmaceutical-business-review.com>

Medivir has reported that it is collaborating with Tibotec Pharmaceuticals to develop HCV NS3/4A protease inhibitors for the treatment of chronic hepatitis C virus infection.

The drug candidate, **TMC435350**, recently advanced into Phase II of the clinical trial program. The first Phase IIa study was initiated in Europe by Tibotec Pharmaceuticals at the end of November.

Under the terms of the research development and license agreement of November 2004, Medivir is entitled to a number of pre-specified milestone payments. Medivir has achieved one of the clinical milestones in the agreement and has thus secured a milestone payment of E5 million.

The second payment is due because Medivir has opted to decline a contractual opportunity to obtain from Tibotec, at some point in the future, the marketing rights for an approved pharmaceutical in the Nordic countries. In return Tibotec will make a cash payment of E12 million.

Lars Adlersson, Medivir's CEO, said: "This will be our largest ever licensing payment. A robust financial position will facilitate the creation of a Nordic sales and marketing organization and strengthen us in coming partnership negotiations. Our goal is to achieve revenues from sales of licensed pharmaceuticals in the Nordic market in the coming 12 months."

December 19th, 2007

GlobeImmune Announces Initiation of Phase 2 Clinical Trial of GI-5005 in Patients With Chronic Hepatitis C

<http://www.earthtimes.org>

LOUISVILLE, CO -- 12/19/07 -- GlobeImmune, Inc. announced today the initiation of the Company's Phase 2 clinical trial to evaluate **GI-5005 Tarmogen®** for the treatment of patients with chronic hepatitis C infection. GI-5005 is being evaluated as a potential therapy in combination with standard of care, pegylated interferon plus ribavirin.

The Phase 2 clinical trial is a randomized, open-label, multi-arm, multi-center trial evaluating GI-5005 in combination with full duration standard of care, versus standard of care alone in patients with chronic genotype 1 hepatitis C infection who are either treatment-naïve or non-responders to previous therapy. Endpoints will include improvement in alanine aminotransferase (ALT) levels, early virologic response (EVR), end of treatment response (ETR), sustained virologic response (SVR), serum markers of liver fibrosis / necrosis and liver biopsy in a subset of patients. This study is designed to enroll 120 patients randomized 1:1 in the 2 arms at approximately 50 centers in the U.S., India and Europe. A majority of the centers will be based in the U.S.

"With the initiation of this trial, we continue to make excellent progress in advancing our GI-5005 development program," said David Apelian, M.D., GlobeImmune's Chief Medical Officer. "Our clinical data to date have shown GI-5005 to have an excellent safety profile, to be capable of generating a robust immunologic response and to have the potential to provide clinical benefit to patients with chronic HCV. While the current standard of care and the newer class of small molecule inhibitors primarily act by inhibiting viral replication, we believe the immunogenicity generated by GI-5005 will improve the rate of immune clearance of infected liver cells, be complementary with treatments that inhibit viral replication and have the potential to favorably impact clinical outcomes."

About GI-5005

GI-5005 is GlobeImmune's lead infectious disease product for the treatment of chronic hepatitis



C infection from the Company's proprietary Tarmogen active immunotherapy platform. GI-5005 is whole, heat-killed recombinant yeast genetically modified to express HCV-specific protein targets. The mechanism of action for GI-5005 (i.e. immune elimination of infected hepatic cells) may work synergistically in combination with the current or emerging standard of care, which directly inhibits viral replication, to more effectively eradicate hepatitis C virus from the liver. Additionally, this mechanism of action may offer an option for interferon-intolerant or interferon-contraindicated patients as a long term monotherapy.

About Hepatitis C Infection

The World Health Organization (WHO) estimates that 170 million people globally are infected with hepatitis C virus (HCV), with 3-4 million new infections each year. Roughly 80-90% of these cases fail to resolve acutely and evolve into a chronic state. The population of subjects with chronic HCV infections is estimated at approximately 4 million cases in the U.S. and 5-10 million in Europe. Of the 4 million subjects infected in the U.S., only 20-40% are estimated to be currently diagnosed given the largely asymptomatic nature of HCV infection. The current standard of care for genotype 1 HCV patients, the most common subtype in the U.S., is 48 weeks of pegylated interferon plus ribavirin. This treatment is often poorly tolerated and only results in cure rates (sustained virologic response) of approximately 50%.

