

The Best in the News on HCV, HBV and HIV/HCV Coinfection from November 15th, 2002 to December 15th, 2002



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November 16th, 2002

Drugmaker Schering-Plough Changes CEOs, Struggles to Regain Earlier Growth

For years, Richard Jay Kogan helped turn the watery eyes of allergy sufferers into tears of joy for investors in his company, Schering-Plough Corp.

The drug maker's prescription pill Claritin became a blockbuster brand in the late 1990s and led to explosive growth and booming profits under Kogan, the company's chief executive officer.

Investors aren't crying for joy anymore. With the company soon to lose its exclusive rights to Claritin, Schering-Plough's earnings are expected to swoon next year, and its share price is less than half of what it was two years ago. Schering-Plough has also been beset by regulatory clouds the past two years, particularly manufacturing violations that led to a \$500 million fine.

If Kenilworth-based Schering-Plough is to relive its growth times, it will be under new leadership. The company, which employs about 7,000 people in New Jersey, announced Kogan's retirement in a news release Wednesday, saying he will stay until the firm's April annual meeting at the latest.

Some analysts speculate he was pushed out. Regardless, Kogan's departure punctuates a difficult two years for Schering-Plough as it prepares for a future with lower sales from its most famous and lucrative drug. The next leader will take over a Schering-Plough focused on driving sales of a top hepatitis C therapy franchise and a new cholesterol-buster.

A company spokesman said neither Kogan nor Richard de J. Osborne, the new board chairman, was prepared to comment further on Kogan's departure.

News of a leadership change will likely lift the spirits of shareholders who called for Kogan's ouster at recent annual meetings.

A management switch was at the top of Todd Lebor's list for things that had to change at Schering-Plough.

Lebor, an analyst with Morningstar.com, a Chicago-based equity and mutual fund research firm, said that under Kogan, Schering-Plough has had a "hush mentality" with respect to investors.

"We could not get behind the company," Lebor said. "We were very uncomfortable with who was sitting in the throne. I think this is a necessary first step, a good first step." Lebor said he was not ready to recommend the stock before finding out the choice for the new CEO.

But attracting a quality leader to Schering-Plough will be a chore, said David Moskowitz, an analyst with Friedman, Billings, Ramsey, an Arlington, Va.-based investment bank. Schering-Plough faces several product challenges and the uncertainty of a rudderless ship, he said.

"It's going to be difficult to attract new senior management into this company given the risks," Moskowitz said. "Who really wants to take the reins given these product issues?"

It could be that another drug maker grabs the reins. Even before last week, Schering-Plough was one of the most rumored candidates to merge with another firm. Merck & Co. is the most talked-about suitor, because of a partnership to develop and market a cholesterol-lowering drug, Zetia, deemed critical to the future of both firms.

"Kogan's departure, in our opinion, would remove what we consider the largest obstacle to drug-industry mergers, the question of who would manage a combined company," Michael Krensavage, an analyst with Raymond James, wrote in a report to investors. "The answer perhaps is Raymond V. Gilmartin, chairman of Merck." Chris Loder, a Merck spokesman, said the company does not speculate on rumors.

A Bronx native, Kogan started at Schering-Plough in April 1982 from rival Ciba-Geigy Corp. Initially the

company's vice president of pharmaceutical operations, Kogan in 1986 rose to president and chief operating officer, the right-hand man to CEO Robert Luciano. With Luciano's blessing, Kogan became the company's CEO in 1996.

The 1990s were boom times at Schering-Plough. Once a company that owned radio stations and sold home repair products and Maybelline cosmetics, Schering-Plough focused its attention on health care and pharmaceuticals. From 1991 through 2000, annual sales nearly tripled from \$3.5 billion to \$9.8 billion. Profits nearly quadrupled in that time to \$2.4 billion.

Critical to the growth in the latter part of the decade was Claritin. Claritin, which treated allergy symptoms without causing drowsiness, was the first drug to plunge headfirst into consumer advertising, and its success triggered the boom of such marketing. Claritin topped expectations and eventually became a \$3 billion-a-year blockbuster.

But Claritin's success would haunt Kogan and Schering-Plough. Profits and sales from prescription drugs are not eternal, because when patents lapse, generic versions hit the market and eat away at the original's sales.

Jon Fisher, head of equity research and health-care analyst at Fifth Third Bank in Cincinnati, said Schering-Plough failed to capitalize on its Claritin profits while it could.

Fisher compares Schering-Plough to Indianapolis-based Eli Lilly & Co., a similarly sized drug maker that also relied heavily on one blockbuster drug, the anti-depressant Prozac. Prozac's patent expired, but Eli Lilly has at least a half-dozen products in line to be approved over the next several years, Fisher said. Schering-Plough--through its own labs or by licensing products--has been unable to fill the Claritin gap.

Schering's earnings are expected to fall slightly this year and then plummet 33 percent next year.

