

The Best in the News on HCV, HBV, and HIV/HCV Coinfection from August 15th, 2003 thru September 1st, 2003

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Editor-in-Chief

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August 15th, 2003

Immtech Compounds Show Promise Against Flavivirus (Hepatitis C and BVDV) And Animal Market Applications

Immtech International, Inc. (Amex: IMM) announced today publication of scientific data describing the activity of aromatic cationic molecules against the Bovine Diarrhea Virus ("BVDV"). BVDV is an RNA Flavivirus genus commonly found in cows, and is similar to both the human hepatitis C virus and the virus that causes West Nile infections.

In the paper, published in *Antimicrobial Agents and Chemotherapy*, July 2003, Volume 47, entitled "Detection of Inhibition of Bovine Diarrhea Virus by Aromatic Cationic Molecules," the lead authors, Daniel Givens, (Auburn University) and David Boykin, (Georgia State University) presented data on the activity of compounds screened in an assay that evaluates the total life cycle of viral propagation. The scientists identified five Immtech compounds demonstrating exceptional efficacy,

inhibiting propagation of the BVDV virus at low (nanomolar) concentrations with low toxicity. Such activity makes these compounds excellent candidates for advanced testing against the hepatitis C virus.

Stephen Thompson, President & CEO of Immtech said, “The results observed by our scientists demonstrate the promise of cationic molecules as anti-viral agents and possibly against hepatitis C. We believe that there is an advantage in having a reliable assay system that evaluates the complete viral life cycle for screening compounds for anti-hepatitis C activity. We are using the information generated from these studies to further evaluate specific cationic compounds for anti-hepatitis C activity.”

While the exact mechanism by which these compounds exert anti-viral activity is unknown, their known capacity to interact with nucleic acids and inhibit proteases suggests multiple modes for anti-viral activity. Potential outcomes from this research include developing a drug to treat Bovine Diarrhea Virus infections in calves and preventing viral contamination of embryos during in vitro fertilization, placing Immtech in the multi-billion dollar animal health market. One of the lead candidates has advanced into research using bovine embryos to determine if the compound could prevent BVDV contamination of the embryos during in vitro fertilization and embryo transfer (BVDV infections are a common cause of abortion in cows). The study demonstrated that the compound was safe to use during in vitro fertilization and that embryos developed after transfer resulted in the birth of normal calves. The successful elimination of BVDV from embryos implanted in cows can greatly reduce the abortion rate of calves during the in vitro fertilization process. This market can potentially be very profitable because in vitro fertilization is the most common method used to impregnate cows. This BVDV research was supported by a grant from the National Institutes of Health. Immtech International, Inc. is a pharmaceutical company focused on the commercialization of oral treatments for infectious diseases such as pneumonia, fungal infections, malaria, tuberculosis, hepatitis and tropical diseases such as African sleeping sickness and Leishmania. The Company has worldwide, exclusive rights to commercialize a dicationic pharmaceutical platform from which a pipeline of products may be developed to target global markets.

Interferon Induction Therapy Does Not Enhance SVR and Relapsers with Genotypes 1 and 4 Retreated with High Dose Interferon Plus Ribavirin for 48 Weeks Have 50% Response Rate

by hivandhepatitis.com

Retreatment of relapser patients with chronic hepatitis C with the standard dose of interferon (IFN) of 3 million units (MU) thrice weekly (tiw) plus ribavirin for 24 weeks achieves a sustained response in 30 and 73% of patients with genotype 1 and 2 or 3, respectively.

The aim of this study was to evaluate the efficacy and safety of IFN alfa-2b (Intron A) induction therapy, followed by prolonged treatment with a high dose of IFN alfa-2b plus ribavirin in relapser patients.

A total of 119 patients were randomized to receive IFN alfa-2b 5 MU daily (Group A: 59 patients) or IFN alfa-2b 5 MU tiw (Group B: 60 patients) for 4 weeks followed by IFN (5 MU tiw) and ribavirin (1000-1200 mg/day) for 48 weeks in both groups.

The primary end point was hepatitis C virus (HCV)-RNA clearance at week 24 after the end of treatment.

A sustained virological response (SVR) was achieved in 68 and 60% of Group A and B patients, respectively ($P = 0.37$). Logistic regression analysis identified genotype 2 or 3 as the only independent factor associated with response, whereas induction regimen and baseline viremia levels did not affect the response.

The overall SVR was 53 and 72% in patients with genotype 1 or 4 and 2 or 3, respectively.

In conclusion, induction IFN therapy does not enhance the SVR to a 48-week combination therapy. Our study suggests that relapsed patients with genotype 1 or 4 may achieve significant response rates of approximately 50%, if retreated with 5 MU tiw IFN plus ribavirin for 48 weeks.

HCV Infection of the Central Nervous System May Cause Neuropsychological Symptoms and Cognitive Impairment

by hivandhepatitis.com

A number of studies have reported an association between chronic hepatitis C (HCV) infection and significant impairments in health-related quality of life (QOL). These impairments are independent of the severity of liver disease.

There are numerous reports documenting the prevalence of symptoms such as fatigue and depression in chronic HCV infection, which may in part account for the reductions in quality of life.

Although there are a large number of potential explanations for these symptoms, including depression and anxiety associated with the diagnosis of HCV infection or substance abuse, there has been recent interest in the possibility of a biological effect of HCV infection on cerebral function.

There is emerging evidence of mild, but significant neurocognitive impairment in HCV infection, which cannot be attributed to substance abuse, coexistent depression or hepatic encephalopathy.

In vivo magnetic resonance spectroscopy and neurophysiological studies have suggested that a biological mechanism may underlie these cognitive findings.

The recent detection of HCV genetic sequences in post mortem brain tissue raises the intriguing possibility that HCV infection of the central nervous system may be related to the reported neuropsychological symptoms and cognitive impairment.

Austrian Study Recommends Twice-Weekly Dosage of PEG-Intron

by newsrx.com

University of Vienna internists are recommending at least twice-weekly dosing of peginterferon-alpha-2b for their patients with chronic hepatitis C.

They say this schedule is necessary to continually expose the virus to the drug and to improve initial viral clearance.

“The decline in hepatitis C viral load on treatment with peginterferon-alpha-2b is not continuous,” said E. Formann and colleagues. “The aim of this study was to investigate whether twice weekly dosing of peginterferon-alpha-2b [PEG-IFN-a-2b] may improve viral kinetics.”

Study subjects were 10 interferon-naive patients with chronic hepatitis C - genotype 1a or b. They were “randomized to receive either 10 mcg/kg PEG-IFN-a-2b once (group A) or twice weekly (group B) for 4 weeks.”

Formann and colleagues reported that “PEG-IFN-a-2b reached maximal blood concentrations 24 hours after the first dose, followed by a linear decline during the subsequent days. On the day before administration of the next dose, PEG-IFN-a-2b was undetectable in nine patients in group A (once-weekly dosing). The same pattern was observed during the next 3 weeks of therapy.”

They could detect PEG-IFN-a-2b at any time point in patients under the twice-weekly regimen, the researchers said, adding that the drug levels always were “higher than in group A (p between 0.01 and <0.0001).”

“Viral load decreased in all patients within 2 days after the first dose of peginterferon-alpha-2b, but increased again on day 3. In group A, it further increased until day 7. A similar pattern was observed in the second week.

“In contrast, in group B, viral load decreased again on day 4 and remained lower until the end of the study (p<0.001),” reported Formann’s team.

“To achieve continuous drug exposure and to improve initial viral clearance, peginterferon-alpha-2b has to be given at least two times weekly,” they concluded.

Formann and coauthors published their study in the *Journal of Viral Hepatitis* (Twice-weekly administration of peginterferon-alpha-2b improves viral kinetics in patients with chronic hepatitis C genotype 1. *J Viral Hepatitis*, 2003;10(4):271-276).

Time on Anti-HIV Therapy Is a Protective Factor for Liver Fibrosis in HIV-HCV Coinfected Patients

by hivandhepatitis.com

To assess the factors associated with liver fibrosis in HIV and hepatitis C virus (HIV/HCV) co-infected patients eligible for anti-HCV therapy, researchers performed an observational, single-centred, cross-sectional study of 180 HIV/HCV co-infected patients who underwent liver biopsy between May 1998 and November 2001.

A total of 126 patients with a known date of HCV infection were evaluated. Liver fibrosis was defined as a Knodell stage of fibrosis 1-4.

The mean age was 36.7 (3.8) years, 81% were male and had a mean age of 20.5 (3.8) years at HCV infection. Mean CD4 cell count and plasma HIV-1 RNA load at the time of biopsy were 552 cell/mm³ (239) and 2.5 log₁₀ (0.9), respectively; 118 patients had been on antiretroviral therapy (ART) for a median of 45 months (Q1-Q3: 21-75) and 84 on protease inhibitor for a median of 12.0 months (Q1-Q3: 0-29.5); 55 had an AIDS event or a CD4 cell count nadir < 200 cells/mm³ prior to biopsy.

Median histological activity index was 6 and 27% had a Knodell stage of fibrosis 0. On the multivariate analysis time on ART, CD4 cell count at the time of liver biopsy, age at HCV infection acquisition and alcohol intake (> 50 g/day) were associated with liver fibrosis.

The authors conclude, "ART should be a priority in HIV-HCV co-infected patients eligible for anti-HCV treatment as it is a protective factor for liver fibrosis."

Antiviral Therapy of Patients for Patients Awaiting Liver Transplantation: A Strategy to Prevent Hepatitis C Recurrence After Transplantation

by gastrohep.com

The utilization of antiviral therapy in hepatitis C virus infected patients awaiting liver transplantation is a useful strategy to prevent hepatitis C recurrence after transplantation, according to a study published in *The Journal of Hepatology* (*Journal of Hepatology* 2003; 39(3): 389-396).

After liver transplantation infection of the graft with the hepatitis C virus is almost universal. This leads to the development of chronic hepatitis and cirrhosis in a significant proportion of patients.

One of the possible strategies to prevent recurrence of hepatitis C is to eradicate hepatitis C virus prior to liver transplantation.

A team of Spanish doctors evaluated the efficacy and safety of antiviral therapy to prevent hepatitis C recurrence in 30 patients with hepatitis C and cirrhosis awaiting liver transplantation.

Antiviral therapy was initiated when the expected time for liver transplantation was less than 4 months away and continued until the transplant took place. The median duration of treatment was 12 weeks.

Antiviral therapy consisted of interferon-2b (3 MU/day) and ribavirin (800 mg/day).

9 out of the 30 patients achieved a virological response and 21 did not respond to therapy. Viral load decreased in 9 of the 21 non-responders during treatment.

The 9 patients who responded to antiviral therapy have since undergone liver transplantation. 6 of the 9 patients remain free of infection after a median follow-up of 46 weeks, while hepatitis C viral infection recurred in the remaining 3.

30% of patients had a virological response to antiviral therapy.

Side effects were frequent and dose reduction was necessary in 19 of the 30 patients.

The authors of the study conclude “Our data support the utilization of antiviral therapy in hepatitis C-infected patients awaiting liver transplantation as one of the strategies to prevent hepatitis C recurrence after liver transplantation.”

However, in an editorial which appears in the same issue of The Journal of Hepatology, Dr Jean-Pierre Zarski adds a note of caution.

“Antiviral therapy should be considered experimental and not be administered outside of prospective trials.”

Liver Transplant Recipients Over 60 Years Old Have Lower Survival and Higher Incidence of Malignancy

by gastrohep.com

Older liver transplant recipients have a significantly lower survival than younger patients and malignancy is responsible for this decreased survival, concludes a study in the American Journal of Transplantation.

Older age is not considered a contraindication for liver transplantation.

A team of Doctors in Spain reviewed 111 liver transplants to compare the survival of patients over 60 years old who undergo liver transplantation with the survival of younger patients.

They also investigated any factors involved in a potential difference in mortality.

After transplantation, older patients had a significantly lower survival.

Of the 111 patients analysed 54 were older than 60 years of age and 57 were younger. After transplantation, older patients had a significantly lower survival. Higher age was associated with increased mortality independent of other variables.

The incidence of de novo neoplasia and nonskin neoplasia was significantly higher in older patients.

Malignancy was the cause of death in 12 patients older than 60 years, but only 1 patient younger than 60 years.

Higher age as well as smoking were significantly associated with the incidence death due to de novo neoplasia.

Increased frequency of malignancy in older transplant patients appears to lead to increased mortality.

Defective Memory Function in Early Hepatic Encephalopathy

by gastrohep.com

A study in the September issue of The Journal of Hepatology (Journal of Hepatology 2003; 39(3): 320-5) finds that although patients with early hepatic encephalopathy score lower than controls in memory tasks, this is predominantly due to deficits in attention and visual perception.

Early hepatic encephalopathy is characterized by deficits in motor performance, visual perception, visuo-constructive abilities and attention.

Whether defective memory is a feature of early hepatic encephalopathy remains controversial.

Dr Karin Weissenborn and colleagues in Hannover, Germany, attempted to resolve this controversy by analysing memory function in 45 patients with early hepatic encephalopathy.

Memory tests were applied to cirrhotic patients with minimal, grade 0, or grade 1 hepatic encephalopathy and the results were compared with those seen in 52 control subjects.

Tasks included short and long term memory tests requiring free recall or recognition.

Patients' deficits were in attention and visual perception, rather than memory.

Patients with early hepatic encephalopathy scored lower than the controls in all of the memory tasks.

Dr Weissenborn's team conducted a detailed analysis of test performance, which revealed that the patients' deficits were in attention and visual perception, rather than memory.

Dr Weissenborn concludes "Although patients with early hepatic encephalopathy score lower than controls in memory tasks, this is predominantly because of deficits in attention and visual perception."

Previous HBV Infection Does Not Affect Liver Histology or the Response to Interferon-based Therapy in HCV Patients

by hivandhepatitis.com

Patients with chronic hepatitis C frequently have antibodies to the hepatitis B core antigen (anti-HBc), indicative of prior hepatitis B virus (HBV) infection. In these patients, persistence of HBV may exacerbate liver injury and diminish the response to treatment.