About GlobeImmune, Inc.

GlobeImmune is a private Colorado-based company developing active immunotherapies called Tarmogens for the treatment of cancer and infectious diseases. The Company's lead product candidate, GI-5005, is a Tarmogen being developed for the treatment of chronic hepatitis C infection that has completed a Phase 1b clinical trial. GI-5005 is designed to complement both the current and emerging standard of care for hepatitis C infection through the direct elimination of chronically infected cells. The Company has initiated a randomized, placebo-controlled Phase 2 study of GI-5005 in combination with standard of care for chronic hepatitis C infection. The Company's lead oncology program, GI-4000, is designed to be a treatment for cancers of the lung and gastrointestinal tract. A randomized, placebo-controlled Phase 2 trial in patients with resectable pancreas cancer in combination with adjuvant gemcitabine is ongoing.

For additional information, please visit the company's website at www.globeimmune.com

This press release contains forward-looking statements that involve risks and uncertainties, including statements relating to initiation and progress of the Company's clinical trial programs and potential advantages of the Company's technology and product candidates. Actual results could differ materially from those projected and the Company cautions readers not to place undue reliance on the forward-looking statements contained in this release.

Standard Hepatitis B Treatment Bested by Newcomer

By Serena Gordon
HealthDay Reporter

WEDNESDAY, Dec. 19 (HealthDay News) -- New research suggests that a newer medication approved for treating hepatitis B is more effective than the standard treatment, lamivudine.

Additionally, the Chinese scientists found that a significantly smaller number of people developed resistance to the newer drug, known as **telbivudine (Tyzeka, Sebivo)**.

The study, which is published in the Dec. 20 issue of the *New England Journal of Medicine*, found that about 8 percent more people responded to telbivudine than lamivudine, and the risk of resistance was at least halved for people taking telbivudine.

"The multiple therapeutic choices now available for hepatitis B will enhance the ability of clinicians to maintain long-term control of HBV replication, ultimately improving clinical outcomes for more patients. These results support telbivudine as an effective therapy for patients with chronic hepatitis B," the study authors wrote.

Hepatitis B is a viral infection that attacks the liver. It can be spread in many ways, including through the exchange of blood and other bodily fluids when having sex, from sharing needles, or from a mother to her baby during pregnancy, according to the U.S. Centers for Disease Control and Prevention.

As many as one third of people infected have no symptoms, according to the CDC. When symptoms do occur, they may include jaundice, fatigue, abdominal pain, loss of appetite, nausea, vomiting and joint pain. For most people, the infection is transient, lasting no more than six months or so. However, the infection can become chronic. This occurs in only about 6 percent of people over 5 who are infected with the hepatitis B virus, in about 30 percent of infected children between 1 and 5 years old, and in as many as 90 percent of babies who are infected with the virus. Chronic hepatitis B can cause scarring of the liver, which can lead to liver cancer or liver failure.

The goal of treatment is to keep levels of the hepatitis B virus as low as possible. Even if hepatitis B levels become so low that they're undetectable, long-term treatment is still required to prevent recurrence. People with hepatitis B are tested to see if they are positive or negative for E-antigens. A positive result on the E-antigen test often indicates a stronger infection, according to the Hepatitis B Foundation. Someone with a positive result is referred to as HBeAg-positive.

While there are several treatment options available to suppress the virus, one problem is that people can develop resistance to these drugs. Two new drugs, entecavir (Baraclude) and telbivudine, have been approved to treat hepatitis B since 2005.

The current study looked at how effective telbivudine is compared to the standard first-line treatment, lamivudine.

The researchers randomly assigned 1,370 people with chronic hepatitis B to receive either 600 milligrams of telbivudine or 100 milligrams of lamivudine once daily.

After a year of treatment, 75.3 percent of HBeAg-positive people taking telbivudine showed a therapeutic response versus 67 percent of those on lamivudine. In HBeAg-negative people, 64.7 percent of those on telbivudine had a response compared to 56.3 percent of those on lamivudine.

The number of study volunteers who had undetectable levels of hepatitis B virus by the end of the treatment year were much greater for those on telbivudine. In HBeAg-positive people, 60 percent achieved undetectable levels on telbivudine versus 40.4 percent for those taking lamivudine. For HBeAg-negative study participants, telbivudine brought viral levels down to undetectable for 88.3 percent compared to 71.4 percent for lamivudine. Telbivudine also got those viral levels down about five to six weeks faster, on average, than lamivudine.

