

The Best in the News on HCV, HBV and HIV/HCV Coinfection from September 15th 2002 thru October 15th 2002

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September 16th, 2002

1. Hepatitis worse during immunocompetence with HIV/hepatitis C coinfection

by Sonia Nichols, senior medical writer (Hepatitis Weekly via NewsRx.com.)

Ironically, liver disease may worsen when there is immunocompetence in hemophiliacs coinfecting with human immunodeficiency virus (HIV) and hepatitis C virus (HCV). Medical investigators in Athens, Greece, drew this conclusion after studying several factors associated with liver histology in 21 hemophilia patients with HIV and HCV coinfections.

With an average age of 35.7 - 8.7 years, the evaluated patients were in various stages of liver disease, HCV, and HIV. Upon histological evaluation a majority of them demonstrated moderate hepatitis.

"Statistical analysis showed a significant association of CD4 count <50 with minimal hepatitis and of CD>200 with mild and moderate hepatitis (p=0.33)," reported J. Delladetsima, University of Athens Medical School, Athens, Greece.

Stage C is a classification for greater symptomatology in HIV infection. Most of the patients with this stage of

disease demonstrated only minimal hepatitis, whereas those at stage A, a classification for lesser HIV symptomatology, had mild-to-moderate hepatitis, according to researchers. This data is published in an article titled "Significance of immune status, genotype and viral load in the severity of chronic hepatitis C in HIV infected haemophilia patients". *Haemophilia*, September 2002;8(5):668-673).

"No relationship was found between hepatitis severity, HIV or HCV RNA levels, patient's age and duration of HIV or HCV infection," researchers noted.

Immunocompetence, rather than immunodeficiency, may be a hallmark for more aggressive hepatitis in hemophilia patients coinfecting with HIV and HCV, Delladetsima and colleagues suggested.

Key points reported in this study include:

- ◆ Having a lower T-cell count associated with minimal hepatitis in hemophilia patients coinfecting with HIV and HCV
- ◆ Stage A HIV correlated with greater liver disease than did stage C HIV
- ◆ Immunocompetence may foster an environment for hepatitis aggravation in hemophiliacs coinfecting with HIV and HCV

Additionally on September 16th, 2002

2. Study profiles those likely to discontinue therapy for chronic hepatitis C

by Sonia Nichols, senior medical writer (Hepatitis Weekly via NewsRx.com.)

Adverse effects often lead to chronic hepatitis C patients discontinuing prescribed regimens that include combinations of interferon and ribavirin. The authors of a new study have produced a profile of the major reasons for therapy discontinuation in chronic hepatitis C patients.

According to G.B. Gaeta and colleagues of the Unit of Infectious Diseases at the Second University of Naples in Italy, more than a fourth of hepatitis C virus (HCV)-infected patients enrolled in clinical trials of interferon/ribavirin combination therapy drop out due to adverse effects. In a retrospective study, Gaeta's team evaluated the factors associated with adverse event-related discontinuation, analyzing the records of more than 400 patients enrolled at five treatment centers.

Of the 441 included patients, 108 failed to complete treatment due to undesirable side effects, Gaeta and coauthors said.

"The discontinuation rate was higher during the first 6 months of treatment, anemia was an important cause (36.1% of discontinuations); unexplained lipothymia (syncope or sudden fainting) resulted in discontinuation in 11 patients," the researchers reported.

Being female, being prescribed interferon doses greater than 15MU/week, or using interferon for the first time were the three most important predictors for stopping therapy (Premature discontinuation of interferon plus ribavirin for adverse effects: This data is published in an article titled "A multicenter survey in 'real world' patients with chronic hepatitis C". *Alimentary Pharmacology and Therapeutics*, September 2002;16(9):1633-1639).

"The simultaneous presence of these factors identified patients at high risk for discontinuation," the coauthors stated.

Profiles like the one developed in the study could be useful for improving prescribed protocols for chronic hepatitis C patients, Gaeta's team concluded.

Key points reported in this study include:

- ◆ Over a fourth of chronic hepatitis C patients will typically drop out of trials investigating interferon/ribavirin combination therapy
- ◆ The independent factors predicting combination therapy discontinuation included gender, interferon dosage, and interferon history
- ◆ Using profiles like the ones outlined in the study should enable investigators to improve prescribed regimens for chronic hepatitis C patients

September 18th, 2002

3. One in ten veterans in New York City area infected with HCV

The prevalence of hepatitis C virus (HCV) infection among military veterans in the New York City metropolitan area is 10.6%, much higher than the 1.8% rate reported in the general US population, according to a recent report.

Moreover, nearly one-quarter of HCV-infected veterans studied were also infected with HIV, study author Dr. Norbert Brau, from the Bronx VA Medical Center in New York, and colleagues note.

In the current study, the researchers assessed the prevalence of HCV infection among 1,098 New York City area veterans who underwent phlebotomy for any reason on one day in 1999. Of these patients, 1,016 completed a questionnaire regarding their demographic background and HCV risk factors.

All blood samples that tested positive for anti-HCV antibodies were confirmed by further RNA tests and also assayed for HCV viral load, HCV genotype, and anti-HIV antibodies.

The rates of HCV infection and viremia were 10.6% and 8.2%, respectively. Nearly 78% of HCV-infected patients had HCV viremia, the authors note. By far, the most common HCV genotype associated with viremia was type 1, identified in 87.5% of viremic patients.

The greatest risk factor for HCV infection was injection drug use. Injection drug users were 35.6 times more likely to be infected with HCV than nonusers. Other risk factors for infection included exposure to blood during combat, alcohol abuse, and service during the Vietnam War.

Nearly 25% of anti-HCV-positive patients were also infected with HIV, the authors note in the August issue of *The American Journal of Gastroenterology* (Am J Gastroenterol 2002;97:2071-2078.)

On multivariate analysis, the only risk factor independently associated with HIV coinfection was age less than 50 years.

The findings indicate that HCV infection is relatively common among New York City area veterans and that treatment will be challenging because most are infected with genotype 1, which is less responsive to therapy than other types, the authors write. Veterans with any of the risk factors identified should be offered HCV testing, the researchers emphasize.

September 20th, 2002

4. FDA OKs Chronic Hepatitis B Drug

Patients suffering from the liver-destroying hepatitis B virus will be able to use a new drug therapy.

The Food and Drug Administration approved the drug, adefovir dipivoxil, on Friday. It will be sold as Hepsera, and is the first new therapy in years for an estimated 1.2 million Americans who suffer with the potentially deadly infection.

The treatment, made by Gilead Sciences Inc., is just one of three therapies for patients with hepatitis B - a virus that can lead to cirrhosis and liver cancer. It is transmitted through blood, bodily fluids, shared needles and from mother to child.

The drugs, interferon and lamivudine, are the only other medicines available to hepatitis B patients. But some patients become resistant to one drug and others can't tolerate the side effects of the other. Doctors have long wanted another option.