The aim of this study was to evaluate the relationship between previous HBV infection and liver histology and the sustained virologic response (SVR) to interferon (IFN)-based therapy in patients with chronic hepatitis C.

A total of 132 HBsAg-negative, treatment-naive patients were evaluated. Using multiple logistic regression analysis, the impact of anti-HBc-positivity on the rate of SVR was determined. Progression to bridging fibrosis or cirrhosis was assessed using Cox proportional hazards regression and Kaplan-Meier survival analysis.

The median age of the patients was 47 years (IQR, 37-60), 57% were male, and 73% had genotypes 1, 4, 5, or 6. Fifty-one patients (39%) were anti-HBc-positive. The prevalence of moderate to severe necroinflammatory activity ($P = 0.36$) and progression to bridging fibrosis or cirrhosis (log-rank $P = 0.83$) was similar between anti-HBc-positive and -negative patients.

After a median of 48 weeks (IQR, 26-52) of therapy (IFN, $n = 116$; IFN and ribavirin, $n = 16$), 23 patients (17%) achieved a SVR; the rate of response was similar in anti-HBc-positive and -negative patients (18% vs 17%, $P = 1.00$).

After controlling for age, gender, genotype, fibrosis, and treatment regimen, anti-HBc status did not independently affect the rate of SVR ($P = 0.58$).

In conclusion, previous HBV infection does not affect liver histology or the response to IFN-based therapy in patients with chronic hepatitis C.

Schering-Plough Says It Is Running Out of Cash

by Lewis Krauskopf

In the latest fallout from its waning Claritin franchise, Schering-Plough Corp. warned investors Tuesday it may have to borrow to fund this year's cash needs.

The Kenilworth-based drug maker said that for the rest of 2003 -- and "possibly beyond"—cash from its operating activities may not be enough to fund working capital, capital expenditures, and dividends. The situation particularly relates to its U.S. operations.

Schering-Plough, which has a solid, investment-grade credit rating, said it plans short-term borrowing to cover its needs. But the company has not ruled out job cuts or

reducing its dividend. Schering-Plough employs about 7,000 people in New Jersey, and nearly 30,000 worldwide.

Sales of the allergy pill Claritin—once a \$3 billion-a-year cash cow making up more than 30 percent of company sales—have evaporated after the company lost marketing exclusivity and converted it to an over-the-counter product. In the second quarter alone, prescription Claritin sales in the United States dropped to \$13 million from \$677 million in the 2002 period. Other products, such as its Intron hepatitis C franchise, have failed to pick up the slack.

Schering-Plough gave its cash warning as part of an SEC document filed Tuesday designed to answer frequently asked questions by investors. The company had described the situation in previous filings. Shares slipped 15 cents to \$16.10, recovering after falling as much as 11 percent early in the day.

Schering-Plough's net cash from operating activities totaled \$429 million in the first six months, compared with \$870 million in the first half of last year.

Cash from operations was sufficient in the first quarter. But in the second quarter, the company paid \$250 million as part of a fine levied by the U.S. Food and Drug Administration over manufacturing practices. That payment offset cash flow from operations, the company said, so the company borrowed to pay for capital expenditures and dividends.

“For the remainder of 2003 and possibly beyond, cash provided by operating activities will not be sufficient to fund working capital, capital expenditures, and dividends if these items remain at levels comparable to that in the first and second quarters,” the company said.

However, the company also said it has “adequate internal and external resources” to meet its financial requirements.

Further, the company said it might have further payments related to other legal and regulatory problems. For example, the SEC may bring action against the company and its previous CEO, Richard Jay Kogan, for meetings with investors and analysts last fall. And the company is a target of a criminal investigation by the U.S. Attorney's Office in Massachusetts for its sales and marketing practices.

During Schering-Plough's earnings slide, the company's dividend has come under scrutiny. At 17 cents per common share, the quarterly dividend is costing Schering-Plough about \$1 billion a year. Schering-Plough has increased its dividend 19 times since 1986.

As the company has stated before, Fred Hassan, the new chief executive, has been asked to do a “360-degree review” of the company's operations, including its dividend.

“The company is generating cash to pay capital expenditures,” said Todd Lebor, an analyst with Morningstar Inc. “What it's not doing is generating enough cash at the end of the day to pay the dividend as well.” However, Lebor said, the company's hole

is temporary and it should be generating enough cash to do both within two years. He said the company's new cholesterol treatment Zetia is expected to be a bigger revenue contributor by then.

Hassan said last month he would seek to wring out \$200 million in annual savings from the company's current cost structure. Schering-Plough hired Hassan, the former CEO of Pharmacia Corp., in April to turn around the company's fortunes.

August 17th, 2003

HBV Detected in Livers of Patients Said 'Cured'

Yomiuri Shimbun

The hepatitis B virus (HBV) lingers in the liver for a longer time than previously believed and can reemerge in a carrier's blood after a sufferer of the disease is thought cured, according to findings of research conducted by the Osaka National Hospital and other medical organizations.

It was widely believed that the disease would not become chronic in adult carriers more than six months after acute symptoms had been cured. Such carriers were then allowed to again donate blood.

The team said that it is unlikely the liver virus would have an adverse effect on carriers' health, but it may be a source of infection in a virus-free blood transfusion recipient.

The finding is likely to have a significant impact on the blood donation screening system.

Adults with normal immune systems carry antibodies in their blood to attack HBV and prevent it from becoming a chronic disease.

Once the antibodies in a carrier's blood system have been activated, it was previously believed that the carrier could not be reinfected with the disease.

However, in a reexamination of 14 former carriers whose livers have been functioning normally for between 2 and 9 years after contracting the disease, Nobukazu Yuki, head of the hospital's Department of Gastroenterology, and other researchers detected the virus in the blood of three of the former patients.

Furthermore, an examination of liver tissue from nine of the 14 former carriers, who consented to biopsies, revealed that all had the virus, and seven were suffering from a slight inflammation of the liver.

In the Japanese Red Cross Society's safety checks on donated blood, it is difficult to detect HBV unless the viral count is above 1,000 HBVs per milliliter of blood.

However, there have been cases in which carriers with a viral count thought lower than 50 died from the disease.

The counts in the three former patients found to have the virus were 770, 1,300 and 24,000, respectively.

Blood donated by the two with the lowest counts could have slipped through the society's safety tests and subsequently infected transfusion recipients.

There have been reports in recent years that the virus would linger in the liver after carriers were believed to be cured, but this is the first time the virus was found to have survived in nine former patients who underwent posttreatment check-ups.

After treatment, it was believed that the viral count could not rise as antibodies in the immune system had been activated and were thought to keep the count down. Therefore, it was not expected that a viral count as high as 24,000 HBVs per milliliter would have been detected in a previously cured patient's blood.

August 18th, 2003

In Vivo Immunization Following Suppression of HBV: A New Approach for Inducing Immune Control in Chronic Hepatitis B

by hivandhepatitis.com

Antiviral treatment of patients with active chronic hepatitis B may lead to a significant reduction in morbidity and mortality. However, after stopping nucleoside analogue therapy, relapse rates are high in those without acquired specific immunity.

Researchers at the University Medical Center Rotterdam, The Netherlands have treated two chronic hepatitis B patients with in vivo immunization. In vivo immunization aims to optimize conditions for an effective immune response: following rapid and profound virus suppression by interferon-lamivudine combination therapy, lamivudine is withdrawn intermittently for 4 weeks during continued interferon therapy.

In both patients with profound virus suppression a rapid rebound in viral replication was observed after lamivudine withdrawal, despite continued interferon. These periods of renewed viral replication were followed by rises in hepatitis activity.

After re-introduction of lamivudine, HBV DNA became undetectable by PCR followed by normalization of serum ALT. These observations are a stimulus to further explore the concept of in vivo immunization as a novel therapeutic approach for chronic hepatitis B.

Clearly, these results in two patients require confirmation in a larger study.

Are HBV Vaccine Booster Doses Unnecessary in Immunocompetent Persons?

by hivandhepatitis.com

This review analyses the cumulated data from a number of long-term follow-up studies among infants, children and adults vaccinated against hepatitis B in industrialized and developing countries.

Despite low or undetectable antibody responses years after vaccination, the development of HBsAg was a rarity and, if present, only transient. Some vaccinees developed anti-HBc responses but none developed an HB carrier state or clinical manifestations of disease.

Studies demonstrating anamnestic responses among those with low or undetectable anti-HBs levels following challenge with HB vaccine, together with the production of anti-HBs in circulating B-cells by spot ELISA, confirmed the presence of immune memory among vaccinees.

Anamnestic anti-HBs responses all correlate close in kinetics and magnitude with proliferative T-cell responses.

The accumulated data from studies assessed in this review indicate that protection is dependent on immune memory, rather than declining anti-HBs responses and add additional weight to the European Consensus recommendations that following a complete course of vaccination, booster doses are unnecessary in immunocompetent persons.

If implemented, this recommendation will have considerable cost benefits world-wide.

Task Force Formed to Combat Hepatitis

Islamabad: A task force has been established in North West Frontier Province as part of a province-wide campaign to combat rapidly spreading hepatitis, an official said on Wednesday.

“It is a one week campaign with different components, including seminars, workshops, display posters and walks to create awareness. The NWFP is the first region in Pakistan to launch such a campaign,” Provincial Health Secretary, Dr Ihsan-Ul-Haq, said from Peshawar. He added that the federal government is working on a similar idea for the whole country. A private pharmaceutical company has pledged to provide discounted vaccines, he said.

“Cases of hepatitis C have risen dramatically, making it twice as prevalent as hepatitis B,” said the chairman of the hepatitis task force in Peshawar, Dr Najibul Haq.

“The main objective of the campaign is to increase awareness in people about the simple ways to avoid hepatitis. We are targeting different groups to spread the message,” he said, noting that the task force is also working on legislation with the government in respect to preventative measures.

All the districts in NWFP were involved. The three main components of the campaign were intended to raise awareness among health workers, to hold public meetings in hospitals and arrange walks, Najibul Haq said. He added that his task force wanted to see the activities continue even after the campaign ended.

He said the campaign should involve local religious and community leaders, members of parliament, heads of local government, councillors and health workers.

At present, 18 percent of all patients admitted to general wards in hospitals in the NWFP suffer from some type of hepatitis, the chief of NWFP government's Health Sector, Research and Reform Unit, Dr Mohammed Rafiq, said. "There are nine million hepatitis B carriers in Pakistan." IRIN

Biochemical Markers of Liver Fibrosis and Activity Can Be Used as Surrogate Markers for Liver Biopsy in Patients with Chronic Hepatitis C

by hivandhepatitis.com

In patients infected with hepatitis C virus (HCV), recent studies have demonstrated the predictive value of combinations of simple serum biochemical markers.

Abbreviations:

HCV - hepatitis C virus

FT - Fibrotest

AT - Actitest

ALT - alanine aminotransferase

SVR - sustained virologic response

GGT - glutamyl transpeptidase

ROC - receiver operating characteristic AUROC - area under the ROC curves

These markers include Fibrotest (FT) for the diagnosis of significant fibrosis (ranging from few septa to cirrhosis) and Actitest (AT) for the assessment of necroinflammatory activity fibrosis and activity. Such results were not obtained by other diagnostic tests.

The usual indication for liver biopsy in patients with chronic hepatitis C is to aid in the discussion of treatment options with the patient and for the long-term follow-up of patients to determine whether their disease is stable or whether it has progressed.

Prior data suggest that FT-AT, if accurate, could act as a surrogate and lead to a significant reduction in the number of liver biopsies performed. The aim of this study was to validate the usefulness of FT-AT as surrogate markers of histologic features using the data generated from a recent randomized trial of peginterferon alfa-2b and ribavirin.

Three hundred fifty-two patients who had had 2 interpretable liver biopsies and stored serum sample before and after treatment were selected. Two hundred eight patients received peginterferon alfa-2b 1.5 mcg per kg and ribavirin and 144 patients interferon alfa-2b 3 MU three times a week and ribavirin for 48 weeks.

A fibrosis and an activity index combining 5 and 6 biochemical markers were assessed at baseline and at end of follow-up (24 weeks after treatment).

The biochemical markers have significant predictive values both for the diagnosis of fibrosis and for activity. For the diagnosis of bridging fibrosis and/or moderate necroinflammatory activity, the area under the receiver operating characteristics curve of the activity index was 0.76 ± 0.03 at baseline and 0.82 ± 0.02 at end of follow-up. A cutoff of activity index at 0.30 (range, 0.00-1.00) had 90% sensitivity and 88% positive predictive value for the diagnosis of bridging fibrosis or moderate necroinflammatory activity.

Sensitivity analyses with biopsy specimens of size greater than 15 mm suggest that a part of discordances between biochemical markers and histology were due to biopsy specimen sampling error.

In conclusion, these biochemical markers of fibrosis and activity could be used as surrogate markers for liver biopsy in patients with chronic hepatitis C, both for the initial evaluation and for follow-up.

This study is the seventh demonstrating that a combination of 5 (FT) or 6 biochemical markers (AT) can have high positive or negative predictive values for diagnosing significant fibrosis and significant activity in patients with chronic hepatitis C. Although retrospective, the analyses of this study were made with an independent assessment of FT-AT, of fibrosis stages, and of activity grades.

These scores are derived from tests that are not yet routine in many countries. However, all the 6 components are available in most countries. When compared with routine laboratory tests found to be predictive of activity or fibrosis, the researchers found better diagnostic values for their scores. In addition to superior diagnostic power, FT is not genotype dependent, whereas the Forns et al. index includes serum cholesterol, which varies with HCV genotype.

The results show that FT-AT can also be used as surrogate markers of the histologic impact of treatment. Both indexes were associated with the virologic responses and with the histologic variations.

In chronic hepatitis C, the impact of treatment on fibrosis progression and activity is related to the virologic response and, for virologic nonresponders, to the baseline stage of fibrosis and to the duration of treatment. Therefore, FT-AT could be used as surrogate markers in trials evaluating the risk-benefit of maintenance therapy, without increasing the risk and the cost because of repeated liver biopsies.