Resistance developed in 5 percent of HBeAg-positive people taking telbivudine and in 11 percent of those on lamivudine. For those who were HBeAg-negative, the rates of resistance were 2.3 percent for those on telbivudine and 10.7 percent for those on lamivudine.

According to the study's authors, both medications have a similar side effect profile, and no significant differences were found in the current study volunteers.

"Telbivudine seems to work and be safe. It seems to have shown a better therapeutic and histological response," said Dr. Marc Siegel, an internist at New York University Medical Center.

"It decreases the risk of cirrhosis. It's well-tolerated, and it prevents the progression of hepatitis B better than the standard treatment right now," said Siegel.

The study authors pointed out that telbivudine hasn't yet been compared to the other new hepatitis B medication, entecavir, in a randomized clinical trial. Entecavir has also been shown to be more effective than lamivudine and creates less resistance as well.

More information

To learn more about available treatments for hepatitis B, visit the [Hepatitis B Foundation](http://www.hepatitisb.org).

Gov't rejects uniform compensation for all hepatitis C sufferers

<http://www.japantoday.com>

TOKYO — Health, Labor and Welfare Minister Yoichi Masuzoe rejected Thursday a proposal from hepatitis C sufferers that the government pay compensation uniformly to all people who contracted the disease through tainted blood products, leaving their out-of-court settlement negotiations on the verge of collapse.

Masuzoe said the government will instead agree to a settlement framework compiled last week by the Osaka High Court and pay a total of 14 billion yen to eligible sufferers. The framework limits the scope of responsibility of the defendants — the state and drugmakers. Adding further relief measures to the court plan, Masuzoe proposed that the government pay a total of 3 billion yen to sufferers who are not eligible under the court-crafted plan.

Valeant Pharmaceuticals Sells Hep-C Drug Infergen® to Three Rivers Pharmaceuticals®, LLC for \$91 Million

www.3riverspharma.com

ALISO VIEJO, Calif. & CRANBERRY TOWNSHIP, Pa.--(BUSINESS WIRE)--Valeant Pharmaceuticals International (NYSE:VRX) and Three Rivers Pharmaceuticals, LLC jointly announced today that they have signed a definitive agreement for Valeant to divest the United States and Canadian rights to the hepatitis C drug Infergen (interferon alfacon-1) to Three Rivers. Valeant will receive from Three Rivers approximately \$70.8 million in cash upon closing, and up to \$20.5 million in two noncontingent payments over the following eighteen months. Under the terms of the agreement, Three Rivers will be assigned all United States and Canadian rights to Infergen and will acquire the remaining Infergen inventory from Valeant. The transaction is expected to close during the first quarter of 2008.

“The sale of Infergen to Three Rivers is an important step forward in executing our strategy of simplifying our operations,” said Timothy C. Tyson, Valeant’s president and chief executive officer. “We believe that by focusing our resources on products and regions where we have the greatest potential for market share growth and profitability, we will be able to improve our margins and yield better long-term shareholder value.”

“We are thrilled to add Infergen to our growing portfolio of antiviral agents,” stated Donald J. Kerrish, RPh, Three River’s president and chief executive officer. “This acquisition further promotes Three Rivers’ continuous strategy to expand its product offerings through product acquisition and internal product development in highly specialized therapeutic disease categories like hepatitis C.”

Infergen, or consensus interferon, is a bio-optimized, selective and highly potent type 1 interferon alpha originally developed by Amgen and launched in the United States in 1997. It is currently indicated as monotherapy for the treatment of adult patients suffering from chronic hepatitis C viral infections with compensated liver disease and is dosed three times per week.

According to the Centers for Disease Control and Prevention, an estimated 3.9 million Americans (1.8 percent) have been infected with the hepatitis C virus (HCV). HCV causes an estimated 10,000 to 12,000 deaths annually in the United States and is the leading cause of the need for liver transplants. The prevalence of HCV is increasing and approximately half of all patients with compensated liver disease do not respond to first-line treatment. There are approximately 250,000 of these non-responder patients currently in the U.S. and the number is growing by an estimated 50,000 each year.