"We believe this is really an important advancement for patients," said Amy Flood, a spokeswoman for Gilead.

Adefovir originally was tested as a possible treatment for the AIDS virus, but the FDA rejected that use because the high doses required proved toxic to patients' kidneys.

Gilead was tested far lower doses as a hepatitis B treatment. It didn't cure the infection, but studies concluded that liver cirrhosis improved in between 56 percent and 66 percent of patients testing the drug.

Flood said a patient would take one tablet per day. Studies showed that a 10-milligram, daily dose didn't lead to outright kidney damage.

But it is still a potential side effect: By a more conservative measurement, up to 5 percent of patients who used adefovir for a year showed early signs of some toxicity, according to the studies.

Gilead, based in Foster City, Calif., will begin shipping the drug as early as next week, Flood said.

September 23rd, 2002

5. Regimens altering lamivudine and interferon yield similar results in children

by Sonia Nichols, senior medical writer (Hepatitis Weekly via NewsRx.com.)

Pediatric patients with hepatitis B virus (HBV) tend to respond to therapy that combines lamivudine and interferon without regard to the way the therapies are combined, according to a new study.

Still, the report's authors are recommending more pediatric studies that would discern whether any additional benefits could be derived from having children receive interferon or lamivudine first, last, or at the same time when they begin treatment regimens.

In the October 2002 edition of *Journal of Gastroenterology and Hepatology*, Bunyamin Dikici and colleagues reported the results of a pediatric hepatitis B therapy study they conducted at Dicle University Medical School in Diyarbakir, Turkey. Thirty-two children who had diagnoses of chronic hepatitis B were included in the investigation.

For the study, one group of children was treated with interferon and lamivudine in combination for 6 months, followed by lamivudine monotherapy for an additional 6 months (group 1). Another group of youngsters received lamivudine alone for 2 months, interferon and lamivudine combined for the next 6 months, and lamivudine alone again for the last 4 months of the trial (group 2).

"The same doses of lamivudine and interferon-alpha were used in both groups," Dikici and colleagues stated.

Doctors measured the children for levels of the liver enzyme alanine aminotransferase (ALT) and for virus factors such as hepatitis B e antigen (HBeAg), antibody to HBeAg (anti-HBe), and HBV DNA at baseline, at the end of treatment, and at 6 months follow-up.

Average ALT levels, signaling liver function status, were similar in both groups at the end of the 6-month follow-up period, although ALT levels in group 1 were slightly lower at the end of the 12-month treatment period.

Doctors usually look for HBeAg seroconversion to anti-HBe and reduced levels of HBV DNA as a sign of response to therapy. "After 6 months from completion of therapy, rates of seroconversion to anti-HBe were found to be 64% and 47% in group 1 and 53% and 46% in group 2 (for HBeAg and anti-HBe, respectively)," Dikici and colleagues commented.

Only one patient in group 1 retained detectable HBV DNA at the end of treatment and at follow-up, whereas in group 2 one patient demonstrated HBV DNA at the end of treatment and two patients experienced relapse by the end of follow-up. The data is published in an article titled "Combination therapy for children with chronic hepatitis B virus infection". J Gastroenterol Hepatol, October 2002;17(10):1087-1091).

Given the results, Dikici and colleagues concluded both groups may have benefited equally from the two different treatment regimens although they cautioned that additional evaluations would be needed in order to fully understand the benefits of different interferon and lamivudine treatment protocols in youngsters with chronic hepatitis B.

Key points reported in this study include:

- ◆ Children with chronic hepatitis B who took two different interferon and lamivudine combination treatment regimens responded similarly to therapy
- ◆ Approximately half of the children in each of the groups experienced complete response to the interferon and lamivudine combination treatment regimens
- ◆ More studies are needed to detect the combination of interferon and lamivudine that would yield the most benefits to children infected with HBV

Additionally on September 23rd, 2002

6. Although hepatitis C assays are good, there is still room for improvement

by Sonia Nichols, senior medical writer (Hepatitis Weekly via NewsRx.com.)

The quality of hepatitis C virus (HCV) assays has improved over the years, but the results of data collected through a quality assessment program suggest there is room for more standardization.

Thus were the findings of the members of a European quality assessment consortium, which evaluated the ability of several laboratories across Europe to detect and quantify HCV RNA during proficiency testing.

According to Jurjen Schirm of the Regional Public Health Laboratory in Groningen, Netherlands, the laboratories were given two proficiency panels comprised of two negative and six positive samples. The samples were prepared to contain anywhere from between 200 to 500,000 copies/ml of HCV RNA. At least 57 labs returned data sets for panel 1, while 81 laboratories returned data sets for panel 2.

"Panel 1 had four samples with at least 50,000 copies/ml, and panel 2 had two samples with at least 50,000 copies/ml," noted Schirm and coauthors.

Most of the labs used commercial assays for running qualitative and quantitative assays, according to Schirm and colleagues.

The false positive rate for panels 1 and 2 were 1.3% and 0.8%, respectively, Schirm and associates stated.

"Samples containing at least 50,000 copies/ml were found positive in 97% and 99% of the cases with panel 1 and 2, respectively," researchers said. "In contrast, the positive samples containing h5,000 copies/ml were reported positive in only 71% and 77% of the cases with panel 1 and panel 2, respectively."

Scores of adequate or better were achieved by approximately 80% of the submitted data sets for the qualitative results of both panels, and by 60% and 73%, respectively, of the submitted data sets for the quantitative results for panels 1 and 2. The data is published in an article titled "External quality assessment program for qualitative and quantitative detection of hepatitis C virus RNA in diagnostic virology". *Journal of Clinical Microbiology*, 2002;40(8):2973-2980).

"Our results indicate that considerable improvements in molecular detection and quantitation of HCV have been achieved, particularly through the use of commercial assays," Schirm and colleagues argued. Even so, the group pointed out that the assays still test at detection levels that are too high, and recommended the incorporation of changes that would yield more consistent results.

Key points reported in this study include:

- ◆ Most laboratories in Europe that were enrolled for HCV RNA proficiency testing used commercial assays
- ◆ In a majority of instances, the detection and quantification of HCV RNA among the submitting laboratories was adequate or better
- ◆ HCV DNA detection levels for commercial assays need to be lowered, and assay standardization is needed

September 24th, 2002

7. New assay to distinguish primary vs. chronic infection

An assay for IgG avidity in hepatitis C virus (HCV) infection may be useful in distinguishing primary infection from chronic disease, Japanese researchers report in the October issue of the *Journal of Medical Virology* (J Med Virol 2002;68:229-233.).