Recommendation of Future Management of Chronic Hepatitis C Without Liver Biopsies

From the previous results and those presented here, a simplification of the management of chronic hepatitis C is possible, particularly using a cutoff of 0.30 for

AT. Because this analysis is retrospective, a randomized trial of 2 strategies comparing a strategy without and with biopsy is certainly the best scientific comparison of the respective utilities. However, this type of trial would require a very large number of patients to estimate the severe adverse events.

The authors conclude, “Because of the improvement of biochemical markers and the limits and the risk of biopsy, liver biopsy should not be mandatory anymore. It is perhaps time to leave the decision regarding liver biopsy to the physician and to the patient. There is, worldwide, a lack of screening and an under prescription of treatment despite its efficacy. A simplification of liver damage assessment should accelerate the management of chronic hepatitis C.”

Hepatitis C on the Rise: US Based Doctor

Staff Report

LAHORE: A US based Pakistani physician Dr Farrukh Ali Khan has cautioned that hepatitis C is on the rise in Pakistan and could lead to liver failure or cancer for most of the affected if they were not diagnosed early.

Dr Khan, who is on a short visit to Pakistan, was speaking at a Free Hepatitis Camp arranged by the Mumtaz Bakhtawar Memorial Trust Hospital on Raiwind road. He said the hepatitis virus leads to cirrhosis of the liver, causing it to scar and shrink, and eventually, liver cancer.

He said the Hepatitis C virus was transmitted through improperly screened blood transfusions, inadequately sterilized surgical instruments and syringes, ear piercing and hair salon instruments. To prevent the spread of the disease it is vital to ensure the blood is screened properly, that disposable syringes, razors, needles be made standard practice and sterilized equipment used. He said Hepatitis C has infected three percent of the total world’s population with 180 million carriers worldwide. Early and effective treatment is vital to arrest the infection, he said.

Dr Khan said there are six genotypes of the Hepatitis-C virus of which genotype 3 is present in 80 per cent of those infected with the disease in Pakistan. Genotype 1 is more common in the West. Genotype 3 is the most curable form of the virus with around 80 percent cure rate, he said.

Unchecked the Hepatitis B and C will triple in 10 years. Pakistan needs to take drastic measures to block its growth. Health experts maintained that hepatitis carriers in Pakistan are rapidly increasing due to ignorance about the virus.

In Pakistan, a sense of complacency in the general public and the medical community prevents a holistic approach towards diagnosis and treatment of liver diseases, including hepatitis and different progressive liver ailments.

Roche Replenishing Hepatitis C Medicine

The pharmaceutical company Roche is offering samples of Pegasys (peginterferon alfa-2a) to physicians in the Memphis area through a program designed to replenish vials of the hepatitis C medication that may have been lost as a result of power outages following the July 22 storm.

Patients undergoing treatment for hepatitis C who lost one or more vials of Pegasys should contact their physicians, who can request samples.

Roche will be making samples of Pegasys available until Aug. 15 to physicians in Shelby, Fayette, and Tipton counties.

August 19th, 2003

Regeneration of Hepatocytes From Intrahepatic Stem Cells in Cirrhosis

by gastrohep.com

The biliary tree, from at least its smaller branches up to the canals of Hering, is composed of or at least harbors facultative hepatic stem cells, finds a study in the Journal of Hepatology (Journal of Hepatology 2003 ; 39 (3) : 357-64).

After massive liver cell necrosis, reactive ductules at the periphery of the necrotic area are thought to contain hepatic stem cells which differentiate into intermediate hepatocytes, regenerating the damaged area. In cirrhosis, it is still debated whether the reactive ductules are activated stem cells (so called 'buds') or ductular metaplasia of cholestatic, injured hepatocytes.

Dr. Olga Falkowski and colleagues investigated the differentiation of intermediate hepatocytes from reactive ductules in cirrhosis.

The research team examined tissue explants from patients with cirrhosis associated with alcohol, hepatitis or with primary sclerosing cholangitis and from patients with primary biliary cirrhosis.

"Intrahepatic hepatocytes largely represent 'buds' of newly formed hepatocytes," said Dr. Olga Falkowski 777 out of 830 (94%) intrahepatic hepatocytes (intermediate hepatocytes) were associated with reactive ductules.

In 3-D reconstructions, intermediate hepatocytes were seen to bud directly from the biliary tree.

Intermediate hepatocytes were rarely found to be cholestatic.

Reactive ductules throughout the biliary tree are thought to contain stem cells which give rise to new intermediate hepatocytes in cirrhosis.

Unique Scholarship Program Aims to Support African-American and Hispanic Students Challenged by Hepatitis C: Thurgood Marshall Scholarship Fund and Hispanic Scholarship Fund Partner On New Horizons Scholars Program

The Thurgood Marshall Scholarship Fund (TMSF) and the Hispanic Scholarship Fund (HSF) announced today the launch of the second year of the New Horizons Scholars Program which will provide college scholarships to Hispanic and African-American students entering college in 2004 who have hepatitis C or are dependents of a person with the disease. The New Horizons Scholars Program is funded by The Roche Foundation.

These scholarships will help support the educational imperatives of African-American and Hispanic students in this country. According to a recent report by American Council on Education's Office of Minorities in Higher Education, college participation rates for African-American high-school graduates, ages 18-24 was at 39.4 percent in 2000 while the college participation rate for Latinos reached 36.5 percent in 2000. "The New Horizons Scholars Program is a unique partnership that was established last year, and aims to create additional financial resources to cover the costs of higher education for Hispanic and African-American students impacted by hepatitis C," said Nicole Lee-Haley, major gift officer for TMSF. "We're very excited to continue this program with our partners and hope to positively impact the lives of these students through this important scholarship program."

The New Horizons Scholars Program will provide up to 50 scholarships to students planning to enroll for the first time in a four-year college during the fall of 2004. Scholarships will be awarded to students of Hispanic or African-American heritage who are infected or are dependents of someone infected with hepatitis C. Students will be eligible for \$2,500 per year for four years, and must maintain the program's academic standard of 2.5 G.P.A.

Scholarship winners will be notified in the late spring of 2004. Applications are available at <http://www.hsf.net> or <http://www.thurgoodmarshallfund.org> or by calling Toll-Free 1-866-346-7496. Applications must be postmarked no later than February 20, 2004.

"Supporting the higher education of Hispanics and African Americans is a critical investment in America's future," said Mario De Anda, HSF director of scholarship programs. "The New Horizons Scholars Program is a strong partnership with the Thurgood Marshall Scholarship Fund to help provide educational opportunities to our communities and make a difference in the lives of our students."

"The Roche Foundation is committed to helping create specialized educational opportunities for students impacted by hepatitis C," said Vivian Beetle, Executive Director of The Roche Foundation, "This program is part of The Roche Foundation's ongoing efforts to help lessen the long term impact of hepatitis C on patients and their families."

About Hepatitis C

Hepatitis C virus, a blood-borne disease of the liver, is the leading cause of cirrhosis and liver cancer and the number one reason for liver transplants in the U.S. Hepatitis

C is transmitted through body fluids, primarily blood or blood products, and by sharing needles. Unfortunately, most people infected with hepatitis C are unaware of it because it may take years for symptoms to develop. Approximately 2.7 million Americans are chronically infected with hepatitis C with an estimated 30,000 new infections yearly.

Hepatitis C disproportionately affects the African-American and Hispanic community. In the United States, 3.2 percent of African Americans are infected with hepatitis C, as compared with 2.1 percent of Hispanics and 1.5 percent of Caucasians.

About the Thurgood Marshall Scholarship Fund

The Thurgood Marshall Scholarship Fund, the first and only national organization of its kind, supports 45 public historically black colleges and universities through merit scholarships, programmatic and capacity-building support. Scholarships are awarded based on merit and need. Since 1987, the organization has distributed over \$20 million in scholarships and programmatic support. TMSF serves as an economic gateway to thousands of students who may not otherwise have the opportunity to go to college.

About the Hispanic Scholarship Fund

The Hispanic Scholarship Fund (HSF) is the nation's leading organization supporting Hispanic higher education. Founded in 1975, HSF's vision is to strengthen the country by advancing college education among Hispanic Americans, the fastest-growing segment of the U.S. population. In support of its mission to double the rate of Hispanics earning college degrees, HSF, a 501©3 not-for profit organization, provides the Latino community more college scholarships and educational outreach support than any other organization in the country. Headquartered in San Francisco, HSF has opened regional offices in Southern and Central California, the Northeast, the Southeast, Midwest and Texas. In addition, HSF launched the Washington, D.C.-based Hispanic Scholarship Fund Institute to generate public partnerships in support of its work. During its 28-year history, HSF has awarded more than 61,000 scholarships in excess of \$115 million to Latinos from all 50 states, Puerto Rico and the U.S. Virgin Islands who have attended more than 1,700 colleges and universities.

About The Roche Foundation

The Roche Foundation (formerly known as the Hoffmann-La Roche Foundation) was created in 1947 as an independent charitable entity, solely funded by the company. Today, it continues to complement the corporate contributions program and helps support selected community organizations and initiatives. The Roche Foundation focuses its support on health promotion and science and math education. The establishment of The Roche Foundation over 50 years ago demonstrated the company's commitment to the importance of good corporate citizenship—a belief that remains today.

For More Information on the New Horizons Scholars Program Go To:

<http://www.hsf.net>

<http://www.thurgoodmarshallfund.org>

August 20th, 2003

Preventive Treatment for HCV Recurrence in Patients with Decompensated Post-hepatitis C Cirrhosis Before Liver Transplantation: An Editorial

by hivandhepatitis.com

There is no consensus or compelling evidence for a single, standard approach to treatment for the prevention of HCV recurrence following liver transplantation, which unfortunately occurs almost universally.

In the following editorial, published in the Journal of Hepatology (September 2003), researchers in the Gastroenterology Department at the Michallon Hospital in Grenoble, France review the most recent therapeutic approaches to this serious post transplantation complication:

After liver transplantation (LT), hepatitis C virus (HCV) recurrence is almost universal, particularly if HCV RNA is detectable at the time of transplant and can lead in a great number of patients to recurrent cirrhosis and graft failure.

This recurrence is often rapid. Several studies have shown that combination therapy using interferon alfa and ribavirin is possible after liver transplantation but the virological response rate is low and the treatment is usually associated with major side effects, requiring dose reduction or stopping treatment.

Another strategy is the eradication of HCV RNA before LT in order to prevent HCV recurrence after LT and reduction in the level of HCV RNA to reduce the severity of post-transplantation liver disease.

Forns et al evaluated the efficacy and safety of antiviral therapy in 30 patients with post-hepatitis C cirrhosis awaiting liver transplantation. Only patients having an expected time on the waiting list shorter than four months were included. Patients with hepatic encephalopathy, renal failure or co-infection by hepatitis B virus or human immunodeficiency virus were excluded. Patients were treated with interferon alfa-2b (Intron A) 3MIU/day and ribavirin 800 mg/day. Dose reductions were utilized according to the laboratory recommendations.

Fifty patients were screened during a 15-month period, but 19 (38%) were excluded due to contra-indication or refusal. The median duration of treatment was 12 weeks (2-33). Virological response was observed in nine patients (30%). Variables associated with a good response to treatment were age, ALT level, genotype non 1 and low viral load. A decrease of viral load ≥ 2 log had a positive predictive value of 100% at week 4.

After liver transplantation, among the nine patients with virological response, HCV infection recurred in only three patients at week 2, 4, 5, respectively after liver transplantation. All these patients were infected with genotype 1b.

Six patients became HCV RNA negative after a mean follow-up of 46 weeks (24-80). Indeed, 4/5 patients also tested in the liver were HCV RNA negative. Side effects

were frequent. Two patients developed sepsis; in both cases, neutrophil counts were above $1.2 \times 10^9/l$ at the time of hospital admission.

Interferon dose reduction was necessary in 60% of cases and ribavirin dose reduction in 24% of cases. Eleven patients required filgrastim due to neutropenia and eight erythropoietin due to anemia. No patients died during therapy.

Assessment of interferon in patients with decompensated chronic hepatitis C was until now based on limited small case series. A gradually increasing dose regimen of combination therapy with interferon and ribavirin has been used in patients with both compensated and decompensated cirrhosis due to hepatitis C by Everson et al.

Patients were started on low dose of interferon (1.5 MUI, tiw) and ribavirin (600 mg/day) with slowly increasing dose of both drugs every 2 weeks as tolerated. Preliminary results of treating 91 patients, the majority infected with genotype 1, were recently reported.

On-treatment virological responses occurred in 38% and a sustained virological response in 22% of patients. Sustained responses were more common in patients treated for more than 6 months. Eight patients who were treated and were HCV RNA negative at the time of transplantation remained virus free post-transplantation.

On the other hand, recurrent and persistent HCV infection of the allograft was observed in all patients with detectable HCV RNA at the time of transplantation. No significant change was observed regarding the hepatic synthetic function and/or Child Pugh score. Indeed, 27 of non-responders were reported to develop adverse events.

Less favorable outcome has been reported by Crippin et al. (6) in a collaborative study of five US liver transplant centers. Patients were treated with a common protocol using low dose of interferon with or without low dose of ribavirin. Only half the patients screened for the study were enrolled, many being excluded because of severe cytopenias. All patients had advanced liver disease with a mean Child-Pugh score of 12, as well as elevated serum bilirubin, prolonged prothrombin time and moderated impaired renal function.

On treatment, 33% of patients became HCV RNA negative. Two patients underwent liver transplantation and both developed recurrent infection. Adverse events were common and sometimes severe, including profound thrombocytopenia, marked neutropenia, new-onset hepatic encephalopathy and life-threatening infections that ultimately led to the early termination of the study.

Of course, because both studies did not include an untreated control group for comparison, it is unclear whether interferon and ribavirin combination therapy per se precipitated these life-threatening infections or whether they merely represented complications of end stage liver disease.