Important Safety Information

Alpha interferons, including Infergen, cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Patients with persistently severe or worsening symptoms of these conditions should be withdrawn from therapy. In many, but not all cases, these disorders resolve after stopping Infergen therapy. The most common side effects are

flu-like symptoms (i.e., headache, fatigue, fever, myalgia, and rigors). Physicians and patients can obtain additional prescribing information regarding Infergen, including the product's safety profile and the box warning for all interferon alphas regarding neuropsychiatric, autoimmune, ischemic and infectious disorders, by visiting www.infergen.com.

About Valeant

Valeant Pharmaceuticals International (NYSE:VRX) is a global, research-based specialty pharmaceutical company that discovers, develops, manufactures and markets products primarily in the areas of neurology, infectious disease and dermatology. More information about Valeant can be found at www.valeant.com.

Infergen is a registered trademark of Amgen, Inc., and Valeant Pharmaceuticals North America is the exclusive licensee from Amgen of this mark for use in the United States and Canada. All other trademarks are the trademarks or the registered trademarks of their respective owners.

About Three Rivers Pharmaceuticals

Three Rivers Pharmaceuticals is a privately held company headquartered in Cranberry Township, Pennsylvania and focuses in specialized therapies like hepatitis C. The company's mission is to develop, manufacture, and market the highest quality branded and generic drug products for patients with serious diseases.

The company is dedicated to increasing patient access to its products and providing access to patient support programs. More information about Three Rivers Pharmaceuticals can be found at www.3riverspharma.com.

FORWARD-LOOKING STATEMENTS

This press release contains forward-looking statements within the meaning of the federal securities laws relating to expectations, plans or prospects for Valeant, including our ability to successfully close the transaction with Three Rivers Pharmaceuticals and divest Infergen and inventory relating to Infergen. These statements are based upon the current expectations and beliefs of Valeant's management and are subject to certain risks and uncertainties that could cause actual results to differ materially from those described in the forward-looking statements. These risks and uncertainties include market conditions, whether Valeant will be able to improve our margins, whether we will be able to yield shareholder value and other factors beyond Valeant's control, and the risk factors and other cautionary statements discussed in Valeant's filings with the U.S. Securities and Exchange Commission. Readers are cautioned not to place undue reliance on any of the forward-looking statements in this press release, which speak only as of the date of this press release. Valeant undertakes no obligation to update any of these forward-looking statements to reflect events or circumstances after the date of this press release or to reflect actual outcomes.

Possible New Way to Detect, Monitor Liver Disease Without Painful Liver Biopsy

<http://www.jrj.com>

DOYLESTOWN, Pa., Dec. 19 /PRNewswire/ -- Scientists working at the Hepatitis B

Foundation, in partnership with Drexel University College of Medicine, think they may have discovered a reliable alternative to liver biopsy for the early detection of liver fibrosis and cirrhosis, which afflict more than 5 million Americans. People with hepatitis B and C infections, as well as fatty liver diseases, are at greatest risk for progressing to cirrhosis that can lead to liver cancer.

Successful treatment depends on the early detection of fibrosis and cirrhosis. Currently, detection involves a surgical liver biopsy, which is an unpleasant, expensive procedure and carries some risk. Patients and doctors would prefer tests that are "not invasive" such as a blood test to detect and monitor liver disease.

Lead investigators Drs. Anand Mehta and Timothy Block report in the upcoming *Journal of Virology*, which appears online next week and in print February 2008, their discovery that the blood of most, if not all, people they tested with a diagnosis of liver cirrhosis, contains high levels of a special antibody that recognizes a carbohydrate sugar commonly found on bacteria. Detection of this antibody in the blood of an affected person correlates very well with a diagnosis of increasing fibrosis and cirrhosis in the new study.

"This is a fascinating discovery and is important because, if confirmed, the test could help us replace liver biopsy as a method for staging liver disease. In addition, it may be teaching us something about how liver disease occurs," said David Thomas, M.D., Chief, Infectious Diseases, Johns Hopkins School of Medicine, Baltimore, MD.

Working with the National Cancer Institute (NCI) Early Detection Research Network, the researchers have been able to test this approach in 300 blood samples from people with liver disease, and can conduct the new test in thousands. Although the test is still experimental and more is needed before it can be used to monitor disease, the discovery is promising.