Dr. Atsushi Kanno of Tohoku Koseinenkin Hospital, Sendai, and Dr. Yukumasa Kazuyama of Kitasato-Otsuka Biomedical Assay Laboratories, Sagamihara, note that in HCV it is "important to distinguish acute infection and chronic infection when considering treatment." However, "seroconversion of antibody to HCV (anti-HCV) is currently the only reliable marker to identify primary HCV infection," they write.

To determine whether an enzyme immunoassay for anti-HCV IgG avidity might also be useful in this regard, the researchers tested the avidity assay in 36 anti-HCV-positive immunocompetent patients.

The investigators found that the avidity assay gave a mean avidity index of 7.7 in patients with primary HCV infection, a figure significantly lower than that in patients with histologically confirmed chronic HCV infection (77.0; $p < 0.0001$) or in patients who had previously had HCV infection (44.5; $p < 0.0001$).

Examination of a subset of 6 patients with primary HCV infection showed that the avidity index was low in the acute phase of the infection, but increased over time.

"The avidity assay for IgG anti-HCV is a useful tool to discriminate...primary HCV infection from chronic or past HCV infection," the researchers conclude.

September 25th, 2002

8. New Combination Treatment for Hepatitis C Reported More Beneficial Than Standard Combination Therapy

New England Journal of Medicine this week carries the first published report showing that a combination treatment with peginterferon alfa-2a (Pegasys) -- a new long-acting interferon drug -- and an antiviral

medication is more beneficial than the standard combination therapy for people with the most-difficult-to-treat and most common strain of hepatitis C.

The large international study headed by researchers at the University of North Carolina at Chapel Hill is also the first published to show that treatment with the investigational drug peginterferon alfa-2a in combination with the oral antiviral medication, ribavirin, is linked to a lower rate of troublesome side effects -- depression, flu-like symptoms (chills, headache, fever) -- than the standard interferon (Rebetron) and ribavirin.

"Sixty-five percent of patients in the study were infected with hepatitis C genotype 1, the most prevalent genotype we see here in the United States, and typically the least responsive to therapy," said study co-author Dr. Michael W. Fried, associate professor of medicine and director of clinical hepatology at the UNC School of Medicine. "With this research, we've found the most significant evidence to date suggesting these patients might benefit by taking peginterferon alfa-2a in combination with ribavirin."

According to Fried, side effects of therapy can be very challenging for patients. "The study shows an approach that can offer patients superior efficacy without increases in some of the most common and difficult to tolerate adverse events associated with hepatitis C therapy."

Of the six different strains, or genotypes, of hepatitis C, approximately 70 percent of people in North America are infected with genotype 1.

The study, funded by Hoffmann-La Roche, the maker of Pegasys, was conducted at 81 clinical sites in 18 countries. It involved over 1100 patients in one of three study arms: 453 were treated with peginterferon alfa-2a plus oral ribavirin; 224, with peginterferon alfa-2a plus placebo; and 444 with interferon alfa-2b plus ribavirin. Patients were treated for 48 weeks and then monitored for an additional 24 weeks.

A key variable measured by the study was sustained viral response, defined as undetectable serum hepatitis C RNA after the treatment-free follow-up period.

Overall, patients treated with the peginterferon alfa-2a plus ribavirin combination achieved a 56 percent sustained response rate as compared to patients taking Rebetron (44 percent). Patients with genotype 1 had a sustained response rate of 46 percent, compared to patients on Rebetron (36 percent) and those on Pegasys plus placebo (21 percent).

A retrospective analysis of the data showed that response to PEG interferon alpha-2a plus ribavirin is predictable. At week 12, 86 percent of patients treated with PEG interferon demonstrated an early viral response; of these, 65 percent attained a sustained viral response. However, 97 percent of patients who did not respond by week 12, failed to achieve a sustained response.

"This means that physicians can create an alternate treatment plan for patients who do not show any response by week 12," said Fried. "And for those who do respond, it can be a motivation to continue to adhere to their treatment regimens." Dr. Fried cautioned that these treatment decisions must be individualized for each patient.

The hepatitis C virus (HCV) is a life-threatening viral infection of the liver transmitted primarily through infected blood and blood products. Approximately 2.7 million Americans and 170 million people worldwide are chronically infected with HCV. HCV is often described as "silent" because people may be infected for 10 to 30 years and not exhibit symptoms, yet still be carrying the virus. While many patients with HCV will not develop complications from their liver disease, chronic hepatitis C is still a leading cause of cirrhosis and liver cancer and is the major indication for liver transplants in this country.

The Center for Liver Diseases and Transplantation at the University of North Carolina at Chapel Hill provides highly specialized care for liver diseases for residents of North Carolina and surrounding regions. In addition to its commitment to patient care, the UNC liver program is dedicated to studying novel therapies for viral hepatitis, other chronic liver diseases, and transplantation.

9. Pegasys A POTENTIAL MAJOR ADVANCE IN HEPATITIS B TREATMENT: Clinical studies show significantly improved efficacy over current treatments

Results of a phase II study presented today at the 2002 Meeting of the Asian Pacific Association for the Study of Liver, demonstrate the promise of PEGASYS as an important new treatment for chronic hepatitis B (CHB) patients. PEGASYS has already been approved for the treatment of chronic hepatitis C (CHC) and has been shown to provide superior efficacy when compared to conventional interferon therapy.

“All the study results we have heard today suggest that PEGASYS could be a major advance in the treatment of hepatitis B,” said Prof. Ming Yang Lai, one of the study authors from National Taiwan University College of Medicine, Taiwan. “Each of the currently available treatments has considerable limitations. In contrast, PEGASYS appears to be a treatment that offers significantly improved efficacy, even in patients with treatment resistant disease.”

In a study involving 194 patients, researchers found more than twice as many PEGASYS patients responded to treatment than those using conventional interferon. 28% of patients treated with PEGASYS 180µg once weekly for 24 weeks achieved the combined response of HBeAg clearance (indicating viral replication has stopped), HBV DNA suppression (indicating the virus is effectively controlled) and ALT normalization (indicating normal function of the liver). In contrast, only 12% of interferon alfa-2a patients achieved these results. Similarly, HBeAg seroconversion (loss of HBeAg and presence of anti-HBe) was achieved in 33% of patients treated weekly with PEGASYS compared to 25% of patients treated with conventional interferon alfa-2a. The absence of HBeAg viral protein and the presence of HBV-neutralising antibody anti-HBe indicates that the immune system has regained control over HBV.

In the same study, PEGASYS demonstrated that it is also effective in patients with difficult to treat hepatitis B – that is, those with low pre-treatment ALT levels and high pre-treatment viral load. In a study presented by Prof. Graham Cooksley, Director of Clinical Research Centre, Royal Brisbane Hospital Research Foundation, Australia, 44% of patients with difficult-to-treat HBV treated with PEGASYS achieved HBeAg loss compared to 17% on conventional Interferon alfa-2a.

“As physicians, we are very encouraged by these early results with PEGASYS. It is especially important to find a treatment for patients with hard-to-treat disease, because they typically respond poorly to current therapies” said Prof. Cooksley.