"Lilly and Schering-Plough were on the same paths in the 1990s," said Fisher, who said Fifth Third's portfolios hold Schering shares. "Kogan's departure is a result of Schering choosing the wrong path."

It hasn't helped that the company has had a stream of regulatory troubles. Most critical were manufacturing violations cited by the Food and Drug Administration at four plants -- one in Union, one in Kenilworth, and two in Puerto Rico. The violations led to a consent decree that required Schering-Plough to pay a \$500 million fine. The violations also delayed the approval of Clarinex, the Claritin follow-up whose timely approval was critical if the drug was to get a toehold in the market.

Schering-Plough also faces a Securities and Exchange Commission investigation that centers on meetings Kogan had with investors the week the company issued a release that warned of its gloomy profit forecast. And federal prosecutors are looking at the company's sales and marketing practices.

These problems aside, the next Schering-Plough CEO will not inherit a bare cupboard. Zetia will be hitting pharmacy shelves shortly, and Kogan has called it "the most important drug" in the company's history. Its hepatitis C therapy franchise will eclipse \$2 billion in sales this year, although it is soon to encounter a strong product challenge from rival drug maker Hoffmann-LaRoche. Meanwhile, Schering-Plough holds hope that switching Claritin to a non-prescription product will allow the company to retain sales, and that Clarinex also can keep the allergy franchise churning.

As for a successor, the company says it is not ruling anyone out. "The board will consider all candidates both internally or externally," said spokesman Robert Consalvo.

David Saks, chairman of the Saks Medscience Fund and a longtime industry analyst, said the lack of a publicized succession plan suggests the board will look outside the company for the next CEO.

"Schering will be headed by somebody outside Schering with a fresh viewpoint most likely," Saks said.

No matter, as long as the next chief brings back those tears of joy.

Advisory Panel Unanimously Backs Roche's HCV Therapy

An FDA panel Thursday unanimously recommended approval of Hoffmann-La Roche Inc.'s proposal to use Pegasys in combination with Copegus for the treatment of chronic hepatitis C.

The decision by the Antiviral Drugs Advisory Committee in Bethesda, Md., came one day after FDA staff released a 59-page briefing document in which it described the proposed combination therapy as "superior to peginterferon alfa-2a monotherapy."

Peginterferon alfa-2a, or Pegasys, a pegylated interferon, was approved in October by the agency for hepatitis C. Roche, of Nutley, N.J. received priority review status for the Pegasys plus Copegus application.

While Pegasys is the PEGylated (stays in the body longer) version of Roferon, a Roche product administered subcutaneously three times a week for hepatitis C, Copegus is actually Roche's ribavirin.

Roche presented the panel with data from two trials, the first being NV15801, designed to compare Pegasys plus Copegus with Rebetron, Schering-Plough Corp.'s version of ribavirin in combination with interferon alfa-2b.

NV15801 was a randomized, multicenter, international, partially blinded, controlled study that included 1,149 treatment-naive patients who were assigned to peginterferon alfa 2a monotherapy, peginterferon alfa 2a combined with ribavirin, or Rebetol/Intron A.

Efficacy endpoints for both NV15801 and the second Phase III, NV15942, were sustained virological response (no detectable virus) assessed six months after the end of treatment.

The FDA's comment describing the combination therapy as superior references trial NV15801. According to the agency, "The treatment difference is approximately 20 percent absolute."

Study NV15942 was designed to build on the results of NV15801, by using the combination arm from NV15801 to assess the benefits and risk of lower exposures in patient subgroups. The 1,311-patient study was randomized, multicenter, international and double blinded.

According to the FDA, the study "confirmed the association between lower response to treatment and the following factors: hepatitis C virus genotype and titer, cirrhosis, older age, increased body weight, African-American origin, U.S. participants."

Furthermore, the agency said end-of-treatment virologic response in patients treated for 24 weeks appeared to be higher than the end-of-treatment virologic response for patients treated for 48 weeks, irrespective of HCV genotype.

If Pegasys plus Copegus makes it to market, the combination would compete with Schering-Plough's PEG-Intron, a longer-acting form of Intron A that uses pegylation developed by Enzon Inc., of Piscataway, N.J.

Roche worked with Inhale Therapeutics Inc., of San Carlos, Calif., to develop its PEGylated version of Roferon.

Ribavirin is owned by Ribapharm Inc., of Costa Mesa, Calif., a spin-off of ICN Pharmaceuticals Inc., also of Costa Mesa.

Hepatitis C Outbreak at Nebraska Clinic

At least 81 people treated at a Nebraska cancer clinic have tested positive for hepatitis C in an outbreak that may have been caused by a contaminated vial of medicine, health officials said Tuesday. Dr. Tom Safranek,

the state epidemiologist, said poor medical practices at Dr. Tahir Javed's clinic in Fremont may be to blame.

The patients, who were suffering from cancer or blood disorders, were treated at the clinic in 2000 and 2001. Just before it shut down last month, the clinic advised 612 patients to get tested and nearly 500 did.