All together these three studies suggest that antiviral therapy with post-hepatitis C cirrhosis awaiting liver transplantation is possible and can prevent HCV disease recurrence in several patients, especially in patients with favorable predictive factors of response.

However, recurrence of HCV infection after LT is possible even if HCV RNA is negative in the serum or the liver at the time of transplantation. Two explanations can be proposed to explain this discrepancy: first the method of detection of HCV RNA was not sensitive enough; in this case it would be interesting to compare this result with a more sensitive method of detection such as real-time PCR.

The second explanation could be the persistence of the virus in a second compartment such as peripheral blood mononuclear cells; to confirm this hypothesis, it is necessary to study quasispecies distribution in each compartment.

The best results observed by Everson et al. and Forns et al. suggest that the treatment is better tolerated in patients with Child A and B than in patients with Child C and leads to less severe complications such as neutropenia and thrombocytopenia.

All these studies clearly show also that it is necessary in some cases to use growth factors including GM-CSF and erythropoietin to boost peripheral blood cell counts in patients with severe neutropenia and erythropenia to prevent profound cytopenias and infections.

From these studies, it seems very difficult to define the best regimen. In Forns et al. study, authors used daily dose of recombinant interferon. By contrast, Everson et al. as well as Crippin et al. used low doses of interferon three times a week.

There are no data on the safety and/or efficacy of peginterferon with or without ribavirin in patients with decompensated post hepatitis C cirrhosis. Indeed, the combination of peginterferon plus ribavirin was only tested in patients with severe fibrosis (F3 and F4) and was well tolerated.

However, because peginterferon regimens are associated with higher rate of neutropenia and thrombocytopenia, treatment is likely to be associated with even greater infection complications than regimens using standard infection interferon and slower recovery from these complications when the interferon is stopped [emphasis added--Ed.]

It will be very interesting in the future to compare these different regimens. Indeed, the best duration of treatment remains to be defined.

The rationale for Forns et al. (4) to treat for a short time was that most virological responders had a viral load decrease of $> \text{ or } = 2 \log_{10}$ at week 4 and were HCV RNA negative by week 12. However these results are very surprising, especially in patients with genotype 1b and were not found by others, and we do not know which treatment schedule is more convenient.

In conclusion, in patients with decompensated HCV cirrhosis, antiviral therapy as suggested by Wright et al. in the last American consensus conference should be considered experimental and not be administered outside of prospective trials.

If the results of these prospective trials are confirmed, this strategy could be then used in patients with post-hepatitis C cirrhosis without severe hepatocellular insufficiency awaiting LT.

Treatment of HCV Patients Awaiting Liver Transplantation Helps to Prevent HCV Recurrence Following Surgery

by hivandhepatitis.com

After liver transplantation (LT) infection of the graft with the hepatitis C virus (HCV) is almost universal and chronic hepatitis and cirrhosis develop in a significant proportion of patients. One possible strategy to prevent HCV infection recurrence is to eradicate HCV before LT.

Researchers at four liver transplant units in Spain evaluated the efficacy and safety of antiviral therapy to prevent HCV recurrence in 30 HCV-cirrhotic patients awaiting LT. At the time of inclusion 15 patients were Child-Pugh A and 15 Child-Pugh B/C. The infecting genotype was 1b in 25 patients. Treatment with interferon alfa-2b (Intron A) 3 MU/day and ribavirin 800 mg/day was initiated when the expected time for LT was less than 4 months and continued until LT. The median duration of treatment was 12 weeks.

Study Results

Nine patients (30%) achieved a virological response and 21 did not respond to therapy. In nine (43%) of the 21 non-responders viral load decreased $\geq 2 \log_{10}$ during treatment. A viral load decrease $\geq 2 \log_{10}$ at week 4 of treatment was the strongest predictor of virological response.

All nine virological responders have already undergone LT; six patients remain free of infection after a median follow-up of 46 weeks and HCV infection recurred in three patients after LT. In one of these patients HCV-RNA was still detectable in the explanted liver.

Side effects were frequent and dose reduction was necessary in 19 (63%) of the 30 patients; no patient died while on therapy.

The authors conclude, "Our data support the utilization of antiviral therapy in HCV-infected patients awaiting LT as one of the strategies to prevent hepatitis C recurrence after transplantation."

Geneva Pharmaceuticals Prepares Generic Rebetol(R) - U.S. District Court Rules Patent Non-Infringement

Geneva Pharmaceuticals, Inc. ("Geneva"), an affiliate of Novartis AG, announced today that on July 14, 2003, the U.S. District Court Judge for the Central District of California granted Geneva's motion for summary judgment of non-infringement on U.S. Patent No. 5,767,097; 6,063,772; and 6,150,337 concerning Rebetol® (Ribavirin.) Rebetol® (Ribavirin) is used for the treatment of hepatitis C. According

to IMS data, sales for Rebetol® for the 12-month period ended March 2003 reached \$721 million. Geneva has settled related patent litigation with Schering-Plough Corporation (Schering-Plough) and has entered into a non-exclusive license agreement with Schering-Plough that will enable Geneva to launch its Ribavirin product as soon as it receives final approval from the Food and Drug Administration (FDA) of its Abbreviated New Drug Application (ANDA).

FDA approval of Geneva's ANDA is pending. Additionally, the FDA has yet to determine which company or companies will receive 180 days of marketing exclusivity for the product.

Said John Sedor, Geneva President and Chief Executive Officer, "We believe Geneva will have an exclusive or shared exclusive position with respect to the launch of generic Ribavirin. This could make Geneva the first generic company to launch a generic version of Ribavirin. This product is being manufactured in our Broomfield, Colo., facility using isolation suite technology. We are fully prepared to launch this product and provide a lower-cost drug alternative for patients. We are working closely with the FDA in order to make Ribavirin available in the marketplace as quickly as possible."

Rebetol® is a registered trademark of Schering-Plough.

This release contains certain "forward-looking statements" relating to Geneva Pharmaceuticals, an affiliate of Novartis AG and its business or products, which can be identified by the use of forward-looking terminology such as "will be," "continue to," or similar expressions, or by express or implied discussions regarding strategies, plans and expectations. Such statements reflect the current plans or views of Geneva with respect to future events and are subject to certain risks, uncertainties and assumptions. Management's expectations and sales of Ribavirin could be affected by, among other things, ability to obtain or maintain patent or other proprietary intellectual property, competition in general, and other risks referred to in Novartis AG's Form 20-F on file with the U.S. Securities and Exchange Commission. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those described herein as anticipated, believed, estimated or expected.

Geneva Pharmaceuticals, Inc. is one of the largest prescription generic pharmaceutical companies in the U.S. Geneva produces more than 200 products each year, with an annual manufacturing capability exceeding 10 billion tablets and capsules. Geneva products range across many therapeutic drug categories including anti-infectives, anti-arthritics, cardiovasculars, gastrointestinal agents and psychotherapeutics. Geneva is an affiliate of the Novartis AG (NYSE: NVS) group of companies (the Group), a world leader in healthcare with core businesses in pharmaceuticals, consumer health, generics, eye-care and animal health. Novartis AG (NYSE: NVS) is a world leader in pharmaceuticals and consumer health. In 2002, the Group's businesses achieved sales of CHF 32.4 billion (USD 20.9 billion) and a net income of CHF 7.3 billion (USD 4.7 billion). The Group invested approximately CHF 4.3 billion (USD 2.8 billion) in R&D. Headquartered in Basel, Switzerland, Novartis Group companies employ about 72,900 people and operate in more than 140 countries around the world. For more

information on Novartis, <http://www.novartis.com>. For more information about Geneva Pharmaceuticals, please see our website at genevarx.com

August 22nd, 2003

Prevalence of Hepatitis C Virus Infection in Urban Children in the USA

by gastrohep.com

A study in *The Journal of Pediatrics* (*Journal of Pediatrics* 2003; 143(1): 54-60) reports that only 1 out of 1034 children screened for hepatitis C virus in an urban hospital in Baltimore, USA, was positive for hepatitis C virus antibodies.

Dr Samer El-Kamary and colleagues investigated the prevalence of hepatitis C virus infection in children attending an urban hospital pediatric primary care clinic in Baltimore, USA.

1034 children were tested for HCV antibodies after excluding children known to be HIV-positive.

Dr El-Kamary's team also assessed maternal hepatitis C virus risk factors through structured interviews with a sample of mothers and a review of available medical records.

Intravenous drug use was significantly underreported.

Only 1 child (0.1%) tested positive for hepatitis C virus antibodies.

History of blood transfusion was reported by 7% of mothers and intravenous drug use by 1.8%.

However, analysis of medical records revealed that intravenous drug use was significantly underreported.

Dr El-Kamary concludes. "Universal screening of children for HCV in high-risk urban communities is not warranted."

"Self-report may not be reliable for identifying mothers with a history of intravenous drug use."

Histoacryl Injection or Beta-Blockers for the Eradication of Esophogastric Varices

by gastrohep.com

A study in the September issue of *Endoscopy* (*Endoscopy* 2003; 729-735) finds that repeated injections of histoacryl are no more effective than beta-blocker

administration in the eradication of esophagogastric varices, and are associated with more complications compared with beta-blocker administration.

Histoacryl is highly effective in controlling active bleeding of esophageal and gastric varices. However, it is not known whether repeated histoacryl injections are effective for long-term eradication of esophagogastric varices.

A team of Belgian doctors compared the efficacy and safety of endoscopic histoacryl injection with beta-blocker (propranolol) administration in the secondary prevention of esophagogastric variceal bleeding.

41 patients with primary bleeding from esophageal or gastric varices were included in the study.

Primary hemostasis was achieved with histoacryl obliteration of the varices. Subsequently, the research team randomised patients to undergo complete histoacryl obliteration of the remaining varices with histoacryl or to receive long-term propranolol administration for the prevention of rebleeding.

There was no significant difference in the incidence of early rebleeding between the 2 treatment groups. 5 of the 21 patients who underwent histoacryl injection and 3 of the 20 patients taking propranolol re-bled within the first 6 weeks.

There was also no significant difference in long-term rebleeding or mortality between the 2 treatment groups.

Complications, however, were significantly more likely in patients who underwent histoacryl variceal eradication.

Repeated injections of histoacryl are associated with more complications compared with beta-blocker administration, with similar results in terms of rebleeding rate and survival in the long term.

10 out of 21 patients receiving histoacryl injections suffered adverse effects, compared with only 2 of the 20 patients receiving beta-blockers.

College Students Ignoring Risks of Unprotected Sex

by Gary Gately, HealthDay Reporter

An alarming number of American college students engage in unprotected sex, but most fail to realize the risk of contracting sexually transmitted diseases, says a new national survey.

Among college students who live away from home, 56 percent had been sexually active while attending college, and 73 percent of that group reported having unprotected sex while in college, says the survey by the Society for Adolescent Medicine.

Underscoring widespread ignorance about sexually transmitted diseases, the online survey of 516 students found that 68 percent of those who had unprotected sex did not believe they were at risk of contracting an STD.

And almost half of the sexually active students had never been tested for an STD, even though one in five college students knew someone who has contracted a sexually transmitted disease while in college, according to the survey, which was conducted last spring by Harris Interactive.

“I’m actually troubled by the findings, particularly the one about unprotected sex,” says Helen E. Johnson, co-author of the book *Don’t Tell Me What to Do, Just Send Money: The Essential Parenting Guide to the College Years*.

“I think part of it is people at this age really do feel immortal; they don’t understand that their behavior has real consequences,” says Johnson, who contributed to a free booklet the Society for Adolescent Medicine prepared for parents on ways to help protect children while they’re away at school.

Johnson says parents often share much of the blame for their college-age kids’ risky behavior.

“I think too many parents today want to be their kids’ friends and—sort of by default, not intentionally—they abrogate that important parental responsibility, which is making it really clear to your kids what your values are,” Johnson says.

“Even though they will act like they’re tuning you out, they hear you, and what I found working with college students is that they really care what their parents think about these things, and they generally don’t know,” she adds.

Charlotte A. Gaydos, an associate professor of medicine at Johns Hopkins University School of Medicine, says the survey’s findings came as no surprise.

“Kids are having high-risk sexual behaviors, and they are not getting screened,” Gaydos says. “One of the reasons is most of the sexually transmitted diseases are asymptomatic.” She encourages college students to not be shy about asking to be screened.

But Gaydos says physicians also could do more to prevent STDs among young patients.

“Many pediatricians are hesitant to ask whether [their patients] are sexually active,” she says.

She also believes better high school education about STDs would help.

The survey also found little awareness among students about hepatitis B, which can be spread not only through sex but also through body piercing, tattooing, contact sports and sharing a razor or toothbrush.

Forty percent of college students either have a tattoo or body piercing or are likely to get one or the other before graduating, the survey found, and a third of students admitted to sharing either a razor or toothbrush with a roommate, partner or friend. But while almost all students surveyed had heard of hepatitis B, more than half were not protected by a vaccine or didn't know if they were, the survey says.

Hepatitis B—a potentially life-threatening viral liver disease—is one of the few STDs that can be prevented by a vaccine, the Society for Adolescent Medicine says.

In its booklet, the society also recommends that parents:

- Review your child's health history and make sure all medical information is updated.
- Make sure your child has appropriate medical insurance and carries a health insurance card. Up to 30 percent of college students have no health insurance, the society says.
- Check with your doctor about your child's immunizations for hepatitis A, hepatitis B, influenza, meningococcal meningitis, polio (news - web sites), tetanus-diphtheria, chickenpox and measles, mumps and rubella.
- Get a tuberculosis skin test for your child if it's required by the college or recommended by a health care provider.
- Have your primary health care provider send the campus information about care, medications and restrictions on activity if your child has chronic medical problems. If a disability requires special accommodations, let the campus disabilities office know.
- Check into health resources on and near campus so your child will know about after-hours care, emergency services, pharmacy services and the location of the nearest hospital.

Schering-Plough Slashes Costs, Jobs, Dividend and Perks Among Cutback Targets

by Ed Silverman, Star-Ledger

Fred Hassan has a dramatic prescription for an ailing Schering-Plough: Eliminate jobs and bonuses, cut the dividend, close the executive dining room and sell the company jet.