Lamivudine and conventional interferon alfa, the currently available standard therapies for hepatitis B in Asia, have clear limitations in terms of overall efficacy. Moreover, about 20 per cent of patients treated with lamivudine develop resistance to the drug within one year of therapy. In addition, a number of patients treated with lamivudine are required to continue therapy indefinitely. PEGASYS overcomes these limitations by delivering higher efficacy within a defined treatment duration. In addition, hepatitis B virus does not develop resistance to PEGASYS.

Phase III, randomized clinical trials with PEGASYS, which are currently underway in both HBeAg positive and HBeAg negative patients.

About Hepatitis B

Hepatitis B is a blood-born virus that attacks the liver and is the most common serious liver infection in the world. The Hepatitis B virus is highly contagious and is relatively easy to transmit from one infected individual to another. It is 100 more times infectious than the HIV virus. More than two billion people have been infected by HBV and 350 million people have chronic infection, which can be easily transmitted by blood-to-blood contact, during birth, unprotected sex, and by sharing needles. For those chronically infected with HBV, treatment is the only option. Hepatitis B is the 9th leading cause of death in the world; left unchecked, it can cause liver cancer and death.

About PEGASYS

PEGASYS, a new generation hepatitis therapy that is different by design, has demonstrated superior efficacy to conventional interferon combination therapy in patients infected with HCV of all genotypes. The benefits of PEGASYS are derived from its new generation large 40 kilodalton branched-chain polyethylene glycol (PEG) construction, which delivers sustained therapeutic concentrations over an entire seven-day dosing interval. This results in true seven-day sustained viral suppression. In addition, PEGASYS is preferentially distributed to the liver, the primary site of infection. PEGASYS is administered once weekly in an easy-to-use pre-filled syringe with a fixed 180 mcg starting dose for all patient types.

PEGASYS has been approved for the treatment of chronic hepatitis C in 48 countries, including the European Union. PEGASYS has also been submitted for review by regulatory authorities in the United States and Roche expects approval in monotherapy and combination later this year.

About Roche

Roche is committed to the viral hepatitis disease area, having introduced Roferon-A for hepatitis B and C, followed by PEGASYS in hepatitis C and now PEGASYS is in phase III clinical development for patients infected with the HBV virus. Roche also manufactures HBV and HCV diagnostic and monitoring systems. The COBAS AMPLICOR™ Test, and the AMPLICOR™ MONITOR Test, two testing systems used to detect the presence of, and quantity of, HBV DNA or HCV RNA in a person's blood. Roche's commitment to hepatitis has been further reinforced by the in-licensing of Levovirin, an alternative antiviral. Levovirin will be studied with the objective of demonstrating superior tolerability over the current standard, ribavirin.

October 3rd, 2002

10. Lack of Behavior Change After Disclosure of Hepatitis C Virus Infection Among Young Injection Drug Users in Baltimore, Maryland

Clinical Infectious Diseases (10.01.02) Vol. 35: P. 783-788::Danielle C. Ompad; Crystal M. Fuller; David Vlahov; David Thomas; Steffanie A. Strathdee

Approximately 3.9 million residents of the United States are infected with hepatitis C virus (HCV). The prevalence of HCV is 65 percent to 90 percent among injection drug users (IDUs). Injection drug use accounts for over 60 percent of all HCV infections nationwide.

Previous studies have shown strong associations between acquisition of HCV infection and sharing of drug paraphernalia - both "direct" sharing of needles and syringes and "indirect" sharing of cookers, cotton filters, and backloading - the practice of preparing drugs from the barrel of one syringe and transferring them to another syringe. HCV transmission is also closely related to duration of injection drug use: among persons newly initiated into injection drug use in Baltimore, 65 percent had acquired HCV within 1 year of initiating injection behavior.

The authors of the current study sought to evaluate changes in high risk behaviors associated with HCV transmission through both "direct" and "indirect" sharing of injection paraphernalia after disclosure of a positive HCV antibody test. The study evaluated 60 IDUs through semi-annual interviews, HIV and HCV antibody testing and pre-test and post-test counseling. The authors also assessed changes in alcohol consumption among those with a positive HCV test result. The study consisted of a post hoc analysis of data from the Risk Evaluation and Community Health (REACH) II Study - a study of HIV risk among young, recently initiated IDUs in Baltimore. Participants included 226 IDUs enrolled in the REACH II Study between July 1997 and May 1999. Eligibility for the study included being 15-30 years old; having initiated injection drug use no more than 5 years prior to the study; and having injected illicit drugs at least once in the past 6 months. Informed consent was received from each participant.

Data collection included face-to-face interviews about demographic characteristics and high-risk behavior, as well as blood samples that were tested for HCV and for HIV.

Questionnaires were used to determine demographic elements, risk behaviors and alcohol consumption during the previous 6 months. Follow-up evaluations were conducted 6 months after the baseline visit. Two weeks after baseline visit, participants returned for the results of their HIV and HCV tests and were given post-test counseling. In addition to counseling, participants were given the location and hours of operation of the Baltimore City Needle Exchange Program. Substance abuse treatment was discussed and referrals were provided. Those participants with HCV infection were counseled to avoid sharing needles, syringes and other equipment and they were referred to a counselor with expertise in HCV infection. Safe injection practices were encouraged. Some treatment options for HCV were offered but, at that time, were highly limited. Treatment for active drug use was not recommended.

Among the participants of the REACH II Study, the majority were African-American (61 percent) and female (64 percent). The mean age at enrollment was 26 years; age of first use of injection drugs was 23 years; and the median length of time using injection drugs was 2.1 years. The baseline prevalence of HCV and HIV infection were 60.5 percent and 10.6 percent, respectively; 7.7 percent of participants were coinfecting with HCV and HIV. Baseline demographics were similar for both HCV-positive and non-HCV groups with respect to sex, age, homelessness, and alcohol dependence. At baseline, 43 percent of participants were alcohol dependent.

In the study of young IDUs who were seropositive for HCV and were informed of their serostatus, fewer than one-fifth of the study subjects had reductions in direct sharing of needles. Almost three-quarters of participants reported that they continued to practice backloading drugs. The pattern was especially apparent among HCV-infected subjects aware of their serostatus, of whom over 75 percent continued to backload. Over one-third continued to share needles.

According to the authors, the "...findings suggest that young IDUs may not be aware of the risk of HCV infection and highlight the urgent need for post-HCV test guidelines and behavioral interventions to reduce ongoing high-risk behavior that perpetuates the risk of HCV transmission."

October 7th, 2002

11. Histamine dihydrochloride may augment interferon in patients with hepatitis C

by Sonia Nichols, senior medical writer (Hepatitis Weekly via NewsRx.com)

Patients who take interferon for chronic hepatitis C could benefit by adding histamine dihydrochloride to their treatment regimens.