It is possible that a clinic worker used a syringe to administer medicine to a patient who had hepatitis C, then drew more medicine from the same vial for the patient with the same syringe, Safranek said.

Doing that would contaminate the rest of the medicine in the vial, and infect other patients given the drug, he said.

Medical charts are being examined, and current and past employees of the clinic are being questioned by state health officials.

Javed left the United States in July and returned to his native Pakistan to attend to his ailing mother, Safranek said.

State health officials were notified of the problem in September by an Omaha doctor who had two patients with hepatitis C who also were patients at Javed's clinic.

In all, 485 people sought tests after receiving letters from the clinic. Of the others, some chose not to be tested, others may have been tested by their own doctors, and others died.

The state said it was not aware of any deaths among the patients with hepatitis C. Doctors said they do not know what effect the virus would have on the clinic's already ailing patients.

Hepatitis C is a viral infection of the liver and the most common bloodborne infection in the United States. People who have been infected may experience fatigue, loss of appetite and yellowing of the skin. The virus can eventually lead to cirrhosis or cancer of the liver.

Health officials are confident no other patients have to be contacted because of changes made at the clinic in 2001, Safranek said, declining to elaborate.

In Oklahoma, a hepatitis C outbreak that infected more than 50 people this year was blamed on a nurse anesthetist who told health officials he reused needles and syringes.

November 18th, 2002

Schering Intron-A, Rebetrone Promotions under Investigation

THE-PINK-SHEET, November 18, 2002, Page 14

Schering-Plough is responding to two federal grand jury subpoenas regarding promotional practices for the interferon brands Intron A and Rebetrone, the company disclosed in its Nov. 12 10-Q filing.

Schering received the subpoenas from the U.S. Attorney's Office in Boston "in early November," the 10-Q filing states. The subpoenas "seek a broad range of information concerning the company's sales, marketing and clinical trial practices and programs with respect to Intron A, Rebetrone and [the oncologic agent] Temodar."

In addition, the subpoenas request information about Schering's "sales and marketing contacts with managed care organizations and doctors, and the company's offering or provision of grants, honorariums or other items or services of value to managed care organizations, physician groups, doctors and educational institutions."

The Intron family is one of Schering's most important product lines, with sales of close to \$2 billion through the first nine months of the year. Temodar is a much smaller product, but has been growing rapidly; sales for the first nine months of the year were up 59% to \$209 million.

The Boston prosecutor had previously issued a subpoena to the company (in March 2001) as part of an investigation of price reporting to Medicaid (the potential use of repackaging to circumvent "best price") and Medicare (the potential use of inflated AWP's as an incentive for prescribers).

Several other state and federal claims related to the AWP issues - including actions filed in Florida, Nevada, West Virginia, Montana and Texas - have been consolidated with the Boston investigation.

The Boston U.S. Attorney's Office has been very active in investigating pharmaceutical promotional practices.

The office spearheaded the investigation of TAP Pharmaceuticals, which produced an \$875 million settlement in 2001, and it has open investigations of several other firms, including a whistleblower suit pending against Pfizer related to the promotion of Neurontin ("The Pink Sheet" May 13, p. 21).

Schering said it is "not possible to predict the outcome" of the newest investigation, but notes that the consequences could be severe: "civil or criminal proceedings involving the imposition of fines, penalties and injunctive or administrative remedies, including exclusion from government reimbursement programs."

The use of a grand jury typically implies a criminal investigation. The March 2001 subpoena was apparently issued under civil statutes.

Schering is facing a similar battery of investigations in Philadelphia.

The company received a civil subpoena under the Health Insurance Portability & Accountability Act in 1999 as part of an investigation of pharmacy benefit management practices by the Philadelphia U.S. Attorney's Office ("The Pink Sheet" March 13, 2000, p. 3).

The company began receiving grand jury subpoenas from Philadelphia in March 2002 ("The Pink Sheet" April 1, p. 32).

Schering's description of the Philadelphia investigation suggests a narrower focus than the Boston investigation.

The Philadelphia case relates to "transactions with managed care organizations," Schering said. The "grand jury appears to be investigating, among other things, (i) whether the transactions...and conduct relating thereto violated federal anti-kickback statutes; and (ii) whether the value of the items and services described above should have been included in the company's calculation of Medicaid rebates."

The latest Boston subpoenas help solidify Schering's hold on the dubious distinction of having the longest list of disclosures under the "legal matters" heading in its SEC filings.

The company is also facing investigations related to its manufacturing compliance status, settlements with generic manufacturers, retail pharmacy pricing, consumer product broker commissions and disclosures to investors. The pending investigations will be one challenge facing Schering's new CEO; the company is recruiting a successor to Richard Kogan (see following story).

Higher doses of ribavirin increase risk for anemia in chronic hepatitis C

By Sonia Nichols, senior medical writer of NewsRx.com

Chronic hepatitis C patients who are prescribed doses of ribavirin of a gram or more may sustain a greater

risk for developing anemia.