The eye-popping moves come at a time of turmoil for the Kenilworth-based drug maker, which is reeling from government probes over its business practices and a stunning drop in sales of Claritin, a medicine that was once a franchise product.

The cutbacks, which were announced yesterday after the stock market closed, are designed to save at least \$200 million and come just one week after the company disclosed that cash from operations may not be sufficient to cover expenses this year.

“My review of the situation we inherited confirmed the need for aggressive measures, including aggressive cost containment and cost cutting in order to stabilize the company and to create a realistic base on which to build a turnaround,” Hassan said in a statement.

The belt-tightening pronouncement, which includes reducing head count by about 1,000 positions, capped a “100-day, 360-degree review” of operations by the new CEO. Hassan, who previously headed Pharmacia, was billed as a gifted turnaround artist when he was hired by Schering-Plough in April.

For now, the job cuts will take place through an early retirement program, but still more jobs will be lost, and a company spokeswoman said layoffs are possible. Globally, the drug maker employees about 30,000 people, including 6,900 in New Jersey.

To set the tone, Hassan is foregoing his own bonus this year, which could have been as much as \$2 million, and is eliminating various perks, such as flying first class and exclusive health plans for executives.

“We will all be making sacrifices as a result of these actions,” Hassan’s statement said.

Still, he was criticized last night by Wall Street analysts for not participating in a conference call with company spokespeople.

“He’s leaving us dangling at 7 o’clock at night at the end of August,” complained Barbara Ryan, an analyst at Deutsche Bank Securities, in remarks during the conference call. “It damages his credibility.”

The most unusual cost-cutting move involves slashing the dividend, to 5.5 cents per share from 17 cents. It’s a step rarely taken in the profit-rich pharmaceutical industry, and a further sign of the company’s breathtaking reversal of fortunes.

The dividend costs the company \$250 million every quarter. But with shares down 70 percent over the past two years, it has become a luxury.

Schering’s 4.13 percent dividend yield was among the top 10 percent of companies in the Standard & Poor’s 500 index. With the cut, the yield will be 1.33 percent.

To underscore the financial difficulties, Hassan also noted that earnings for the second half of this year are expected to fall short of the 24 cents per share posted in the first half of 2003. Moreover, 2004 earnings are likely to be lower than this year’s earnings, he said.

Schering-Plough has struggled since its blockbuster Claritin allergy drug lost patent protection last year, resulting in cheaper generic rivals. At one time, Claritin generated \$3 billion in annual revenue. In this year’s second quarter, Claritin sales were just \$83 million.

Since then, competition emerged for yet another huge-selling product, a treatment for hepatitis C. The one-two punch sent this year’s second-quarter sales diving 17 percent, to \$2.3 billion.

At the same time, the company signed a consent decree and agreed to pay a \$500 million fine as a result of a protracted investigation over its manufacturing procedures by the Food and Drug Administration.

Meanwhile, the U.S. Attorney's Office in Newark is investigating manufacturing problems. And federal prosecutors in Massachusetts and Pennsylvania are investigating a host of marketing and sales practices

Among the other cost-cutting measures being ordered by Hassan are freezing routine employee merit increases through 2004; zero payout of profit sharing; and severely restricting hiring.

In trading prior to last night's announcement, Schering-Plough stock closed at \$16.48, up 24 cents, or 1.5 percent.

August 24, 2003

Wane of Hepatitis C Drugs Wound Schering-Plough

by Ransdell Pierson

Schering-Plough Corp., which rocked Wall Street with a warning its earnings will fall again next year, owes much of its troubles to falling sales of a hepatitis C therapy.

The company, already hit by plunging sales of allergy drug Claritin, next year will likely see its hepatitis drugs eclipsed by a cheaper and more convenient treatment recently launched by Roche Holding AG, doctors and analysts said.

Schering-Plough's combination therapy against the hepatitis C virus was introduced two years ago and is now the company's biggest product line. It includes a long-acting interferon medicine called Peg-Intron and the antiviral pill ribavirin.

Sales of the therapy fell 14 percent to \$569 million in the second quarter, hurt by Roche's injectable Pegasys interferon and its version of ribavirin, called Copegus.

"We are seeing a downward slope in sales of our biggest products, including Peg-Intron," Chief Executive Fred Hassan told Reuters in an interview.

Decline of the Schering-Plough hepatitis business comes at the worst possible time, just months after the U.S. patent on Claritin expired. Sales of the allergy pill, once \$3 billion a year, have tumbled almost 90 percent now that it is being sold over the counter at a fraction of its previous price.

The Kenilworth, New Jersey-based drugmaker expects 2003 earnings to fall by two-thirds, and it has slashed its dividend to preserve cash. Its shares sank to a six-year low on Friday after it warned profits will decline again next year.

Hassan, who was hired earlier this year to turn around the company, said Roche spurred sales of Pegasys largely by giving away the first three months of treatment to 15,000 American patients. The same patients then had to pay for remaining months of therapy.

About 4 million Americans are believed infected with the hepatitis C virus, which is the biggest cause of liver transplants. The virus quietly attacks the liver for decades before symptoms develop, but can be eliminated with the Roche and Schering-Plough drugs.

“Roche’s marketing skills are alarming Schering-Plough, which had taken its own hepatitis products for granted and assumed they would prevail in the leadership role,” said Sena Lund, a drug analyst for Cathay Financial LLC.

The Schering-Plough combination had a U.S. monopoly until Swiss drugmaker Roche launched its rival drugs in January, pricing its ribavirin at an approximate 43 percent discount.

Pegasys now boasts a 42.1 percent share of the U.S. market for long-acting interferons, leaving Peg-Intron with less than 58 percent, according to SG Cowen analyst Steve Scala.

Sund said the combined wholesale cost of Roche’s two medicines is \$23,000 for a year’s course of treatment, versus \$26,000 for Schering-Plough’s.

That cost advantage could allow Roche’s products to catch up with or overtake Schering-Plough’s by year’s end, he added, even if other companies launch cheaper generic forms of ribavirin.

“Schering-Plough now has to lower its prices or do something else to protect its market share,” Sund said.

Pegasys has also become popular with many doctors and patients because it comes pre-mixed in a single vial, which is drawn by a syringe and injected once a week. All patients take the same fixed dose.

By contrast, Peg-Intron requires patients to use two syringes and two vials in a process that combines a liquid and a powder. In addition, the dose must be adjusted by body weight.

“I personally now only prescribe Pegasys because so many patients say it is so much easier to use than Peg-Intron,” said Dr. Samuel Daniel, chief executive at North General Hospital in New York, who noted Roche has financial ties to the hospital. Schering-Plough hopes to win U.S. approval for a pen-like device that would allow patients to inject Peg-Intron directly, without need to mix vials. But the company has not predicted when it will be launched or how many patients will embrace it.

Although the battling therapies have never been compared head-to-head in clinical trials, many doctors consider them similarly effective and well tolerated.

Dr. Mitchell Shiffman, a professor at Virginia Commonwealth University Health System, said the greater convenience of Roche's combination therapy could make it the preferred choice within a year.

Schering-Plough is attempting to stem Roche's assault by suggesting that Peg-Intron—with its personalized dosing—may be more appropriate for overweight patients than Pegasys. But it acknowledges a trial directly comparing the two drugs would be needed to draw firm conclusions.

August 25th, 2003

Vaccination and Anti-HIV Therapy Lower Hepatitis B Infection Rates

by Will Boggs, MD, hivandhepatitis.com

Vaccination and antiretroviral therapy lower the very high rates of hepatitis B virus (HBV) infection among HIV-infected patients, according to a report in the August 15th issue of *The Journal of Infectious Diseases* (*J Infect Dis* 2003;188:571-577).

The incidence of acute HBV infection is approximately 0.033 cases per 1000 person-years in the general population, with about 0.4% of the general population having chronic HBV infection, the authors explain. Data are limited about rates of HIV and HBV coinfection since highly active antiretroviral therapy (HAART) for HIV infection became available.

Dr. Scott E. Kellerman and colleagues from Centers for Disease Control and Prevention in Atlanta investigated the incidence of acute HBV and prevalence of chronic HBV, vaccination rates, and potential risk factors in the 16,248 HIV-infected subjects enrolled in the Adult/Adolescent Spectrum of HIV Disease Project.

Among these HIV-infected patients, rates were much higher than in the general population for acute HBV incidence (12.2 cases per 1000 patient-years) and for chronic HBV prevalence (7.6%), the authors report.

The incidence of acute HBV infection was higher among black subjects, subjects with a history of alcohol abuse in the 6 months before an observation, and among those who injected drugs, the report indicates. On the other hand, incidence rates were lower among patients treated with HAART (with or without lamivudine) and among those who had received at least one dose of hepatitis B vaccination.

Chronic HBV infection was more prevalent among men than among women, the researchers note, and was most prevalent among men who had sex with men and were intravenous drug users and was least prevalent among Hispanics.

Antiretroviral drug regimens that contained lamivudine were associated with a much lower prevalence of chronic HBV (2.3%) than were regimens that did not contain

lamivudine (7.8%), the results indicate. Prevalence was 22.1% among subjects not treated with antiretroviral drugs.

“Considering the amount of time that many HIV-positive persons spend in the medical care system, it is unfortunate that many are not being adequately assessed regarding their HBV (and hepatitis A virus, for that matter) immunization status,” Dr. Kellerman told Reuters Health.

“We found that only 14% of HIV positive persons had been previously vaccinated against HBV, despite recommendations for HBV vaccination in HIV-positive persons that have been available for years,” he added.

Dr. Kellerman advises physicians to “ask your HIV-positive patients if they’ve been immunized against HBV, and if they haven’t or can’t remember, consider immunizing. HIV-positive persons can still be at risk for blood-borne or sexually transmitted infections.”

Hyperlipasemia and/or Subclinical Pancreatitis May Represent Extrahepatic Manifestations of HCV Infection

by hivandhepatitis.com

Extrahepatic manifestations of chronic hepatitis C virus (HCV) infection have been well described. However, hyperlipasemia and/or pancreatitis have not been reported.

Following the observation that several HCV patients had elevated lipase levels, this retrospective study, conducted at the Veterans Affairs Medical Center, Baylor College of Medicine, Houston, Texas, assessed the association between hyperlipasemia and/or pancreatitis with hepatitis C infection.

Of 204 subjects who underwent evaluation for hepatitis C, 103 had lipase levels determined at baseline. The control group consisted of 41 non-HCV subjects with a variety of gastrointestinal diseases including 18 with nonalcoholic liver disease. Twenty-five percent of HCV patients had elevated lipase at baseline as compared to 10% of controls ($P = 0.04$). Mean lipase levels were 253 ± 72 units/liter (normal range 114-286 units/liter and 210 ± 42 units/liter for the HCV and control groups, respectively ($P = 0.002$).

No significant difference in amylase was found between the groups. There was a significant association between ALT (> 1.5 times the upper limit of normal) and lipase ($P = 0.02$). Among 30 patients who received interferon-based therapy +/- ribavirin, 11 had elevated lipase at baseline. Six of these patients responded to therapy and demonstrated normalization of lipase levels.

In contrast, all nonresponders with baseline hyperlipasemia continued to have high lipase levels ($P = 0.17$). Furthermore, only 3 of 8 (37.5%) patients with normal lipase responded to treatment as compared to 6 of 10 (60%) of hyperlipasemic patients ($P = 0.36$).

The authors conclude, “Hyperlipasemia and/or subclinical pancreatitis may represent extrahepatic manifestations of HCV infection and should not preclude treatment.”

Twice Daily Dosing with Interferon Beta Improves Viral Kinetics and Enhances Antiviral Efficacy

by hivandhepatitis.com

The aim of the current study was to address the molecular mechanism for enhanced antiviral efficacy associated with a frequent dosing of interferon (IFN)-beta.

Prior studies have indicated that twice daily dosing of interferon beta produces an enhanced antiviral response and that twice daily dosing is the more efficient form for induction therapy for chronic hepatitis C.

Serum hepatitis C viral (HCV) dynamics, double-stranded RNA-activated protein kinase (PKR) mRNA and MxA mRNA levels in peripheral blood mononuclear cells (PBMC) were analyzed serially in 140 patients who were randomly assigned to a twice daily (3MU bid) or once daily (6MU qd) administration group.

In the twice daily group, the rate of HCV decline during the second phase was 2-fold greater than in the once daily group ($P=0.04$). Peak PKR and MxA gene expression levels in the first phase (observed 4 h after a single administration) were 2-fold higher in the once daily group. However, the expression in the second phase was maintained at a significantly higher level in the twice daily group. Initial and peak expression levels were related to initial viral load. Basal expressions in PBMC were significantly correlated with those in the liver tissue (PKR, $r=0.81$; MxA, $r=0.75$, respectively, $P<0.0001$).

These data suggest that elimination of HCV-infected cells is enhanced by twice daily dosing of intravenous (IV) natural interferon beta (Feron), and that this enhanced effect is associated with a higher intracellular expression of PKR and MxA during the second phase.

Management of Hematologic Disorders Associated with Hepatitis C Virus Infection

by hivandhepatitis.com

More than 4 million people in the United States are acutely or chronically infected with hepatitis C virus (HCV). Of those individuals with acute HCV infection, 54% - 86% will develop chronic infection, and at least 20% of individuals who are chronically infected will develop cirrhosis. HCV is the most common cause of cirrhosis and is responsible for >50% of liver transplants performed.

To date, the most effective treatment for chronic HCV infection is the combination of either interferon (IFN) alfa or pegylated IFN-alfa and ribavirin. For a sustained virologic response, treatment adherence and dose maintenance are essential.

However, both IFN-alfa and ribavirin induce hematologic toxicity, which can compromise treatment adherence and dose maintenance. Preliminary data suggest that the infection itself can also induce autoimmune hemolytic anemia, leukopenia, and thrombocytopenia.