The members of an international research consortium reported the finding in the September 2002 issue of *Journal of Viral Hepatitis*.

Researchers believe histamine dihydrochloride (HDC), when used as an adjuvant to interferon (IFN), would confer protection to lymphocytes against attack following IFN induction.

"HDC has been shown to potentiate the IFN-alpha-induced activation of T cells and NK cells by a mechanism that involves the protection of these lymphocytes against oxygen radical-induced functional inhibition and apoptosis," Yoav Lurie of Tel Aviv Sourasky Medical Center in Israel explained.

Lurie and other members of the multicenter study team randomized chronic hepatitis C virus (HCV) patients to receive thrice-weekly doses of interferon in combination with several different regimens of HDC.

"The doses of HDC in combination with IFN-alpha-2b resulted in sustained viral response rates ranging from 31% to 38%," the researchers reported.

The rates for sustained biochemical response were similar, according to data from the study.

Patients who are infected with HCV genotype 1 typically do not respond very well to IFN. In the study, however, genotype 1 patients had sustained response rates ranging from 18-42%, depending on the HDC regimen they received. The data is published in an article titled "A multicentre, randomized study to evaluate the safety and efficacy of histamine dihydrochloride and interferon-alpha-2b for the treatment of chronic hepatitis C". *Journal of Viral Hepatitis*, September 2002;9(5):346-353).

Individuals with high baseline levels of viremia also responded to the therapy at sustained response rates of 15-39% although they usually tend not to do as well with IFN monotherapy.

"We propose that the potential benefit of HDC plus IFN therapy for chronic HCV infection should be the focus of further investigation," Lurie and colleagues suggested.

Key points reported in this study include:

- ◆ Histamine dihydrochloride (HDC) is thought to confer protection to interferon (IFN)-induced lymphocytes against oxygen radical-induced injury
- ◆ IFN and HDC combination therapy was effective for eliciting sustained response in several classifications of chronic hepatitis C patients
- ◆ HDC needs further investigation for its potential to augment IFN effectiveness in those with chronic hepatitis C

Additionally on October 7th, 2002

12. Psychological disorders more frequent in HCV-positive Vietnam veterans

by Sonia Nichols, senior medical writer (Hepatitis Weekly via NewsRx.com)

A study of more than 60,000 Vietnam veterans has shown that those who were infected with hepatitis C virus (HCV) were more likely to have psychiatric, drug, or alcohol use disorders.

U.S. government researchers at the Houston Veteran Affairs Medical Center in Texas argue that the HCV-positive Vietnam veterans need a treatment approach encompassing therapy from clinicians across several disciplines.

For the case-control study, which identified and included Vietnam veterans hospitalized between 1992-1999, 22,341 HCV-positive veterans were compared with 42,267-negative veterans.

"Cases were more likely to have depressive disorders (49.5% vs. 39.1%), post-traumatic stress disorder (PTSD) (33.5% vs. 24.5%), psychosis (23.7% vs. 20.9%), bipolar disorder (16% vs. 12.6%), anxiety disorders (40.8% vs. 32.9%), alcohol (77.6% vs. 45%), and drug-use disorders (69.4% vs. 31.1%)," reported H.B. Elserag and colleagues.

Almost a third of the HCV-positive veterans identified for possible study inclusion had active disorders at the time of the study, with the remainder demonstrating a previous history of such disorders.

After accounting for sex, age, and ethnic background, statistical analysis showed there was a strong relationship between being HCV-positive and having psychiatric disorders or using drugs or alcohol. The data is published in an article titled "Psychiatric disorders among veterans with hepatitis C infection". *Gastroenterology*, 2002;123(2):476-482).

The reasons for increased numbers of such disorders in HCV-positive Vietnam veterans were not listed.

Elserag and colleagues suggested the best way for clinicians to manage the HCV-positive Vietnam veterans would be to use a multidisciplinary approach.

Key points reported in this study include:

- ◆ HCV-positive Vietnam veterans were more likely to have psychiatric, drug-use, or alcohol-use disorders than their non-HCV-positive counterparts were
- ◆ Psychiatric problems among HCV-positive Vietnam veterans included depression, posttraumatic stress disorder, psychosis, bipolar disorder, and anxiety problems
- ◆ Therapy designed for treating HCV-positive Vietnam veterans should incorporate a multidisciplinary treatment approach

October 8th, 2002

13. InterMune and Inhale Announce Agreement to Develop PEGylated Infergen For Hepatitis C Infections

InterMune, Inc and Inhale Therapeutic Systems, Inc. announced today an agreement for use of Inhale's technology to develop a PEGylated version of Infergen(R) (Interferon alfacon-1) (PEG-Infergen) for the treatment of chronic hepatitis C infections. PEGylation is a technology designed to prolong or improve the effectiveness of pharmaceutical products. InterMune currently markets Infergen, the non-PEGylated version of this product, for the treatment of patients with hepatitis C .

"This agreement accelerates our ability to develop PEG-Infergen as a new treatment option for the millions of people in North America suffering from chronic hepatitis C infections," said Scott Harkonen, President and CEO of InterMune. "We believe PEG-Infergen will build on the success we are having with Infergen in this market. We expect this market will grow to \$3 to \$4 billion over the next five years. Based on positive data demonstrating Infergen's clinical advantage compared to other non-PEGylated alpha interferons, we believe PEG-Infergen could become a leading product in this market. We plan to initiate clinical trials with this compound in the first quarter of 2003."

The agreement calls for Inhale to provide the PEGylation expertise and exclusive manufacturing for the reagent used in the PEGylation of Infergen. InterMune will conduct pre-clinical and clinical development of the product and commercialize it in North America. Inhale will receive milestones as the product progresses through the clinic and royalties on product sales. Other deal specifics and financial terms were not disclosed.

"We are pleased to have obtained the technology from Inhale to develop PEG-Infergen, which has been shown in vitro to have improved biological potency compared to other PEGylated alpha interferons," said Peter Van Vlasselaer, Ph.D., Senior Vice President of Technical Operation at InterMune. "We look forward to a mutually rewarding partnership."

"We, too, are pleased to be collaborating with InterMune to improve the performance and delivery of its Infergen product and to address a significant medical need for hepatitis C patients. This collaboration is another validation of the use of PEGylation as the industry standard method for enabling improved performance of macromolecules," said Ajit Gill, President and CEO of Inhale. "Further, it represents a continuation of the accelerated rate of collaborations for Inhale seen in the first half of 2002."

About Hepatitis C

Hepatitis is a liver disease caused by the hepatitis C virus that is found in the blood of people with this disease. According to the National Center for Infectious Diseases, there are an estimated 3.9 million (1.8%) Americans who have been infected with hepatitis C , of whom 2.7 million are chronically infected. The current standard of care is a combination of interferon alpha and ribavirin, which has been shown to eliminate the virus in up to 40% of those infected.