The results of a meta-analysis of Asian and non-Asian trials of chronic hepatitis C patients on ribavirin monotherapy or ribavirin and interferon combination therapy has revealed anemia may be a major complication of ribavirin.

Researchers at Harvard University's School of Public Health performed a search of a major medical journal database to collect their data, extracting information from randomized control trials that met certain study criteria to complete their data set.

"The outcomes evaluated were withdrawal from the study due to anemia, ribavirin dosage reduction to a decrease in hemoglobin, and hemoglobin levels below 10 g/dL," said C.H. Chang and coauthors.

In the 17 studies evaluated, the risk difference for developing anemia between taking ribavirin or not taking ribavirin was 0.09 [95% CI, 0.04-0.13], according to Chang and coworkers. There were greater risk differences for ribavirin-related anemia in the two Asian studies included in the meta-analysis, researchers said. They attributed several factors such as ethnic vulnerability, study design, and other elements as possible reasons for greater risk differences in those two studies. The data is published in *Alimentary Pharmacology and Therapeutics*, 2002;16(9):1623-1632).

"The risk associated with 1 g or more of ribavirin per day was higher (risk difference, 0.09; 95% CI, 0.04-0.14) than that for 0.8 g of ribavirin per day (risk difference, 0.01; 95% CI, -0.04-0.06)," Chang and coauthors commented.

The correlation between high doses of ribavirin and the risk for anemia implies patients who receive the therapy for chronic hepatitis C should be closely monitored.

Key points reported in this study include:

- ◆ High doses of ribavirin are associated with a heightened risk for anemia in HCV-positive patients
- ◆ Patients in Asian studies exhibited a higher risk for ribavirin-related anemia
- ◆ Chronic hepatitis C patients who take ribavirin, especially high-dose therapy, may be at risk for anemia and should be closely followed

Combination therapy effective for hemophiliacs with chronic hepatitis C

By Sonia Nichols, senior medical writer of NewsRx.com

Doctors believe a drug regimen combining interferon and ribavirin is the best method for treating hemophilia patients diagnosed with chronic hepatitis C.

People with hemophilia sustain a greater risk for acquiring hepatitis C virus (HCV) infection than do others without hemophilia. A U.S. multicenter study comparing combination therapy with interferon (IFN) monotherapy in adult and adolescent hemophilia patients with chronic hepatitis C suggests the combination therapy is significantly more effective.

Physicians at the University of North Carolina at Chapel Hill randomized the 113 patients treated during the study to receive 48 weeks of IFN/ribavirin combination therapy or 48 weeks of IFN alone. "Patients started on interferon alone who remained positive for HCV RNA at week 12 crossed over to treatment with interferon plus ribavirin," explained M.W. Fried and coauthors.

Follow-up evaluations conducted at the end of treatment revealed three times as many individuals who received combination therapy became HCV RNA negative as compared with those who received IFN monotherapy.

Extended follow-up revealed a sustained response rate of 29% among those treated with IFN/ribavirin, but a

rate of only 7% among those who received interferon alone at the beginning of the trial. The data is published in *Hepatology, 2002;36(4 Part 1):967-972*.

"Among adolescents younger than 18 years who were treated with combination therapy, 10 of 17 (59%) had sustained response compared with 6 of 39 (15%) of adult patients on the same regimen," Fried and colleagues noted.

Based on the evidence, Fried's group declared IFN/ribavirin more effective for eliciting a sustained virological response in adult and adolescent hemophilia patients with chronic hepatitis C.

Key points reported in this study include:

- ◆ Interferon/ribavirin combination therapy was better than interferon monotherapy for producing sustained virological response in adults and adolescent hemophilia patients with chronic hepatitis C
- ◆ Combination therapy appeared to be more effective in adolescents than in adults who were enrolled in the multicenter trial
- ◆ For patients with hemophilia who are diagnosed with chronic hepatitis C, combination interferon/ribavirin is a more favorable treatment choice

November 19th, 2002

HIV-1 disease progression in individuals with hemophilia coinfecting with HCV

Low concentrations of albumin in individuals infected with HIV-1 may indicate a poor outlook and should prompt concern at any stage of infection, find researchers in the latest issue of the *Lancet* (*Lancet* 2002; 360: 1546-51).

Low serum albumin concentration is associated with short-term survival in individuals with HIV-1. However, it is unknown whether individuals with a low serum albumin concentration have delayed progression to AIDS, or survive in the long term. Albumin not associated with progression to AIDS, but strongly associated with death in the short term.

In this study, a team of researchers from London, England, assessed the relation between markers of liver function, and progression to AIDS and death, in individuals with hemophilia infected with HIV-1 and hepatitis C virus.

The team measured markers of liver function, and also took CD4 counts every 3 months, in 111 patients at the Royal Free Hospital Haemophilia Centre, London. In addition, they measured HIV RNA concentrations yearly and then every 3 to 6 months from 1996. The research team used Cox's regression models to assess the independent prognostic value of these markers for AIDS and death.