"If this work is validated, it may offer a new, non-invasive way to test for liver disease, allowing people to either avoid biopsy or to know when they really need one. It also implies that bacteria may have a much bigger role in initiating liver disease than realized, and even lead to new therapies," said Block.

Complications from bacteria in people with cirrhosis are well understood; however, bacteria are not usually seen early in the disease. The significance of this new discovery may suggest earlier treatments with antibiotics could benefit patients with chronic liver disease.

About the Hepatitis B Foundation

The Hepatitis B Foundation is the only national nonprofit organization solely dedicated to finding a cure and improving the quality of life for those affected with hepatitis B worldwide through research, education and patient advocacy. Visit www.hepb.org or call (215) 489-4900 for more information.

Source: Hepatitis B Foundation

Conatus Pharmaceuticals Initiates a Phase 2 Clinical Trial for the Treatment of Hepatitis

<http://www.prnewswire.com>

SAN DIEGO, Dec. 20 /PRNewswire/ -- Conatus Pharmaceuticals Inc. today announced the initiation of a clinical trial with a novel drug candidate for the treatment of liver disease associated with Hepatitis C Virus (HCV) infection in patients who have failed the approved standard of care treatments.

The oral, small molecule drug candidate, **CTS-1027**, is being studied as a treatment for the inflammatory damage to the liver resulting from infection by HCV. CTS-1027 inhibits the activity of key members of a class of protease enzymes, the matrix metalloproteinases or MMPs. In the liver and in other solid organs, MMPs play an important role in regulating inflammation as well as in maintaining the integrity of the extracellular matrix. CTS-1027 has been shown to be effective in multiple preclinical models of liver disease.

The clinical trial is a double-blind, placebo-controlled, multiple-dose trial lasting for four weeks followed by a voluntary open label period of up to eight additional weeks. The Company expects approximately 100 patients to be enrolled. The clinical trial will be conducted at up to ten medical centers in the U.S. Additional information about the trial can be found at <http://www.clinicaltrials.gov> (Identifier NCT00570336) or <http://clinicaltrials.gov/ct2/show/NCT00570336?term=CTS-1027&rank=1>.

"We are excited to initiate this proof of concept trial in HCV patients with CTS-1027," said Steven J. Mento, President and CEO of Conatus. "We believe that CTS-1027 represents a novel approach to treating liver inflammation and look forward to developing this drug candidate to fill an important medical need in HCV-infected patients."

Conatus Pharmaceuticals Inc. is a privately-held specialty pharmaceutical company engaged in the development of innovative human therapeutics to treat liver disease. Chronic liver disease affects millions of people worldwide and can be caused by many different conditions or "insults" to the liver including Hepatitis C and other viral infections, obesity, chronic alcohol abuse or autoimmune diseases. Conatus was founded by the executive management team of Idun Pharmaceuticals in July 2005 following the successful sale of Idun to Pfizer. For additional information, please visit <http://www.conatuspharma.com>.

SOURCE Conatus Pharmaceuticals Inc.

December 21st, 2007

Data About Zetia Risks Was Not Fully Revealed

<http://www.therapeuticsdaily.com>

New evidence shows that the drug makers Merck and Schering-Plough have conducted several studies of their popular cholesterol medicine Zetia that raise questions about its risks to the liver, but the companies have never published those results.

Partial results of the studies, alluded to in documents on the Food and Drug Administration's Web site, raise questions about whether Zetia can cause liver damage when used long term with other cholesterol drugs called statins.

Most of the millions of people who use Zetia take it along with a statin like Lipitor, Crestor or Zocor. Or they take it in a single pill, Vytorin, that combines Zetia with Zocor.

The discovery of the unpublished research comes as Merck and Schering are already under criticism for not yet releasing data from an important Zetia study, called Enhance, that they completed early last year.

The Enhance data may also contain important information about Zetia's liver risks. At least some patients were dropped from the Enhance study after testing revealed that they had elevated liver enzymes, a Schering-Plough spokesman confirmed this week.

But a full report on that trial, including the number of patients who had liver problems, will not be available until March.

Doctors say that by failing to disclose promptly all their research, Merck and Schering-Plough may be leaving the public with a misleadingly favorable view of Zetia's safety and benefits.

"You don't want to have data missing," said Dr. Bruce Psaty, a professor of medicine and epidemiology at the University of Washington. "When there have been adverse effects, when the benefits don't look impressive, those are the trials that historically don't make it to press."