About Infergen

Infergen is a bio-engineered type I interferon alpha that is FDA-approved for the treatment of patients with chronic hepatitis C infections. Positive interim Phase IV clinical trial results first reported last year indicated that patients treated for chronic hepatitis C infections with Infergen in combination with ribavirin achieved a sustained virology response (SVR) of 56% compared with an SVR of 31% in patients treated with Interferon alfa-2b ribavirin (Rebetron™).

About PEGylation

Inhale's proprietary advanced PEGylation technology was developed by its subsidiary, Shearwater Corporation. PEGylation is a technology for the chemical attachment of polyethylene glycol (PEG) polymer chains to a broad range of drug substances such as peptides and proteins including antibody fragments; small molecules, and other drugs. The effect of PEGylation is to increase drug circulation time in the bloodstream, improve drug solubility and stability, and reduce immunogenicity. The potential advantages of PEGylation are to decrease dosing frequency, improve drug efficacy and safety, improve stability, and simplify drug formulation.

About InterMune

InterMune is a commercially driven biopharmaceutical company focused on the marketing, development and applied research of life-saving therapies for pulmonary disease, infectious disease and cancer. For additional information about InterMune, please visit www.intermune.com.

About Inhale

Inhale Therapeutic Systems, Inc. provides a portfolio of leading performance-enabling drug delivery technologies and expertise to help pharmaceutical and biotechnology companies maximize the performance of their drug products. For additional information about Inhale, please visit www.inhale.com.

Except for the historical information contained herein, this press release contains certain forward-looking statements by InterMune that involve risks and uncertainties, including without limitation the statements indicating that InterMune believes that PEG-Infergen will build on the success of Infergen, expects that the chronic hepatitis C infections market will grow to \$3 to \$4 billion over the next five years and expects that PEG-Infergen could become a leading product in the hepatitis C market. All InterMune's forward-looking statements and other information included in this press release are based on information available to InterMune as of the date hereof, and InterMune assumes no obligation to update any such forward-looking statements or information. InterMune's actual results could differ materially from those described in InterMune's forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to those discussed under the heading "Risk Factors" and the risks and factors discussed in InterMune's 10-K report filed with the SEC on March 21, 2002, and other periodic reports (i.e., 10-Q and 8-K) filed with the SEC. The risks and other factors that follow, concerning the InterMune forward-looking statements in this press release, should be considered only in connection with the fully discussed risks and other factors discussed in detail in the 10-K report and InterMune's other periodic reports filed with the SEC. InterMune's forward-looking statement indicating that InterMune expects that the chronic hepatitis C infections market will grow to \$3 to \$4 billion over the next five years is subject to the risks and uncertainties associated with whether a cure is discovered for chronic hepatitis C infections; only a subset of patients respond to therapy; the actual dosage is different than currently anticipated; the treatment regimen is different than currently anticipated; InterMune cannot sell its drug at the price that is currently anticipated; or a competitor's drug is more effective or costs less than InterMune's. InterMune's forward-looking statements concerning PEG-Infergen building on the success of Infergen and becoming a lead product in the hepatitis C market is subject to the risks and uncertainties associated with the uncertain, lengthy and expensive clinical development and regulatory process; achieving positive Phase I, II and III clinical trial results; patient enrollment and retention in the clinical trials; budget constraints; third-party manufacturers; whether InterMune is able to obtain, maintain and enforce patents and other intellectual property; and significant regulatory, supply, intellectual property and competitive barriers to entry.

Additionally on October 8th, 2002

14. Faced with generic competition, Ribapharm would prefer to settle ribavirin dispute with Roche

Ribapharm Inc. would prefer to settle its dispute over its hepatitis C drug ribavirin with Switzerland's Roche AG rather than follow through with its patent infringement lawsuits, as similar litigation with three generic drugmakers continues. Ribavirin was for a long time exclusively licensed by Ribapharm to Schering-Plough Corp., which sells the drug as Rebetol for use in combination with either Intron-A (interferon alfa-2b) or Peg-Intron (pegylated interferon alfa-2b) for hepatitis C.

However, a year-old settlement of patent disputes between Schering-Plough and Roche -- whose own pegylated interferon product Pegasys is approved in Europe and close to approval in the US -- gives Roche the right to seek its own license to ribavirin from Ribapharm. Although Ribapharm and Roche have held

discussions over a possible license to ribavirin, no agreement has materialized. Determined to protect its intellectual property, in August Ribapharm filed patent infringement suits against Roche in the US and several European nations.

Despite this, Roche has publicly announced its intention to continue with its plans to launch its combination product in the US and abroad, contending that there are no valid ribavirin patents that would block the move and therefore a licensing deal is not needed.

Speaking at the UBS Warburg Global Life Sciences conference here on Tuesday, Ribapharm's Vice President of Investor Relations Joseph Schepers disagreed. "We feel very strongly about our patent position," he told investors, noting that Ribapharm holds three US patents on ribavirin covering the antiviral's use as an immunomodulator, its use in conjunction with interferon, and its use against hepatitis C. In Europe, he added, Ribapharm holds a particularly broad patent not offered in the US.

Still, Schepers told Reuters Health, Ribapharm would prefer a licensing settlement with Roche rather than a full-fledged legal battle.

Currently, both Ribapharm and Schering-Plough have filed separate US lawsuits against three generic drug firms that have filed with US regulators to market their own generic versions of ribavirin: Geneva Pharmaceuticals Technology Corp., Three Rivers Pharmaceuticals LLC, and Teva Pharmaceuticals USA Inc.

The stakes are high for Ribapharm, which generates all its revenues from royalties paid by Schering-Plough on ribavirin. Last year, Ribapharm posted revenues of \$139 million, and this year it is expecting between \$240 million and \$250 million.

If Roche is able to bring its own ribavirin product to market without taking a license, Ribapharm could see its revenues decline significantly as Roche's hepatitis C product cuts into sales of Schering-Plough's drug. More importantly, Schepers said, it would undermine the legitimacy of Ribapharm's patents and set a legal precedent further opening the door to generic competition.

In Tuesday trading on the NASDAQ, shares of Costa Mesa, California-based Ribapharm fell \$0.05 to \$3.10, well off the initial public offering price of \$10 set earlier this year. Ribapharm was spun off from ICN Pharmaceuticals Inc. in April 2002.

October 13th, 2002

15. A word, a gesture -- a company unravels: How a routine meeting for Schering-Plough turned to mayhem on Wall Street

By David Schwab, Star-Ledger Staff

The setting could pass for any conference room in any hotel: Gray carpeting, beige walls, plain tables and chairs. The only decorating touch is a mottled, 4-by-6-foot painting of something hard to make out.

Behind the closed door, the gathering 10 days ago might have resembled any luncheon sales meeting.