The team found that as a fixed covariate, albumin concentrations measured shortly after HIV-1 seroconversion were associated with risk of AIDS (relative hazard 0.91) and death (0.89) over a 15-year period. These findings were independent of the CD4 count and HIV-1 RNA concentration.

The researchers determined that, as a time-updated covariate (after adjustment for CD4 count and HIV-1 RNA concentrations), albumin was not associated with progression to AIDS (0.96), but was strongly associated with death (0.88) in the short term.

Dr Caroline Sabin's team concluded, "Low concentrations of albumin in individuals infected with HIV-1 could indicate a poor outlook and should therefore prompt concern at any stage of infection".

Collgard Biopharmaceuticals Announces New Pre-Clinical Study Results

Indicating That Tempostatin Reverses Existing Liver Fibrosis

These pre-clinical results are the "strongest ever observed with potentially anti-fibrotic drugs," reports study investigator Professor Detlef Schuppan

Collgard Biopharmaceuticals (www.collgard.com), the tissue therapeutics company, announced today that two new pre-clinical studies show that Tempostatin(TM) (Halofuginone hydrobromide) can reverse existing liver fibrosis in animal models that closely resemble human disease.

The study results were recently presented at the 53rd Annual Meeting of the American Association for the Study of Liver Diseases in Boston on November 3, 2002 by Professor Detlef Schuppan, Vice Director of the Department of Medicine I in the University of Erlangen-Neurnberg, Germany and Dr. Mark Pines of the Volcani Center research institute in Rehovot, Israel.

Previous studies have shown that Tempostatin(TM), Collgard's lead drug candidate, has the capacity to suppress tissue fibrosis (scarring) in response to injury, suggesting that it could potentially arrest the development of cirrhosis in patients with chronic liver disease such as Hepatitis C. The new pre-clinical study results announced today confirm that Tempostatin(TM) not only has the ability to protect liver tissue from fibrosis during the immediate period of tissue injury but also demonstrates a dramatic capability in reversing existing fibrosis. The fibrolytic finding makes Tempostatin(TM) the first agent to reverse fibrosis in an already fibrotic liver, restoring the ability of the tissue to regenerate, and challenging the current clinical belief that liver fibrosis is an irreversible condition.

The newly reported pre-clinical studies suggest that Tempostatin(TM) has both antifibrogenic and novel fibrolytic activity, working to prevent the formation of fibrosis as well as break down the distorting extra-cellular matrix by inducing the enzymes MMP 3 and MMP 13. The MMP molecules are highly specialized molecular scalpels that cut and remove the abnormal matrix proteins responsible for maintaining fibrosis. Thus, Tempostatin(TM) combines the powerful tissue regenerative effects of suppressing Collagen type I synthesis and inducing MMP 3 and MMP 13 working at a submicromolar concentration.

"The new findings are of great interest. It appears that once the abnormal matrix proteins have been removed, the tissue regenerative process can then proceed without interference and restore functional tissue. The current study provides a powerful example of how tissue therapeutics may offer great promise for the prevention and reversal of one of the most challenging and complex clinical conditions in medicine today," said Collgard CEO Dr. Bruce Bach, M.D. Ph.D.

Chronic liver disease resulting in liver fibrosis is a global health problem affecting more than 800,000 people in the U.S., Europe and Japan. Liver fibrosis and cirrhosis are two of the major causes of liver failure. At present, the only cure for fibrosis is transplantation and the supply of organs is extremely limited. Because fibrotic liver disease may not be detectable until an advanced stage, the possibility of reversing fibrosis represents a critical unmet need for patients with chronic liver disease.

"The unique contribution of Tempostatin(TM) in restoring normal tissue structure after injury is further extended by the promising data in these pre-clinical studies. It provides further evidence that slowing, rather than accelerating the cellular response to injury may provide a significant clinical advance for those patients suffering from fibrotic diseases," Dr. Bach added.

About Collgard Biopharmaceuticals

Founded in 1996, Collgard Biopharmaceuticals is a clinical stage tissue therapeutics company, led by a global team of medical and drug development experts in Boston, Atlanta and Tel Aviv. The company is currently engaged in Phase II human clinical studies evaluating Tempostatin(TM) for the prevention and treatment of organ failure, restenosis, and specific cancers. Scientific and clinical collaborators include the U. S. National Cancer Institute (NCI), and the European Organization for Research and Treatment of Cancer (EORTC).

About Tempostatín(TM)

Tempostatín(TM) is a fully synthetic small molecule, identified by Collgard as a "master switch" in the body's tissue repair process. Tempostatín(TM) works by influencing both the activation of repair cells and the production and clearance of the extra-cellular matrix protein.

November 20th, 2002

CMV Co-infection Predicts Mortality in HCV-Infected Liver Transplant Recipients

The mortality rate after liver transplantation for patients with hepatitis C (HCV)-induced cirrhosis is significantly elevated when infection with cytomegalovirus (CMV) is present, reports a team of investigators from the Mayo Clinic in Rochester, Minnesota.