A Schering executive, when asked by a reporter about the unpublished studies, confirmed their existence. But the executive, Dr. Robert J. Spiegel, said the companies had not considered the studies scientifically important enough to publish their findings. Some may eventually be published, he said.

"We're pretty comfortable that people don't have trouble tolerating Zetia," said Dr. Spiegel, the chief medical officer of the Schering-Plough Research Institute, Kenilworth, N.J.

Schering also said that the F.D.A. had reviewed the data from the unpublished studies and had approved Zetia for use alongside statins. But experts on drug safety say that the agency has been slow to issue warnings about many widely used drugs that have turned out to carry serious risks, including the painkiller Vioxx, the diabetes medicine Avandia and the anti-psychotic drug Zyprexa.

Even doctors critical of Zetia generally say it is safe for most patients. But before the drug was approved in 2002, one F.D.A. reviewer said it should not be cleared for use with statins because the combination had caused liver damage in animals. And in the last two years, scattered case reports of severe liver damage in patients taking Zetia in combination with statins have appeared in medical journals.

In the United States, the product label for Zetia contains only mild warnings about the drug's potential for liver damage.

But in Australia and Canada, regulators have been more cautious. Since 2005, they have issued a series of warnings about Zetia's potential to cause hepatitis, pancreatitis and depression -- warnings that have largely gone unnoticed in the United States.

All drugs have potential risks and side effects, of course, and doctors and patients must weigh those against a drug's medical benefits. But in the case of Zetia, despite its widespread use, there is no evidence proving that Zetia can reduce heart attacks and strokes, as cholesterol drugs are meant to do. There is extensive medical evidence showing that Lipitor and other statins provide such protection.

The unpublished Zetia studies, devised as safety tests, would not prove the drug's effectiveness. But they would give the public more information about Zetia's potential risks. All the unpublished studies covered periods at least one year in length and were intended to show whether long-term use of Zetia might pose dangers that short-term use did not.

Most of the studies about Zetia in which Merck and Schering have published the results covered periods of only 12 weeks -- not enough time for liver problems to develop in most patients.

The unpublished studies, conducted from 2000 to 2003 according to the F.D.A. documents, were not listed on the industry Web sites where companies are supposed to register the results of all drug trials that were ongoing after October 2002. The New York Times discovered references to the studies in briefing papers on the F.D.A. Web site.

"We keep telling people we want to practice evidence-based medicine, and what we keep finding out is that much of the evidence is obscured," said Dr. Harlan Krumholz, a cardiologist at Yale, when told about the previously undisclosed studies. "There is important evidence, but it's not in public view. It's hidden from investigators."

Schering and Merck -- which are on track to earn \$5 billion this year from sales of Zetia -- had already been criticized for not promptly releasing results of the Enhance trial, which was completed in April 2006. Under pressure from Congress and prominent cardiologists, the companies said recently that they would release the full results of the Enhance trial by March.

In response to questions from The Times, the Schering spokesman, Lee Davies, disclosed this week that some patients in the Enhance trial had been dropped from it after tests showed that they had elevated liver enzymes -- a potential sign of organ damage. But Mr. Davies said he could not disclose how many, and said the companies did not even know if the patients who had been dropped were taking Zetia and a statin, or just a statin. The delay in releasing the Enhance trial data is unrelated to the patients who were discontinued, Mr. Davies said.

The Enhance data are expected to provide the clearest picture yet of Zetia's long-term affects. But the F.D.A.'s documents show that Merck and Schering conducted several other long-term trials of Zetia without releasing their findings.

Together those studies cover several thousand patients who took Zetia along with statins for one to two years. The statins include Lipitor and Crestor, as well as Zocor, which is usually

prescribed generically as simvastatin and is the statin used in the Vytorin pill. Doctors often add Zetia to a low dosage of a statin, because Zetia reduces cholesterol in a different way than the statins do and leads to deeper overall cholesterol reductions.

One open question is whether Zetia's method of lowering cholesterol provides the same medical benefits as fighting cholesterol with a higher-dose statin by itself. Last year, Merck and Schering began a separate study -- a 10,000-patient clinical trial to prove that Zetia's ability to lower cholesterol will translate into fewer heart attacks and strokes in patients. But data from that trial will not be available until at least 2011.