The two dozen invited guests helped themselves at a buffet table to ham and cheese sandwiches, cans of soda and potato chips served out of a bowl. For dessert there were oatmeal and chocolate chip cookies.

Yet, something happened in Room 1007 at Schering-Plough's headquarters in Kenilworth sometime after noon that Thursday put the company in hot water -- again.

With a few words, or maybe just an off-the-cuff remark or gesture, Richard Jay Kogan, Schering-Plough's chairman and chief executive, capped an unlikely chain of events that rattled Wall Street and offered a rare glimpse at the relationship among companies, analysts and big investors.

To some analysts in the room, Kogan seemed to sound the alarm about Schering-Plough's already shaky finances. The executive, known for his sarcasm, even cracked a joke or two about how dire 2003 was shaping up to be. He suggested the results appeared so dismal, he might not want to be around at next year's meeting, according to one analyst.

Kogan hit a nerve with some of the analysts at the meeting. More than one concluded Schering-Plough was in deeper trouble than they had thought. In Wall Street lingo, what he said behind closed doors seemed to be "material information," or news that might cause investors to sell their shares.

Schering-Plough says it did nothing wrong. No "inside" information was discussed, a spokesman said, and the company followed regulations, as it has in dozens of similar meetings during the past decade. Some of the two dozen analysts in the room agree nothing out of the ordinary occurred.

But four days later, the Securities and Exchange Commission -- the powerful federal agency that regulates Wall Street -- launched an inquiry into the meeting and another Kogan held two days earlier in Boston with managers of one of the nation's biggest mutual funds. Now, Schering-Plough, one of the nation's leading pharmaceutical companies and one of the state's biggest employers with some 6,800 workers, has another potentially serious problem on its hands.

What happened in Room 1007 became a big deal because of an SEC rule known as Regulation FD that prohibits companies from sharing important information with selected analysts and investors. It was enacted two years ago to make sure the playing field is level for everyone.

"The sequence of events shows bad judgment," said Richard Evans, a senior research analyst at Sanford C. Bernstein & Co., a securities firm in New York. "While it may have begun very innocently, by the time we got to the meeting, clearly they were conducting it without full disclosure."

This account of the meeting in Kenilworth is based on interviews with company representatives; interviews with half a dozen analysts who have attended Schering-Plough meetings in the past, including two who were there this month who spoke on condition their names not be used, and a review of notes analysts sent afterward to their clients.

John Heine, an SEC spokesman, declined comment, as did Kogan.

FACE TO FACE

Like most big publicly traded corporations, executives from Schering-Plough meet periodically with the analysts who follow the company and report back to Wall Street brokerages or the institutional investors they work for.

The company sends invitations in February asking analysts to pick one of three such meetings to attend.

The sessions in Kenilworth are designed to complement a larger, more formal meeting for analysts typically held in July at the elegant St. Regis Hotel on Fifth Avenue in Manhattan, which attracts about 300 people. One big difference is the annual meeting is broadcast over the Internet.

This year's gatherings promised to be especially interesting. A former over-achiever, Schering-Plough has become an industry laggard. Its patent on the blockbuster allergy medicine Claritin is set to expire, and earlier this year it agreed to pay a record \$500 million fine to resolve manufacturing problems.

Even so, analysts who attend these informal sessions don't expect to hear significant news. But it is a chance to meet face-to-face with key executives.

Over the years, analysts have referred to the annual trek to Kenilworth as simply the "ADAM" meeting. The tradition dates to when Schering-Plough was headquartered in Madison and the meetings were called "A

Day at Madison." The tradition was so ingrained that when Schering-Plough moved its executive offices 10 miles to Kenilworth, the sessions were renamed: A Day Among Management. Analysts will call and ask, "When is the next 'ADAM'?"

But there was a critical difference with this ADAM.

Even as the invited guests arrived Oct. 3 before 9 a.m. in their hired cars, even before they began picking at bagels spread out on the buffet table, Schering-Plough was in the midst of a crisis. What was supposed to be an ordinary meeting was being held in extraordinary circumstances.

Something bad was happening to Schering-Plough's stock.

Hour after hour, investors were selling millions of shares, pushing prices down by 15 percent in the previous two days. In all, about \$5 billion in value had evaporated. The shares, already off 40 percent for the year, hit a five-year low.

There was no apparent reason for the freefall. The company had made no major announcements. Other drug makers were posting solid gains. The mystery was apparent to anyone who followed trading on a computer screen and saw large red numbers beside ticker symbol SGP.

Even so, the meeting went along as if it were business as usual. Senior executives, including Cecil Pickett, the company's head of research and development, and Jack Wyszomierski, the chief financial officer, answered questions one by one. As is his custom, Kogan, 61, a native of the Bronx whose first job was selling peanuts at Yankee Stadium, arrived last, in time for lunch around the U-shaped table.

While the analysts ate -- their BlackBerry wireless communicators ready to beam critical information back to Wall Street -- Kogan sat in the middle and answered questions. Everyone had name cards in front of them, but Kogan knew most and addressed them by first names.

Knowing the routine, some avoided asking Kogan questions about earnings or stock trading because they knew he would not answer. Kogan said nothing had happened to explain the stock sales.

But, unbeknownst to the analysts, up on the fourth floor, Schering-Plough employees were working on a press release that would warn that earnings for the third quarter and next year would be below expectations.

'TERRIBLE' OR 'HORRIBLE' Perhaps 20 minutes into the discussion, Kogan turned to the subject of earnings. He would have to pick his words carefully. The SEC's Regulation FD is precise: A CEO can't share information on earnings with a small group unless the information is broadcast to the investment world.

There is some disagreement over precisely what Kogan said or meant. Schering-Plough said there is no transcript and the company won't comment on his specific language.

Whatever the precise word, it got noticed.

"Did my eyebrow sort of raise when he said that? Perhaps. It's a bit of an alarmist word," said one analyst who was there. "Whether he used the word 'terrible' or 'horrible,' everyone in that room knew that earnings were going to be negative. ... He was capitulating to what everyone in the room knew, showing a sign of respect that we knew what was going on with the company."

Schering-Plough says Kogan did not provide new information beyond confirming what the company had been saying for the past year: 2003 would be a bad year, mostly because of the loss of Claritin as a cash cow.

Indeed, Kogan's remarks did not seem to cause a ruckus, as happened last December at Merck's annual analyst meeting at its Whitehouse Station headquarters. After Merck's Chief Financial Officer Judy Lewent shocked the audience by saying earnings would be flat for 2002, the meeting broke up and analysts ran for

the phones to call in the news, much like newspaper reporters at the scene of an accident.

By contrast, immediately after the Schering-Plough meeting, Anthony Butler, the Lehman Brothers analyst, issued a note entitled "Much Ado About Nothing."

But others reacted differently. Mike Krensavage, an analyst at Raymond James, wrote Kogan had "hinted" at an earnings shortfall. Krensavage focused on Kogan's use of the word "terrible" to describe results for next year.