More aggressive treatment to prevent CMV reactivation in liver transplant recipients may improve outcomes, Dr. Carlos V. Paya and associates suggest in the October 15th issue of *Clinical Infectious Diseases* (Clin Infect Dis 2002;35:974-981).

The group evaluated 92 consecutive HCV-infected liver transplant recipients whose records included follow-up data for at least 4 months. Allograft failure occurred in 18 (19.6%) patients; 8 (8.7%) died. These two primary endpoints were observed in 11 (48%) of 23 patients with CMV disease, 6 (35%) of 17 with subclinical reactivation, and 9 (17%) of those without CMV infection. The difference between those with any CMV reactivation and those not infected remained significant after adjusting for donor age, recipient age, and use of mycophenolate mofetil (risk ratio = 3.708, p = 0.0017).

Based on the finding that all deaths that occurred within 6 weeks of transplantation were among patients with CMV replication, detection of CMV reaction could be a predictor of outcome, Dr. Paya's group suggests. "The use of universal prophylaxis in predisposed HCV-infected liver transplant recipients, or the aggressive implementation of CMV surveillance by use of highly sensitive assays to guide anti-CMV therapy, may positively influence the outcome of HCV-infected patients who have undergone liver transplantation," the authors state.

They advocate further research to evaluate a possible CMV and HCV interaction even in immunocompetent patients. "The association between CMV and HCV may be analogous to the proposed interaction between HIV and HCV," they write.

Although their original intent was to determine the effect of beta-herpesviruses on graft failure and mortality, the Mayo Clinic investigators note that there was no significant association between HHV-6 infection and outcome.

November 21st, 2002

De novo HBV infection in liver transplantation with hepatitis B core antibody positive donors

Lamivudine for patients receiving anti-HBc positive liver grafts is a simple, inexpensive and effective prophylactic regimen for prevention of de novo HBV infection, find researchers in the December issue of *Clinical Transplantation* (Clin Transplant 2002; 16(6): 405-9).

Exclusion of liver grafts from hepatitis B core antibody (anti-HBc) positive donors to prevent de novo hepatitis B virus (HBV) infection after liver transplantation is not feasible in some areas.

In countries like Taiwan, approximately 80% of adults are anti-HBc positive.

No patients given lamivudine developed de novo HBV infection during follow up. The efficacy of lamivudine monotherapy to prevent de novo HBV infection after living donor liver transplantation, using grafts from anti-HBc positive donors, remains to be clarified.

In this study, researchers from Kaohsiung, Taiwan, assessed 42 patients who received living donor liver transplantation, between 1994 and 2000; 57% of the donors were anti-HBc positive.

The research team administered pre-transplant HBV vaccination to all recipients irrespective of anti-HBc status at monthly intervals for 3 months.

Prior to December 1997, recipients received liver grafts from anti-HBc positive donors without prophylaxis (n = 8). However, since January 1998, prophylaxis with lamivudine monotherapy was given to recipients of liver grafts from anti-HBc positive donors (n = 16).

The research team found that de novo HBV infection occurred in 38% of recipients who did not receive prophylaxis.

However, none of the 16 patients given lamivudine developed de novo HBV infection after a mean follow-up of 25 months. Furthermore, the team found that lamivudine was well tolerated, and no side effects were noted.

Dr Yaw-Sen Chen's team concluded, "These results suggest that lamivudine monotherapy for recipients receiving anti-HBc positive liver grafts is a simple, relatively inexpensive and effective prophylactic regimen for prevention of de novo HBV infection".

"The additive protection provided by vaccine-induced or natural immunity is uncertain".

November 25th, 2002

Study looks at hepatitis drug, depression risk

Up to one third of patients with hepatitis C who are treated with interferon may become depressed, according to the results of a small study. However, many patients can take antidepressants while continuing their interferon therapy, the researchers report.

Besides being used to treat the potentially life-threatening liver disease hepatitis C virus (HCV), interferon is also used to treat adult leukemia, certain kidney cancers, the skin cancer melanoma and hepatitis B.

"The good news is that, in most cases, we could successfully treat the depression," lead study author Dr. Peter Hauser of the Portland VA Medical Center in Oregon said in a prepared statement.

While previous studies have identified depression as a potential side effect of interferon therapy, little is known about how common depression occurs in such patients. And, while physicians have been inclined to halt interferon therapy when depression arises, Hauser and colleagues now say that, according to their study findings, most patients can be treated with antidepressants while remaining on the drug.

Writing in the November issue of *Molecular Psychiatry* (*Molecular Psychiatry* 2002;7:942-947), Hauser's team reports on a group of 39 HCV-infected patients who were treated with interferon. All of the patients were monitored for depression each week during the study period.