In the meantime, some doctors say, they must essentially take on faith that Zetia's cholesterol-lowering ability will translate into real-world benefits and that its long-term use with statins does not have major risks.

Dr. Eric J. Topol, a cardiologist and director of the Scripps Translational Science Institute in La Jolla, Calif., said that he had asked Merck and Schering more than four years ago to conduct a large, long-term trial to prove that Zetia could reduce heart attacks and strokes. But the companies had little interest, he said.

"They looked at me like I was an alien," Dr. Topol said.

Two months ago, President Bush signed a new law intended to strengthen penalties for companies that do not release information promptly. And in 2004, the drug industry promised to improve disclosure of research results.

But the new law applies only to new trials, meaning the unpublished Zetia trials are not covered by those new rules and guidelines.

The F.D.A. has reviewed the unpublished studies, according to the agency's briefing papers.

The companies' own published studies have generally played down the risk of liver problems. But Dr. Mark Stolk, a gastroenterologist in the Netherlands, last year reported two cases of patients who had developed hepatitis, a liver disease, after taking Zetia alongside Lipitor. One of the patients has since died, Dr. Stolk said in an interview last month. While Zetia is safe for most patients, doctors should carefully monitor patients for liver damage, he said.

"I think other cases will emerge," he said.

When the F.D.A. approved Zetia in 2002, it relied on trials that covered only 3,900 patients and lasted no more than 12 weeks. Still, the data from even those trials contained signals that Zetia might be dangerous in some patients when it is taken alongside statins, as it usually is.

In those trials, 11 times as many people who took Zetia along with a statin subsequently had serious health problems, compared with those who took a statin alone. Nearly all the serious problems were liver-related. Still the F.D.A. regarded the risks as relatively minor and approved Zetia without asking the companies to conduct longer trials.

The agency did not respond to requests for comment.

All drugs have risks, of course. Doctors who prescribe Zetia say that while they would prefer to see long-term trial data, they are comfortable using it because decades of evidence demonstrated that lowering LDL, or so-called bad cholesterol, is good for patients.

But Dr. Beatrice A. Golomb, an associate professor at the University of California, San Diego, said doctors have lost sight of the purpose of prescribing drugs like Zetia.

The goal of prescribing cholesterol-lowering drugs is not reducing cholesterol, Dr. Golomb said. It is reducing the number of deaths and heart attacks in patients, he said. And without data to prove that Zetia actually reduces heart attacks, doctors cannot be sure they are helping patients when they prescribe the drug, she said.

Infection in blood, donors unaware

<http://www.telegraphindia.com>

SANJAY MANDAL

Kanad Majhi (name changed) had donated blood at a camp organised in his locality, on the city's northern fringes. During the mandatory screening of the blood sample at Medical College and Hospital, Kanad was found to have contracted Hepatitis B.

Hepatitis C virus was detected in the blood sample of Swapan Nag (name changed), a regular blood donor, during a screening at a private blood bank.

None was informed about the infection.

Like Majhi and Nag, blood donors are never told whether they are carrying any infection. Hence, there is always the risk of them unknowingly passing on the infection to others.

Year after year, millions of blood donors are being deprived of their right to be informed and counselled about the transmittable diseases they are carrying.

Both state-run and private blood banks stand accused of violating a guideline of the National AIDS Control Organisation (Naco), which states that the donor has the right to know about his health and should be counselled if he is found to be carrying any disease like HIV and Hepatitis that spreads through blood.

“An infected donor, if not informed about the disease, can infect others unknowingly,” said Sharmila Chanda, a consultant haematologist. If the infected donor gives blood for the second time and the reagents used for testing the sample are faulty, the infection will go unnoticed.

Naco's guidelines on blood safety state that every donor at blood donation camps must be asked to fill up a form and specify where he would like to be informed about disorders in the blood, if any. The donor is supposed to mention his contact numbers and address on the form.

“No blood bank ever gets back to the donor even after a virus is detected in the blood,” a state health department official said.

Every year, on an average, 5.5 lakh units of blood are collected at camps across the state and brought to the blood banks. Health department statistics said that of the total blood samples, 0.6 per cent are found to be HIV seropositive, 1.6 per cent infected with Hepatitis B and 0.4 per cent infected with Hepatitis C.

“These donors do not get to know about the infection unless there is some manifestation. The infected samples and the corresponding blood pouches are destroyed and the responsibility of the blood bank ends there,” said the official.