Although no approved treatments for HCV-related hematologic complications exist, this review by Dr. Dieterich (Mount Sinai Medical Center) and Dr. Spivak (Johns Hopkins Medical Institutions) summarize the pharmacology, risks, and benefits of the investigational use of hematopoietic growth factors for treating such complications.

The most important factors in successful eradication of HCV are adherence to therapy and dose maintenance. Optimal results have been obtained in patients infected with HCV genotype 1 when treatment with at least 80% of the IFN-alfa dose and at least 80% of the RBV dose was maintained for at least 80% of the time.

However, combination therapy significantly increases the risk of dose modifications and discontinuations due to treatment-related adverse effects and dose modifications appear to be less than optimal for HCV eradication.

Thus, treatment success may be compromised by the adverse effects of HCV therapy. As detailed in the 2002 National Institutes of Health Consensus Statement on the Management of Hepatitis C, "There is a need to assess the effectiveness of supportive therapy to ameliorate the side effects of antiviral therapy."

Side effects of IFN-alfa and PEG-IFN-alfa (hereafter, where both IFN-alfa and PEG-IFN-alfa are meant, "[PEG]IFN-alfa" is used) include depression, transient flu-like symptoms (headache, fatigue, myalgia, chills, and fever), more severe or persistent fatigue, alopecia, and bone marrow suppression leading to anemia and neutropenia.

Leukopenia and thrombocytopenia are also common; however, they tend to be mild and generally are not associated with complications. Neutropenia and thrombocytopenia appear to occur at higher rates with use of PEG-IFN-alfa than with use of nonpegylated IFN-alfa, whereas anemia tends to occur less frequently with PEG-IFN-alfa than with nonpegylated IFN-alfa.

The major side effect of treatment with RBV is dose-dependent hemolytic anemia. At RBV doses of \geq 800 mg/day, RBV-induced hemolytic anemia causes a dramatic decrease in hemoglobin levels (of 2 - 3 g/dL), usually \geq 4 weeks of initiation of treatment. When combination therapy with IFN-alfa/RBV is used, hemoglobin levels $<$ 11 g/dL occur in 25% - 30% of patients. Anemia has been found to be more pronounced with combination therapy than with IFN-alfa monotherapy.

The incidence of dose modifications due to anemia increased from 0% with IFN-alfa monotherapy to 7% - 9% with combination therapy. Similarly, the incidence of dose reductions due to anemia increased from 1% with PEG-IFN-alfa monotherapy to 22% with PEG-IFN-alfa/RBV therapy. In addition, dose reductions due to neutropenia and thrombocytopenia were more common in association with PEG-IFN-alfa/RBV therapy than with standard IFN-alfa/RBV therapy.

Some of the consequences of anemia include impaired tissue oxygenation, organ function, and quality of life, as well as increased susceptibility to thrombocytopenic bleeding, increased risk of postoperative mortality, and increased likelihood that blood transfusions will be needed. In addition, anemia may be associated with decreased survival rates among patients with HIV infection and cancer. These clinical sequelae of anemia indicate the importance of its treatment, especially in patients with a chronic disease.

Strategies for Treating Hematologic Disorders in HCV-Infected Patients

Recombinant human erythropoietin: Pharmacologic enhancement of erythropoiesis is an effective strategy for alleviating anemia without exposing the patient to allogeneic blood and the accompanying risks. Epoetin alfa (Procrit; Ortho Biotech) is the only recombinant human erythropoietin that has been evaluated in clinical trials for the treatment of anemia in patients with HCV.

Granulocyte colony-stimulating factor (G-CSF): Recombinant human G-CSF (filgrastim, an agent that enhances granulopoiesis in neutropenic patients with cancer who are receiving IFN-alfa), stimulates production of multipotent hematopoietic progenitor cells and mature granulocytes.

Although there are no guidelines for the use of G-CSF in the HCV-infected population, the rationale for its use is predicated on its success in patients with cancer who are receiving chemotherapy.

Interleukin (IL)-11: Recombinant human IL-11 (rhIL-11; oprelvekin) is the only currently approved agent for enhancing platelet production, which it does by stimulating megakaryocytopoiesis.

Independent case studies have demonstrated that patients with chronic HCV infection can develop autoimmune hemolytic anemia in the absence of treatment with IFN-alfa. In these HCV-infected patients, autoimmune hemolytic anemia was reversible with prednisolone therapy. In addition, fatigue, a major symptom of anemia, was recently reported to be the most common extrahepatic complication in HCV-infected patients, and, in one study, it was considered by almost one-half (48%) of all untreated HCV-infected patients to be the initial or worst symptom.

Conclusion

Due to the slow course of HCV-related liver disease, the burden of co-morbidities in patients chronically infected with HCV will have a large impact over the course of the next 30 years. The most effective treatment for HCV infection is combination therapy with (PEG)IFN-alfa and RBV. The eradication of HCV is possible; however, treatment adherence and dose maintenance are essential. Both IFN-alfa and RBV induce hematologic disorders that may exacerbate or compound an already fragile hematologic state in the HCV-infected individual and may compromise treatment adherence.

Therapies (e.g., epoetin alfa) to counter these disorders (e.g., anemia) have been successful in allowing the maintenance of critical dose levels of RBV and thus providing optimal HCV treatment that should improve adherence and treatment success.

Chinese Scientists Decode New Hepatitis B Virus Genes

by Xinhua News Agency via Pinnacor

Chinese scientists have decoded two new genes found in the hepatitis B virus (HBV) genome. It is hoped that the discovery will lead to a new treatment for the disease.

A research team at the No.302 Hospital of the Chinese People's Liberation Army found the new genes after cloning and analyzing the gene sequencing of HBV taken from blood of HBV patients in China, said Cheng Jun, leader of the research team, here Wednesday.

For the past 25 years, scientists have believed that HBV genome contained four open reading frames. The new discovery brings the number of open reading frames to six.

The finding will not only enhance research into the HBV virus and treatment of the disease, for instance, by helping develop a new antigen for the virus, but also the treatment of liver cancer, he said.

Some 350 million people worldwide are victims of hepatitis B, only one third of whom show a favorable response to presently available treatment. Many of the other sufferers will develop liver cancer.

Further research will be needed to identify how far the new genes will contribute to the treatment of hepatitis B and liver cancer, Cheng said.

Antioxidants May be Beneficial For Transplant Patients

by John C. Martin, hepatitisneighborhood.com

People who undergo organ transplants may benefit by taking supplements of both vitamins C and E, says a 2002 study by doctors at medical institutions in Oregon and Massachusetts.

While the study focused on heart transplantation, the researchers say patients who undergo other types of transplants, including those of the liver, may also benefit.

“Cardiac transplantation is associated with oxidant stress, which may contribute to the development of accelerated coronary arteriosclerosis,” wrote researchers in the cardiovascular division of Brigham and Women's Hospital in Boston. “We postulated that treatment with antioxidant vitamins C and E would retard the progression of transplant-associated arteriosclerosis.”

Vitamins and Transplant Oxidation

In the study, patients who received supplements of these two antioxidant vitamins had very little coronary arteriosclerosis associated with their transplants. Ordinarily, this is one of the most important limitations to the long-term survival of heart transplant patients; their arteries tend to clog unusually fast after surgery. The condition is present in over 70 percent of recipients within three years, according to estimates.

Arteriosclerosis is a condition in which arteries become clogged due to fibrosis or calcium deposits. The term is typically used to describe several diseases associated with this condition of the arteries.

The Culprit: Oxidation

The study found that oxidation in the body tends to contribute to increased coronary blockage following a transplant procedure, and the body's natural antioxidant defenses are often reduced. So, treatment with antioxidant vitamins appears to have significant value in addressing this problem, the researchers found.

Oxidants are harmful molecules that cause oxidation of cholesterol, which results in the buildup of plaques in arteries, among other things. Antioxidants, by contrast, are vitamins that block the action of oxidants in the body, and prevent the buildup of these plaques.(2)

“Like oxidants, antioxidants constitute a diverse group of compounds with different properties. They operate by inhibiting oxidant formation, intercepting oxidants once they have formed, and repairing oxidant-induced injury,” wrote Diane Tribble, Ph.D., in an advisory letter to the American Heart Association.

“In many cases, increased antioxidant intake has been shown to be associated with reduced disease risk,” Tribble wrote. “This generally has involved increased consumption of antioxidant-rich foods, although some, but not all, recent results have suggested the possible importance of supplemental levels of antioxidants.”

According to the latest statistics, nearly a third of Americans are taking some form of antioxidant supplement today.

Acute Oxidation After Transplantation

“Arteriosclerosis is a health condition that's a problem for many people, but it is much more acute and occurs more rapidly in people who have had heart transplants,” said Balz Frei, Ph.D., professor and director of the Linus Pauling Institute at Oregon State University, who took part in the study.

Forty heart transplant patients were recruited for the double-blind research. Half received 1000 milligrams of vitamin C and 800 international units (IU) of vitamin E each day. The others received a placebo, or dummy pill with no therapeutic value, as a comparison.

Antioxidants' Effect

After one year, the patients who had taken placebo saw had increased thickening and narrowing of their coronary arteries, but those who had received antioxidants had arterial conditions that were relatively unchanged.

“During one year of treatment, the intimal index increased in the placebo group by 8 percent, but did not change significantly in the treatment group,” wrote the cardiologists. (The intima refers to the inner layer of blood vessels.)

The research team also found that antioxidant use did not appear to interfere with the immunosuppressive drugs that the patients were required to take, or cause any increase in transplant rejection.

The authors cited previous studies that tested the effect of vitamin E alone as a supplement in patients with arteriosclerosis, but the outcome was not as dramatic as the latest study, which combined vitamins E and C. They may be complementary to each other, providing more beneficial results than if either one of them were used alone, the researchers speculate.

This type of antioxidant therapy may also have value in other types of organ transplants, such as those of the kidney, lung and liver, said Frei, or in medical procedures like angioplasty. Angioplasty, in which a balloon catheter is fed into a blocked artery to open it up, has to be repeated after several months when arteries again become clogged.

Risk of Cancer Higher in Patients with Fatty Liver, Say Japanese Doctors

by John C. Martin, hivandhepatitis.com

It appears that steatosis, otherwise known as fatty liver, increases the risk of developing hepatocellular carcinoma (HCC), the liver cancer that sometimes results in patients with late-stage hepatitis C (HCV).

That's the conclusion of a group of Japanese medical researchers who analyzed more than 100 patients to determine whether steatosis is a cancer risk factor.(1)

"Hepatic steatosis is one of the "features of chronic hepatitis C," wrote Katsumi Eguchi, M.D., OF Nagasaki University School of Medicine, and his colleagues. "According to previous reports, the prevalence of hepatic steatosis ranges from 31 to 72 percent."

"The objective of this study was to determine whether hepatic steatosis is an independent risk factor in the development of HCC in patients with chronic HCV," the investigators wrote.

They launched the study based on previously reported research that showed a protein associated with hepatitis C in mice caused liver cancer in relation with steatosis evidence.

While steatosis is common in people with HCV, it has been unclear about how this liver condition might affect a patient's risk for developing cancer. What does remain clear is that factors such as the scarring of the liver called cirrhosis, the strain of hepatitis C virus that a person has, and total alcohol intake have been confirmed as higher risk factors for liver cancer.

Origins of Liver Cancer

Hepatocellular carcinoma is the most common form of liver cancer because it comes from hepatocytes, the main type of liver cell. About 75 percent of primary liver cancers are of this type.

Hepatocellular carcinoma develops using different growth patterns. Sometimes, it begins as a single tumor that grows by expanding, and spreads to the rest of the liver only during later stages.

A second type spreads tentacle-like growths throughout the liver, and is not confined to a single tumor. This is the most common pattern seen in the U.S.

In a third type, the cancer develops as nodules in several parts of the liver.

Sometimes, however, the pattern is not clear, and the cancer does not fit any of these profiles.

In steatosis, fat accumulates in the liver cells. Simply fatty liver does not damage the liver, but can be identified through a liver biopsy. Fat may accumulate in the liver in people with extreme weight gain, those with poor diet, or with certain illnesses. A patient has fatty liver when at least 10 percent of the liver is made up of fat.(3)

Assessing Steatosis' Risk For HCC

The findings of the Japanese study are based on an examination of 161 patients who were diagnosed with chronic hepatitis C between 1980 and 1999. All of the patients had no detectable hepatocellular carcinoma when they enrolled in the study. The average follow-up period was about 6 and a half years.

Among the analyses conducted were body mass index (the measure of a person's weight related to height), drinking habits, whether the patient had diabetes, levels of a liver enzyme known as alanine aminotransferase (ALT) that may indicate liver disease, interferon treatment, fibrosis, and of course, whether each patient had fatty liver or not.

The team found that the incidence of hepatocellular carcinoma was about 24 percent five years after diagnosis, climbing to 63 percent at 15 years. "Multivariate analysis identified hepatic steatosis, together with aging, cirrhosis, and no interferon treatment, as independent and significant risk factors for [cancer]," the Japanese research team noted.

Other Associations

The doctors also found that steatosis was directly linked to higher body mass index and with blood levels of ALT and triglycerides. "We did not find direct effects of diabetes or obesity on [liver cancer]. This may be attributable to the fact that our study did not include patients who had advanced cirrhosis at baseline and/or that the studied population included relatively small numbers of obese patients and patients with diabetes," Eguchi and his team wrote.

But they added that people with HCV who lose weight may reduce their steatosis and liver enzyme levels. "However, it is unclear whether weight reduction leads to a

favorable outcome in patients with chronic HCV because BMI [body mass index] had no significant effect on the development of HCC in our study,” the team wrote.

The Bottom Line

“Patients with chronic HCV and hepatic steatosis should be monitored carefully for [liver cancer],” they wrote, but adding that “the factors responsible for steatosis could not be identified clearly.”

In an accompanying editorial, Andrew Zhu, M.D., Ph.D., and Raymond Chung, M.D., both of Massachusetts General Hospital, wrote that steatosis might still be a risk factor for cancer even in patients who have cleared the hepatitis virus. But they stressed that it will be imperative to show how steatosis may cause liver cancer before jumping to conclusions.