"Our results showed that 13 of 39 patients (33%) developed interferon-induced major depressive disorder," the authors write. Notably, the investigation revealed depressive symptoms typically developed between the

6th and 22nd week of interferon therapy. "We found that when depression developed in our patients it developed rapidly," Hauser and colleagues write. As such, the investigators recommend that patients be screened for depression every 2 weeks. Of the 13 patients who developed depression, 11 of them responded positively to antidepressants, the report indicates.

"Treating HCV patients with antidepressants may ultimately reduce deaths as well as permit HCV patients to complete a full course of interferon therapy and possibly avoid the complications of advanced liver disease," the authors conclude.

The study was funded by grants from Integrated Therapeutics, a subsidiary of Schering-Plough Pharmaceuticals, and Forest Laboratories.

Combination therapy appropriate for treating hepatitis C-related glomerulopathy

By Sonia Nichols, senior medical writer of NewsRx.com

Therapy combining interferon and ribavirin may be the best way to treat patients with hepatitis C virus (HCV)-related kidney disease.

HCV infections are known to cause complications in other organs such as the kidneys. Interferon monotherapy is beneficial for treating some but not all patients with HCV-related kidney complications, according to doctors in Egypt and the United Kingdom.

"Results of treatment of these patients with interferon therapy have been disappointing, since relapse of the viremia and subsequent relapse of the renal disease are major problems," said Alaa A. Sabry and colleagues, Mansoura University, Mansoura, Egypt.

Interferon plus ribavirin therapy, though, may offer a better alternative, according to a study performed by Sabry's team. In that study, doctors conducted follow-up evaluations of 20 patients with HCV-associated glomerulopathy who were treated with 12 months of combination therapy. Physicians had diagnosed the HCV-positive patients with membranoproliferative glomerulonephritis (MPGN), membranous nephropathy (MN), or mesangioproliferative glomerulonephritis. Mixed cryoglobulinemia was apparent in over half of the patients, according to Sabry and coauthors.

After 12 months of therapy, 25% of the patients had no detectable viremia, and 75% of the patients had normal enzyme levels. Other indices, including protein levels, serum albumin levels, viral titers, and C3 and C4 concentrations, also improved after 12 months of therapy. The data is published in *Nephrology, Dialysis, and Transplantation*, November 2002;17(11):1924-1930).

"Basal serum creatinine and viral titers were important determinants of response to treatment," said Sabry and coauthors.

Given the association between kidney disease and HCV infection, combination therapy that includes both interferon and ribavirin may be the most effective means of managing treatment in patients with such a diagnosis.

Key points reported in this study include:

- ◆ Kidney disease may develop as a result of hepatitis C virus (HCV)-related infection
- ◆ Interferon monotherapy is often inadequate for treating patients with HCV-related kidney disease
- ◆ Combination therapy that includes interferon and ribavirin may be better for treating patients with HCV-related kidney disease

Hepatitis C Virus activates a protein sometimes linked to onset of cancer

By Sonia Nichols, senior medical writer of NewsRx.com

New evidence has linked hepatitis C virus (HCV) infection with the activation of STAT3 protein, which has been implicated in cancer pathogenesis.

"The signal transducer and activator of transcription (STAT) family proteins are transcription factors critical in mediating cytokine signaling," described researchers at Kyushu University of Fukuoka, Japan. STAT3, they explained, has been linked to tumorigenesis, but until now, knowledge of how its activation becomes persistent has been sketchy.

Based on new studies, the researchers have discovered that the core protein of HCV, an infection that causes primary liver cancer, may be responsible for long-term STAT3 activation in some people. "...HCV core protein directly interacts with and activates STAT3 through phosphorylation of the critical tyrosine residue," said T. Yoshida and colleagues. When STAT3 became activated, Bcl-XL, an antiapoptosis protein, and cyclin-D1, a G1 cell cycle regulation protein, also became upregulated. The data is published in the *Journal of Experimental Medicine*, 2002;196(5):641-653).

Cells with HCV core-linked STAT3 expression demonstrated anchorage independent activity and exhibited signs of cancer transformation, according to Yoshida's group.

"We propose that the HCV core protein cooperates with STAT3, which leads to cellular transformation," Yoshida and colleagues concluded.

Key points reported in this study include:

- ◆ STAT3 protein has been implicated in cancer pathogenesis
- ◆ Hepatitis C virus (HCV) protein activates STAT3 proteins
- ◆ HCV and STAT3 may work hand-in-hand to generate liver cancer

November 26th, 2002

Intercell moves HCV vaccine to Phase II

Austria's Intercell AG has started a Phase II clinical trial of its therapeutic hepatitis C vaccine in Europe. The dose-escalation study will be conducted on hepatitis C virus-positive patients who exhibit no response to the current standard combination therapy of interferon alfa and ribavirin. The firm estimates that around 15%-30% of patients do not respond to or cannot tolerate interferon-ribavirin and, for these patients, there is currently no alternative treatment.

The therapeutic vaccine combines a pool of five peptides, which make up various components of HCV, and poly-L-arginine, an adjuvant known to stimulate both antibody- and cell-mediated elements of the immune system. The treatment course consists of six injections given over five months, according to the firm.