Officials in charge of blood safety said a rule is being framed, making it mandatory for HIV positive persons to be informed about their status through confidential counselling. “Informing donors individually is a problem. On certain days, there are huge collections and it becomes impossible for the banks to track down the donors and inform them about the infections,” argued Bhaskar Bhattacharya, the deputy director of blood safety in the state health department.

“We ask donors to contact us if they want to know about their blood status,” said Abhijit Banerjee, the medical director of Ashok Blood Bank.

Pair indicted on fraud charges in medical-device probe

<http://seattletimes.nwsourc.com>

By Christine Willmsen and Michael J. Berens
Seattle Times staff reporters

A Mount Vernon couple operated a clandestine health-care clinic that offered bogus treatments for hepatitis and cancer with unproven medical devices, according to a federal grand-jury indictment.

Donald Brandt, 77, and Sharon Brandt, 65, who ran a clinic out of their home, face three felony counts involving fraud, according to the indictment. They will make an initial appearance on Jan. 3 in U.S. District Court in Seattle.

From 2002 through 2005, Donald Brandt posed as a medical doctor and used devices that purportedly fired radio frequencies that cured disease, according to a federal search warrant and state records.

He had no health-care license or degree.

His wife, Sharon, was in charge of scheduling appointments, and allegedly told patients, their family members and undercover state investigators to "keep quiet" about their treatments or the clinic would be in trouble for their "unapproved and clandestine" work, according to state and federal records.

Wednesday's indictment follows an extensive investigation by the U.S. Food and Drug

Administration and Washington state Department of Health. The state investigation showed Brandt earned \$807,950 in treatment fees since 1995.

At least one person — a 32-year-old Bellingham man — died while being treated by the Brandts with an unproven machine, the search warrant states.

Donald Brandt treated the man, who was diagnosed with testicular cancer, for more than a year. The man's physician recommended immediate surgery to save his life. After refusing surgery and spending several thousand dollars on the device treatments, the man died Dec. 14, 2004, of cancer, leaving a wife and three young children.

"Unless the illegal use of this adulterated and misbranded device is stopped, these persons will likely die, or will have shortened life spans, absent contemporary medical intervention," stated FDA investigator Jim Burkhardt in the search warrant.

A recent Seattle Times investigation, "Miracle Machines," found that many energy devices flourish in the underground market — through alternative health conferences and the Internet.

The three-day series revealed how manufacturers and practitioners profit from treating people with unproven or fraudulent machines, some of them potentially dangerous, others illegal.

These devices are part of a growing and largely unregulated field called "energy medicine" — alternative therapies based on the belief that the body has energy fields that can be manipulated to improve health.

The Brandts had several energy devices known as Rife machines or wave form generators and a Vibe Machine for use at the clinic. None is registered for use by the FDA.

Rife machines are named after inventor Royal Rife, who in the 1930s created a device that purportedly destroyed disease with radio frequencies. There is no credible scientific evidence to substantiate that Rife devices work, according to the National Institutes of Health.

The Brandts also fraudulently used an unproven, pain-relief device called the Electro-Acuscope Model 70-C, according to the indictment.

They allegedly are part of a widespread underground movement of unlicensed health-care practitioners who use unproven devices to treat patients.

Last year more than 300 people attended the Rife International Health Conference in Seattle, where dozens of unregistered devices were sold, The Times investigation found.

Christine Willmsen: 206-464-3261 or cwillmsen@seattletimes.com; Michael J. Berens: 206-464-2288 or mberens@seattletimes.com

Romark raises \$18 million

Tampa Bay Business Journal

Romark Laboratories LC received \$18 million in institutional financing with the D.E. Shaw Group.

The funding will enable Romark to advance development of its lead compound, **nitazoxanide**, for the treatment of hepatitis C, and advance its next-generation thiazolide drug candidates for the treatment of hepatitis B and C and other viral diseases, according to a release.

Romark is currently conducting a U.S. Phase 2 trial of nitazoxanide in hepatitis C patients who have failed standard treatments, and expects to begin a U.S. Phase 2 trial in treatment naive patients in the first quarter of 2008.

Romark is a privately owned company based in Tampa.

D.E. Shaw Group is a global investment firm headquartered in New York with about \$35 billion in aggregate investment capital.