The problems for Schering-Plough were just starting.

The company took calls from the media and other analysts wondering what had happened. Shares slipped an additional 2 percent. Some analysts who received invitations back at the start of the year demanded to know why the company held a special meeting and why they weren't invited.

By 8:30 p.m., stories hit the news wires quoting unnamed analysts saying Kogan had warned next year would be "terrible." For a company that goes to great lengths to control its message, the speculation was a disaster in the making.

So, Schering-Plough decided "to set the record straight." Calls went out to key executives at home to verify critical financial numbers. Then about 10:30 p.m., a four-page press release was issued over the Internet.

The news was bad. Profit would fall 35 percent next year, a much greater drop than had been expected.

"They had given no guidance at all and then they come out with what I think is probably the end-of-the-world, Kenilworth, N.J., falls-into-the-sea type of outlook," said Larry Smith, an analyst at Gerard Klauer Mattison in New York, who was not at the Oct. 3 meeting, but has attended four other sessions over the years.

But Schering-Plough was making sure everyone knew exactly where it stood, even if the timing was unusual. (Typically, companies issue earnings releases in the hours just before the stock markets open at 9:30 a.m. or after they close at 4 p.m.)

The next day, a whopping 33 million shares were traded, and prices slipped 2 percent more to \$17.30, for a total drop of 19 percent during the week.

Mara Goldstein, an analyst at CIBC WorldMarkets who was at the ADAM meeting, wrote the sequence of events "continues to add to investor angst over management's credibility."

Shortly before the markets closed that day, things got worse.

Reuters reported the George Putnam Fund, one of the nation's biggest mutual funds with \$260 billion in assets and one of the biggest institutional investors in Schering-Plough, confirmed fund managers had met with Kogan Oct. 1, the day the stock started plunging. Putnam said Kogan provided no inside information and the fund had started selling a week earlier based on its own research.

This past Monday, at about 7:30 p.m., Schering-Plough issued another press release: The SEC would conduct an inquiry into the two meetings. It is not clear when that probe will be completed.

UNANSWERED QUESTIONS

By week's end, the steady drumbeat of corporate life was back to normal in Kenilworth. On a recent morning, Room 1007, situated around the corner from the employee cafeteria, was decorated with red, white and blue balloons to thank employees who volunteered to run the United Way campaign.

But plenty of questions remain.

Some analyst are speculating about the future of such informal meetings. Others wonder what more executives must do to be fair to investors.

Kogan "may not have said anything, but they just picked up something from his facial expression," Rita Freedman, an analyst at PNC Advisors in Philadelphia who attended the ADAM meeting in the spring. "I have done that as an analyst, asked a question and you can just tell something. You can read his face. So who knows?"

"Are they going to wear a paper bag over their heads? What are they supposed to do? I don't know."

October 14th, 2002

16. Liver failure a possibility after discontinuing therapy for hepatitis B

by Sonia Nichols, senior medical writer (Hepatitis Weekly via NewsRx.com)

A report from Singapore suggests patients who receive lamivudine or other nucleoside analogues for chronic hepatitis B face the possibility of developing liver failure after discontinuing therapy.

At least three cases have been reported by medical investigators at National University Hospital in Singapore in the October 2002 edition of *Gut*. Given the risk for death, researchers cautioned that patients who discontinue nucleoside analogues for chronic hepatitis B should be watched closely.

Despite these three cases, the investigators recognize that lamivudine has proven to be a beneficial therapy for many patients with chronic hepatitis B.

"Nucleoside analogues such as lamivudine for chronic hepatitis B have an excellent safety profile while patients are on therapy but reactivation flares occur in 19-50% of patients after stopping therapy," said S.G. Lim and colleagues, noting that liver decompensation sometimes occurs in those patients.

In the three reactivation cases reported, one patient had been enrolled in a famciclovir trial for chronic hepatitis B, whereas the others were not in medical trials but were receiving lamivudine, a standard hepatitis B virus (HBV) therapy. Initially, all three cases were positive for HBV DNA.

After therapy discontinuation when HBV DNA became undetectable, the patients began to show evidence of liver problems. "All three patients developed decompensated liver disease despite one patient having had a prior liver biopsy showing absence of cirrhosis," Lim and coauthors stated.

Liver failure progressed although lamivudine was reinitiated. The data is published in an article titled "Fatal hepatitis B reactivation following discontinuation of nucleoside analogues for chronic hepatitis B". *Gut*, October 2002;51(4):597-599).

Laboratory analyses demonstrated no presence of drug-resistant HBV mutants in the serum of treated patients.

"Hepatitis B virus reactivation, leading to decompensation and death, are possible complications of treatment withdrawal and patients should be monitored closely if therapy is ceased," Lim and colleagues warned.

Key points reported in this study include:

- ◆ Hepatitis B virus reactivation may occur after nucleoside analogues such as lamivudine are discontinued
- ◆ Viral reactivation may lead to liver decompensation and death, based on a Singapore case study
- ◆ People who discontinue taking nucleoside analogues for chronic hepatitis B should be followed

closely by their doctors

Additionally on October 14th, 2002

17. Hepatitis C nonresponders benefit from interferon by avoiding cancer

by Sonia Nichols, senior medical writer (Hepatitis Weekly via NewsRx.com)

Even if patients with chronic hepatitis C don't respond to interferon, they may benefit from retreatment by becoming less susceptible to forming liver cancer, a current study indicates.

The authors of a Japanese study reported the new finding after following over 300 patients who did not develop a virological response to therapy after receiving a single course of interferon. They compared prevalence of hepatocellular carcinoma (HCC) in retreated and nonretreated individuals.

"Ninety-nine patients received interferon retreatment and 210 did not," described Keisuke Hino, a study coauthor from Yamaguchi University School of Medicine in Japan.

A majority of retreated individuals received two courses of therapy, with a few others receiving three courses and at least one patient receiving five rounds of interferon therapy.

"The cumulative incidence of HCC was significantly lower in retreated patients," reported Hino and colleagues.

Statistical analysis suggested number of interferon treatments and patient age were the only significant indicators for whether a patient with chronic hepatitis C would develop liver cancer. The data is published in an article titled "Interferon retreatment reduces or delays the incidence of hepatocellular carcinoma in patients with chronic hepatitis C". *Journal of Viral Hepatitis*, 2002;9(5):370-376).

The study supports interferon retreatment for reducing or delaying HCC in nonresponders, Hino and coauthors said.

Key points reported in this study include:

- ◆ There was a lower incidence of liver cancer among chronic hepatitis C patient nonresponders who were retreated with interferon
- ◆ Number of interferon treatments and age were correlated to liver cancer after nonresponse to interferon
- ◆ Interferon retreatment may reduce or delay liver cancer in chronic hepatitis C interferon nonresponders