“Before we contemplate targeting steatosis as a strategy to decrease the risk of HCC development in patients with chronic HCV infection, it will be important to demonstrate that steatosis is a critical step in the hepatocarcinogenesis pathway [origins of liver cancer],” wrote Zhu and Chung. “Further study to define the relation between steatosis, HCV, and fibrosis will be essential to clarify the individual contributions of these potentially carcinogenic factors.”

August 27, 2003

Accelerated Schedules for Vaccinations Against Hepatitis A and B

by hivandhepatitis.com

The availability of accelerated schedules of vaccination, as well as the development of combination vaccines, has enhanced the methods of protection against infectious disease, in particular that of hepatitis A and B viruses.

The benefits of using accelerated schedules include:

- (1) Enhanced adherence to and subsequent completion of vaccine courses;
- (2) Convenience for the recipient of the vaccine;
- (3) Reduced administration costs of providing the vaccine; and, most importantly,
- (4) The ability to provide protection against these serious infections to those who will be imminently exposed to the risk and so require protection as quickly as possible.

Active immunization against both hepatitis A and B viruses has only been recognised within the last 20 years. During this time clinical studies have demonstrated the safety and efficacy of administering the monovalent hepatitis B vaccine by way of accelerated schedules.

There are now several accelerated schedules of administration of hepatitis B vaccine that can be tailored to the needs of the individual at risk of exposure to infection.

One such schedule allows the primary course to be administered within a period of 1 month [Emphasis added-Ed]. This schedule of day 0, 7 and 21, with a booster at 12

months, is licensed for use with the recombinant hepatitis B vaccine Engerix B trade mark and results in a seroprotection rate of 65% at day 28 which increases to 99% at month 13.

In more recent years, the development of a multivalent or combination vaccine against hepatitis A and B (Twinrix trademark) has been a welcome advance in the protection against viral hepatitis, and has been of particular benefit to those who are at risk of infection with both viruses.

The advantages of accelerated schedules have also been recognized with this combination vaccine. The primary course may be administered within a period of 1 month so providing protection for those at risk and, in particular, the last minute traveler.

High Dose Infigen (Consensus Inter-feron) Produces Sustained Response in Low Percentage of Nonresponders to Interferon Alfa and Ribavirin

by hivandhepatitis.com

Approximately 60% of patients with chronic hepatitis C treated with a combination of interferon (IFN) alfa-2b and ribavirin are nonresponders. The purpose of the present study was to evaluate the efficacy of treatment with high dose Infigen (consensus IFN/CIFN) 15 microgram/day in nonresponders.

Patients were administered 15 microgram CIFN/day. Treatment was stopped in those whose serum hepatitis C virus (HCV) RNA remained detectable at 12 weeks. Those with undetectable HCV RNA at 12 weeks continued on 15 microgram three times per week for a further 36 weeks.

Twenty-four patients were recruited; six (25%) withdrew before 12 weeks because of side effects. Of the 18 patients who completed 12 weeks of therapy, nine (38%) had undetectable HCV RNA. Seven of nine patients who were HCV RNA-negative at week 12 completed 48 weeks of treatment and two withdrew because of intolerable side effects.

At 48 weeks, HCV RNA remained undetectable in three patients. After six months of follow-up off treatment, two patients (8%) continued with no detectable HCV RNA in their sera.

The authors conclude, "High dose induction therapy with CIFN 15 microgram/day in prior nonresponders to IFN alfa-2b and ribavirin led to loss of detectable HCV RNA in 50% of patients, but this response was only sustained in 8% of patients on completion of therapy."

Prediction at Week 4 of Treatment Effect with Interferon Alfa and Ribavirin in HCV Patients Identifies One-half of All Nonresponders and Allows Them Benefit of Early Cessation of Therapy

by hivandhepatitis.com

Treatment of chronic hepatitis C virus (HCV) infection with interferon alfa-2b (Intron A) and ribavirin is costly in terms of side effects, medical resources and drug costs. Furthermore, less than 50% of patients overall have a sustained virological response (SVR).

The objective of the current study was to determine if the log fall in HCV RNA between baseline and week 1 (b-wk1) and between baseline and week 4 (b-wk4) after starting treatment could identify the nonresponders.

Sixty-three patients who had completed a full course of therapy were identified. Quantitative measurements of HCV RNA were analyzed from stored sera, collected prospectively.

SVR was achieved in 47.1% and 47.3% of patients in the b-wk1 and b-wk4 groups, respectively. No patients had an SVR with a fall in HCV RNA of less than 0.35 log₁₀ and 1.05 log₁₀ at week 1 and week 4, respectively. This accounted for 44.4% and 51.7% of the nonresponders in the b-wk1 and b-wk4 groups, respectively.

Once the decline in viral load was known, genotype, age, sex and baseline viral load did not provide additional power in predicting treatment responses.

The authors conclude, "A fall of 1.05 log₁₀ in HCV RNA at week 4 predicts those patients who will not respond, identifying one-half of all nonresponders; this allows therapy to be stopped early, without depriving any patient who would have an SVR from treatment."

Early Response to Individualized Weight-Based PegIntron(R) and Rebetol(R)

Hepatitis C Therapy Allows Accurate Prediction of Treatment Success -
80 Percent of Early Responders Achieve Sustained Response After
Full 48-Week Treatment

Early Response Can Motivate Patients to Complete Treatment

Early virologic response (EVR) in patients with chronic hepatitis C following 12 weeks of individualised, weight-based dosing of PegIntron® (peginterferon alfa-2b) and Rebetol® (ribavirin) combination therapy can accurately predict the likely outcome of a full, 48-week course of treatment, according to a paper appearing in the current issue of Hepatology.(1) The findings show that EVR is important to physicians in making treatment decisions and to patients as a treatment milestone. This analysis is consistent with the current European Union (EU) labeling for PegIntron.

As noted in the paper, 76 percent of patients demonstrated an EVR following 12 weeks of individualised, weight-based dosing of PegIntron and Rebetol combination therapy, and, of those, 80 percent of patients went on to achieve a sustained virologic response (SVR) after full treatment. EVR is defined as at least a 99 percent (2 log₁₀) reduction in hepatitis C virus (HCV) load at week 12 of therapy. SVR is defined as the sustained undetectability of HCV six months following 48 weeks of treatment and is the accepted criterion for efficacy.

The paper also noted that, of the patients who failed to attain an EVR at 12 weeks, none achieved an SVR (100 percent negative predictive value). When cost was considered, it was estimated that discontinuing treatment in early non-responders could reduce total overall drug treatment costs nearly 20 percent.

“A 12-week EVR provides patients and physicians with an early goal, and, for the majority of patients who attain EVR, can motivate treatment adherence and completion to achieve a sustained virologic response,” said Michael P. Manns, M.D., professor, Department of Gastroenterology and Hepatology, Medical School of Hannover, Germany. “On the other hand, as noted in the EU labeling for PegIntron, for patients who do not demonstrate an EVR or take longer to respond to therapy, physicians should consider discontinuing treatment or continuing it based on other prognostic factors,” he added.

Dr. Manns said that the positive predictive value of individualised, weight-based dosing of PegIntron and Rebetol combination therapy in this study is very encouraging in that, of those patients who achieved an EVR, 80 percent went on to achieve an SVR. He also stated that the 100 percent negative predictive value of this combination therapy indicates that physicians can predict, with a high degree of confidence, which patients will not respond to further treatment, and ensure that therapy is not prematurely discontinued for any potential responders.

PegIntron and Rebetol combination therapy is the most prescribed treatment for hepatitis C worldwide and is indicated for the treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha and are at least 18 years of age. More than 300,000 hepatitis C patients worldwide, including 150,000 U.S. patients, have received this combination therapy since its introduction in 2001.

About PegIntron and Rebetol Combination Therapy

PegIntron and Rebetol combination therapy for hepatitis C was approved in the EU in March 2001. PegIntron had previously received centralized marketing authorization in the EU and is marketed as a monotherapy in cases of intolerance or contraindication to ribavirin for the treatment of adult patients with chronic hepatitis C.

PegIntron is a longer-acting form of Intron® A (interferon alfa-2b, recombinant) Injection that uses proprietary PEG technology developed by Enzon, Inc. (NASDAQ: ENZN) of Bridgewater, N.J. PegIntron, recombinant interferon alfa-2b linked to a 12,000 dalton polyethylene glycol (PEG) molecule, is a once-weekly therapy dosed according to patient body weight that is designed to achieve an effective balance between antiviral activity and elimination half-life. Schering-Plough holds an exclusive worldwide license to PegIntron.

Rebetol is an oral formulation of ribavirin, a synthetic nucleoside analog with broad-spectrum antiviral activity. It is approved worldwide for use in combination with PegIntron or Intron A for the treatment of adult patients with chronic hepatitis C. Schering-Plough has rights to market oral ribavirin for hepatitis C in all major world markets through a licensing agreement with ICN Pharmaceuticals, Inc. (NYSE: ICN) of Costa Mesa, Calif.

Schering-Plough Europe, based in Brussels, Belgium, is part of Schering-Plough Corporation (NYSE: SGP) of Kenilworth, N.J., USA, a research-based company engaged in the discovery, development, manufacturing and marketing of pharmaceutical products worldwide.

Note to Editors: PegIntron and Rebetol are licensed to Aesca in Austria, Essex Pharma in Germany and Essex Chemie in Switzerland.

References

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August 28th, 2003

Early Virologic Response to Treatment in Patients with Chronic Hepatitis C by gastrohep.com

Patients with chronic hepatitis C who fail to achieve early virologic response will not clear the virus even if an additional 9 months of therapy is received, find researchers in the September issue of *Hepatology* (*Hepatology* 2003; 38: 645-52).

Interferon-based therapy for patients with chronic hepatitis C is increasingly effective. The virus may be eradicated in over half of cases. The early identification of non-responding patients is desirable as it allows treatment to be stopped.

In this study, a team from the United States examined differing degrees of viral inhibition during early treatment (early virologic response [EVR]) with pegylated interferon alpha-2b and ribavirin (PEG/R). The team's aim was to identify patients who would not respond to therapy.

They considered that the best definition of EVR was a reduction in hepatitis C virus (HCV) RNA by at least 2 logs after the first 12 weeks of treatment when compared to baseline.

The team found that up to 76% of patients achieved this threshold, depending on the treatment regimen. A sustained virologic response (SVR) was achieved in 67% to 80% of these patients.

The researchers determined that patients who did not reach EVR did not respond to further therapy. Up to 76% of patients achieved early virologic response.

Furthermore, they calculated that if treatment was stopped in patients without EVR, drug costs would be reduced by more than 20%.

Dr Gary Davis's team concluded, "Early confirmation of viral reduction following initiation of antiviral therapy for chronic hepatitis C is worthwhile", "It provides a goal to motivate adherence during the first months of therapy and a milepost at which to reassess the need for continued treatment". "Most patients who are able to complete the first 12 weeks of therapy achieve EVR and have a high probability of SVR". "Patients who fail to achieve EVR will not clear virus even if an additional 9 months of therapy is received". "Therapy can be confidently discontinued in those cases".

August 29th, 2003

Outcomes and Indicators of Upper Digestive Bleeding in Cirrhosis

by gastrohep.com

Prognosis of digestive bleeding in cirrhosis has much improved over the past 2 decades, find researchers in the September issue of Hepatology.

There are several treatments which are for variceal bleeding in patients with cirrhosis.

In this study, a team of physicians assessed how these treatments are used in clinical practice. They also evaluated the posttherapeutic prognosis and prognostic indicators of upper digestive bleeding in patients with cirrhosis.

The researchers included a training set of 291 and a test set of 174 bleeding cirrhotic patients in this study.

The treatments were allocated according to the preferences of each center.

There was a follow-up period of 6 weeks.

5-day failure rate was 13%.

The team developed predictive rules for 5-day failure (uncontrolled bleeding, rebleeding, or death) and 6-week mortality using a logistic model in the training set. These rules were validated in the test set.

They established that initial treatment controlled bleeding in 90% of patients. Therapy included vasoactive drugs in 27% of patients, endoscopic therapy in 10%, combined endoscopic and vasoactive treatment in 45%, balloon tamponade alone in 1%, and none in 17%.

They determined that the 5-day failure rate was 13%, 6-week rebleeding was 17%, and mortality was 20%.

The physicians found that for 5-day failure, variceal bleeding occurred in 15%, compared to nonvariceal bleeding in 7%. For 6-week rebleeding 19% was variceal and 10% nonvariceal, and when mortality occurred 20% of bleeding was variceal and 15% nonvariceal.

They determined that active bleeding on endoscopy, hematocrit levels, aminotransferase levels, Child-Pugh class, and portal vein thrombosis were significant predictors of 5-day failure. However, alcohol-induced etiology, bilirubin, albumin, encephalopathy, and hepatocarcinoma were predictors of 6-week mortality.

Prognostic reassessment including blood transfusions improved the predictive accuracy.

The team found that all the developed prognostic models were superior to the Child-Pugh score.

Drs Gennaro D'Amico and Roberto De Franchis concluded that the, "Prognosis of digestive bleeding in cirrhosis has much improved over the past 2 decades".

"Initial treatment stops bleeding in 90% of patients".

"Accurate predictive rules are provided for early recognition of high-risk patients".

Factors Influencing the Outcome of Liver Retransplantation

by gastrohep.com

Liver retransplantation is associated with a greater rate of complications, and lower patient and graft survival, find physicians in the September issue of Liver Transplantation (Liver Transpl 2003; 9: 897-904).

Whether the outcome of liver retransplantation is dependent on the indication for retransplantation or the cause of liver disease is unknown.

In this study, physicians from Baltimore, Maryland, compared the outcome of retransplantation in adults with that of primary liver transplantation (PLT). They assessed whether the outcome of retransplantation was dependent on its indication.

The research team used data from the United Network for Organ Sharing from 1988 to 2001.

Hepatitis C virus infection is an independent predictor of mortality after liver retransplantation.

Overall, the team identified 34,267 patients who met their inclusion criteria. Of these, 761 patients underwent liver retransplantation for primary graft nonfunction (PGNF) (group 1), 3428 patients underwent retransplantation for other reasons (group 2), and 30,078 patients underwent PLT (group 3).

The researchers identified a greater incidence of PGNF and regrafting in the retransplant groups when compared with the PLT group.

In addition, analysis showed significantly lower short- and long-term patient and graft survival in the retransplant groups compared with the PLT group.

Furthermore, the team found that patients in group 1 had lower patient and graft survival compared with group 2.

However, when data was analyzed using Cox regression they found that graft survival not patient survival was lower in group 1. The team also found that patients with hepatitis C virus (HCV) infection who underwent retransplantation had lower patient and graft survival compared with those without HCV infection.

HCV was identified as an independent predictor of mortality after liver retransplantation.

Dr Hwan Yoo's team concluded, "Retransplantation was associated with a greater rate of complications and lower patient and graft survival compared with PLT".

"Retransplantation for PGNF and HCV infection was associated with lower patient and graft survival compared with retransplantation for other causes".

Britain Says It Will Pay Hepatitis C Victims

by Richard Woodman

Thousands of Britons infected with the hepatitis C virus as a result of contaminated blood products and transfusions are to receive compensation, Health Secretary John Reid said on Friday.

The details of the payments have yet to be worked out but a Department of Health spokesman said the sums involved could range from 20,000 to 45,000.

Many thousands of people, especially hemophiliacs, were infected during the 1970s and early 1980s before the hepatitis C virus could be detected in blood and before blood products were heat-treated.

Reid said in a statement a financial assistance scheme would be introduced for people infected with the virus as a result of being given blood products by the National Health Service.

“I looked at the history of this issue and decided on compassionate grounds that this is the right thing to do in this situation. I have therefore decided in principle that English hepatitis C sufferers should receive ex-gratia payments from the Department of Health.”

The ministry spokesman said compensation schemes were also planned in Scotland, Wales and Northern Ireland.

Between 3000 and 5000 people might be eligible for the payments, he said. Possible ballpark figures were 20,000 for people who had not cleared the virus from their system and 45,000 for people with liver damage.

The Hemophilia Society urged the government last year to make 52.6 million available annually for people with hemophilia who were infected with hepatitis C through contaminated blood products.

The charity said that from 1969 to 1985, 95% of people with hemophilia were treated with blood products carrying a high risk of infection with hepatitis C. As a result, 2,829 hemophiliacs alive in the country today were infected with the virus.

It argued that annual payments were needed because of loss of earnings, difficulties in obtaining travel, life and medical insurance, pensions and mortgages, and the progressive impact of hepatitis C on the health of hemophiliacs.

Hundreds of British hemophiliacs have already received government compensation for being infected with HIV via blood products.

Patients with HBV Genotype B Infection Have More Severe Exacerbations of Disease and Higher Risk of Hepatic Decompensation and Mortality Compared with Patients with HBV Genotype C Infection

by hivandhepatitis.com

There is growing evidence that hepatitis B virus (HBV) genotypes may play some role in causing different disease profiles in chronic hepatitis B (CHB). Among Asians, who constitute >75% of the worldwide population of individuals with CHB, genotypes B and C are the 2 most common HBV genotypes.

Though genotype B can be subdivided into genotype Bj, representing genotype B found among infected individuals from Japan, and genotype Ba, representing genotype B found among individuals from the rest of Asia, most infected non-Japanese Asians have genotype Ba only. In this article, references to genotype B refer to genotype Ba unless otherwise noted.

A study from Taiwan shows that young patients with hepatocellular carcinoma are more likely to be infected with HBV genotype B than genotype C, whereas patients with more-advanced liver disease are more likely to be infected with genotype C than genotype B.

Other studies demonstrate that, compared with patients with genotype C infection, patients with genotype B infection have more serious liver disease. Recent studies show that patients with genotype B achieve hepatitis B e antigen (HBeAg) seroconversion a decade earlier than do patients with genotype C. Regarding responsiveness to treatment, there is some evidence that patients with genotype B respond better to IFN- α when compared with patients with genotype C.

However, the effect of HBV genotypes on HBV disease exacerbations has not been studied. We aimed to investigate, in a cross-sectional study, the relationship of HBV genotypes to the probability and severity of HBV disease exacerbations among Chinese patients with CHB.

During the period 2000-2001, 73 patients (group I) who were admitted to Queen Mary Hospital, The University of Hong Kong, Hong Kong, with severe exacerbations of hepatitis B disease and symptoms of hepatitis were recruited for our study. All 73 patients had tested positive for hepatitis B surface antigen for >6 months.

“Severe exacerbation” of disease was defined as an increase of alanine aminotransferase (ALT) levels to >10 times the upper limit of normal (ULN). Patients with evidence of other hepatotropic virus infection, checked by testing with antibodies to hepatitis A, C, D, and E, were excluded. Patients with a history and clinical features of drug-induced hepatitis, alcoholic hepatitis, and steatohepatitis were also excluded.

There were no differences in the median age, sex ratio, proportion of HBeAg to antibody to HBeAg positivity, proportion of patients with ultrasonographic evidence of cirrhosis, and median HBV DNA level between the 4 groups of patients. Group I patients (i.e., with severe exacerbations) had a significantly higher median ALT level, lower median albumin level, and higher median bilirubin level compared with the other 3 groups (all $P < .001$).

There were no significant differences in the prevalence of genotype B and genotype C between the 4 groups (all $P = NS$). In total, there were 102 patients with single genotype B infection and 183 patients with single genotype C infection.

Infection with genotype B was associated with a higher prevalence of precore mutations (84 [82.4%] of 102 patients), compared with infection with genotype C (54 [29.5%] of 183). In contrast, infection with genotype C was associated with a higher prevalence of core promoter mutations (165 [90.2%] of 183 patients), compared with infection with genotype B (35 [34.3%] of 102; $P < .001$).

All patients with exacerbations of disease (groups I, II, and III) were categorized according to whether they were infected with HBV genotypes B or C. Patients infected with genotype B had a higher median ALT level, higher median bilirubin level, and lower median albumin level during periods of exacerbation, compared with

patients infected with genotype C. This means that patients infected with genotype B had more severe exacerbations compared with those had by patients infected with genotype C.

Because nearly all patients we studied with HBV infection in the Chinese population became infected during the perinatal period or within the first 1-2 years of life, it is unlikely that there is any difference in the duration of infection for patients infected with genotypes B and C.

The higher rates of hepatic decompensation and mortality among patients infected with genotype B compared with patients infected with genotype C suggests that HBV genotype B may be more immunogenic and hence cause more severe immune-system-mediated damage. Studies have shown that patients infected with genotype B have earlier HBeAg seroconversion, compared with patients with genotype C.

Infection with genotype B was associated with precore mutations and infection with genotype C was associated with core promoter mutations.

The present study suggests that patients with HBV genotype B infection had more severe exacerbations of disease and a higher risk of hepatic decompensation and mortality due to severe exacerbations, compared with patients with HBV genotype C infections.

Previous longitudinal studies of acute exacerbations in patients with chronic HBV infection have demonstrated convincingly that acute exacerbations are usually not associated with infection with viral genotypes other than the original genotype. Further longitudinal studies should be designed to follow up a large population of patients with CHB and define the impact of the difference in exacerbations of disease among patients infected with genotypes B and C on the progression of the disease and the development of complications.

Clinical Features and Outcome in HCV-positive Patients with Aggressive Non-Hodgkin's Lymphoma

by hivandhepatitis.com

The clinical features and outcome of 25 previously untreated aggressive non-Hodgkin's lymphoma (NHL) patients with hepatitis C virus (HCV) infection were evaluated retrospectively by researchers at the Yokohama City University School of Medicine, Yokohama, Japan.

The patients included 18 males and 7 females with a median age of 66 years. The median observation period for survivors was 32 months. Although there were no patients with hepatocellular carcinoma during the follow-up period, 7 patients had cirrhosis (LC) at the initiation of therapy for NHL. Seventeen patients (68%) had initial extranodal involvement including 2 cases with liver involvement.

Results

The 5-year overall survival (OS) rate in the whole group was 46%, and the 5-year relapse-free survival (RFS) rate of patients with complete response (CR) was 48%.

Patients with non-cirrhosis (n = 18) experienced better OS (P = 0.04) compared with patients with LC (n = 7) and 5-year OS rates were 55 and 21%, respectively. Fourteen patients died in the whole group; 4 of NHL and 2 of liver failure in the LC group and 8 of NHL in the non-cirrhosis group. Among the latter 8 patients, cumulative dose (CD) of doxorubicin (ADR) and cyclophosphamide (CPA) were significantly lower than those of survivors with non-cirrhosis.

The authors conclude, "Patients with HCV-positive, aggressive NHL have a similar prognosis as HCV-negative aggressive NHL. In non-cirrhosis patients, attention should be paid to the CD of drugs required to cure the aggressive NHL."

Retreatment with Interferon Is Effective in Some Partial Responders and Nonresponders with Chronic Hepatitis C

by hivandhepatitis.com

Chronic hepatitis C can progress to end-stage liver cirrhosis or hepatocellular carcinoma. Interferon (IFN) therapy is effective in clearing the hepatitis C virus and in improving liver histology. However, few patients maintain a sustained response (SR) after IFN withdrawal.

Immediate retreatment with IFN is therefore considered to be both effective and necessary, especially for patients who do not respond to the initial course of IFN therapy.

All 145 patients included in the present study, conducted at the Fukuyama National Hospital, Hiroshima, Japan, underwent liver biopsy, followed by a first treatment course with various IFN's (alfa-2a, alfa-2b, OIF, or beta).

If hepatitis C virus (HCV) RNA was positive after the first treatment, the patient was assigned to one of 3 groups, depending on whether his or her alanine transaminase (ALT) level was normalized (incomplete response, IR), partially responsive (PR), or non-responsive (NR).

After an observational interval of 6 to 76 months, a second IFN treatment was initiated with a higher dose or the same dose of the same IFN for the IR group, and with a different IFN for the PR and NR groups.

Results

At 6 months after retreatment with IFN, the overall efficacy of the retreatment was 29.7%. In the case of the IR group, who received the same IFN, the overall efficacy was 45.2%. In patients identified as non-SR after the first treatment, who received a different type of IFN for retreatment, the overall efficacy was 18.6%. Anti-IFN antibody was not detected in most of the breakthrough cases. For some IR patients, retreatment with the same IFN was effective.

Anti-IFN antibody was mostly negative, indicating that the same IFN can be used in both the first treatment and retreatment to obtain an SR.

Switching to a different IFN was effective for some PR and NR patients, suggesting that changing IFN for such cases is a good therapeutic choice.

September 1st, 2003

Finding the Right Combination to Fight Hepatitis C

Linda Marsa

Of the millions of Americans infected with hepatitis C, only half respond to treatment. The others live with the constant threat that their health may suddenly, and fatally, deteriorate.

A new drug could improve those odds. When used with the antiviral drug interferon, a medication called Zadaxin may help thousands of patients better fight the disease.

“This medication looks promising for people who don’t respond to other drugs,” says Dr. Sammy Saab, a liver specialist at UCLA’s David Geffen School of Medicine. “It may also be used as part of a combination drug cocktail for all hepatitis C sufferers, since it seems to work by a different mechanism of action than other medications.”

About 4 million Americans are infected with hepatitis C, and about 2.7 million of those have an active infection, in which the liver is inflamed. Infection is insidious, however. People can be symptom-free for years, but the virus can quietly incubate, causing cirrhosis of the liver, liver cancer or even liver failure. Hepatitis C, which kills 10,000 people a year, is the leading reason for liver transplants in the U.S.

The current treatment—a combination of two antiviral medications, interferon and Ribavirin—helps only about half of those with active infections and less than a third who are infected with the more prevalent and more dangerous form of hepatitis C, known as genotype 1.

The drugs also have serious side effects, leading many people to stop taking them. Ribavirin can cause anemia, which leaves patients feeling extremely fatigued, while interferon can cause flu-like symptoms and birth defects if taken by pregnant women. These side effects “can result in having to reduce the dose and therefore decrease the efficacy of the drugs,” says Dr. Adrian Di Bisceglie, a liver specialist at St. Louis University School of Medicine in Missouri.

Zadaxin has no apparent side effects. It is a synthetic version of thymosin alpha 1, a naturally occurring protein that circulates in the body and stimulates the production of certain immune system cells. Zadaxin is approved for sale in 30 countries as an antiviral drug to treat hepatitis B but in only a few countries to combat hepatitis C.

Results of a 2002 U.S. study of the drug as a hepatitis C therapy were encouraging. The test involved 31 patients who had high levels of genotype 1 and who hadn't responded to standard medications. Zadaxin, used in combination with interferon, greatly reduced levels of the virus in up to 36% of the patients.

The findings were especially significant because patients who don't respond to the initial round of treatment seldom benefit from subsequent therapy.

"We purposely chose the most difficult of the most-difficult-to-treat patients," says Di Bisceglie, who conducted this research. The drug is in the final phase of U.S. trials.

About the disease

Hepatitis C is one of five identified viruses—hepatitis A, B, C, D and E—that attack and damage the liver. Hepatitis C, however, is considered the most grave and is spread mostly through contact with infected blood.

Before a test was available for hepatitis C, some people were unwittingly infected through blood transfusions. Others acquired it by injecting illegal drugs, receiving organs from donors whose blood contained the virus, getting pricked with a needle that had infected blood on it, snorting cocaine using shared equipment, getting a tattoo or body piercing with non-sterile instruments or through sexual activity.

Although Zadaxin may help treat the virus, other drugs—which aren't as far along in development—may ultimately vanquish it. Among the more promising are hepatitis C protease inhibitors, which work by blocking the action of a key enzyme that the virus needs to replicate. Drugs that have a similar mechanism of action, disabling protease, revolutionized AIDS treatment.

Other experimental medications include a monoclonal antibody that latches onto the surface of the HCV (HCV-AB68), preventing the virus from entering the cells, and a fusion protein (albuferon), which may enhance the action of interferon.