Intercell's clinical director, Jurgen Frisch, said that the trial is scheduled for completion towards the end of 2003. If all goes well in this and subsequent studies, Intercell could be in a position to make international regulatory filings for the product beginning in 2007. The HCV vaccine is Intercell's lead project, and has entered Phase II testing just four years after the company was set up in 1998, which reflects a rapid transition from a research firm to one with clinical research capabilities.

"Whole-genome" approach

Intercell specializes in what it describes as a "whole-genome" approach to vaccine development, in which it identifies all the antigens recognized by infected individuals from a wide patient population. This approach is particularly valuable when dealing with pathogens, such as HCV, which have to date shrugged off the best efforts of vaccine developers. The five peptides in Intercell's HCV vaccine were identified through studies of rare individuals who have a natural immunity to HCV; it is hoped that the vaccine will enable other patients to

mimic the immune responses of people with this innate immunity.

The firm recently initiated clinical trials of a prophylactic vaccine against tuberculosis, as well as two cancer vaccines, one targeting melanoma and the other bladder carcinoma. All of these projects are currently in Phase I, and the firm says it intends to bring additional projects into the clinic in the near future. These may include vaccines for traveler's diarrhea and group A streptococcus.

Intercell says its strategy is to generate early out-licensing revenues in order to finance its in-house and co-development programs. The company has raised funds upwards of \$30 million to date, and already has collaborations in place with the likes of Merck & Co, Chiron and Novartis.

November 29th, 2002

Prisoners' Suit Says New Jersey Ignored Hepatitis to Save Money

For a decade, Walter L. Bennett waited to release the pause button on his life, stride through the gates of the South Woods State Prison in Bridgeton, N.J., and begin his life anew. Convicted of armed robbery in 1992, he was finally about to make that walk last June. But before he could resume his life as a free man, he found it endangered by a harsh truth from his captivity: he had tested positive for hepatitis C.

"I trusted that my health was fine, up to par," Mr. Bennett, 42, recalled in an interview yesterday. "But here it is before my release, they drop this bombshell on me. Then they don't give me any information. They just kick me out of the door and tell me to get treatment."

Mr. Bennett is part of what health experts and advocates for inmates' rights say is a growing health crisis in the nation's prison system: the rampant spread of hepatitis C, a potentially fatal liver virus, among inmate populations. A recent federal study indicated that nearly a fifth of the nation's state prison inmates are infected with the disease and that they contract it at a rate 10 times that of the general American population. The problem often goes unchecked because some states do not treat inmates with the disease, the study said.

In a class-action lawsuit filed in a federal court on behalf of Mr. Bennett and 10 unnamed inmates, lawyers hope to change that. Mr. Bennett charges that in order to save money, the New Jersey Department of Corrections and its health care provider did not treat prisoners for hepatitis C.

In papers filed with the suit in Federal District Court in Camden last month, Mr. Bennett's lawyers said the health care provider, Correctional Medical Services, ignored "the issue of hepatitis C virus in order to receive a larger profit from the fees received from New Jersey's Corrections Department."

Corrections officials and the provider declined to comment specifically on the suit, citing internal policies on pending litigation. But Ken Fields, a spokesman for Correctional Medical Services, based in St. Louis, said any allegations that it had placed profits ahead of the medical needs of its patients were "absolutely untrue."

Mr. Bennett, a former intravenous drug user, said he was not told he had tested positive for hepatitis C until two weeks before his release. The suit says Mr. Bennett was not advised on how he might be treated for the disease or cautioned about how the virus, which is blood borne, could be spread to others. A few days after his release, Mr. Bennett was married. He said he later learned that the disease could be spread through unprotected sex. He said his wife has so far tested negative for the disease.

He said he was told after his release that prison officials had misplaced the results of blood tests taken in 2000 that showed elevated levels of liver enzymes, a sign of the disease. "The system betrayed me," he said.

Laura Feldman, a lawyer who filed the suit with her partner Rosemary Pinto, said Mr. Bennett's predicament showed a need for greater education about the disease among prison inmates. "It's a twofold problem," she

said. "It's a problem of hepatitis C being spread in the prison population, and the problem of prisoners being released into society with this disease and the threat to society."

The virus, which is fatal in about one of every 20 cases, causes liver disease in about a fifth of its victims and is the leading reason for liver transplants. About four million Americans have the virus.

Nationally, nearly a fifth of all state prison inmates are infected with hepatitis C, according to a study conducted last year by the Centers for Disease Control and Prevention. Health experts say that the disease is most commonly spread among inmates through intravenous drug use, unprotected sex, the sharing of items like toothbrushes and razors and the use of unsterilized needles by amateur prison tattoo artists.

In New York, about 14 percent of the state's inmates are infected, according to the study. In Connecticut, the figure is about 15 percent.

New Jersey officials, who have not tested prisoners extensively for the disease, reported recently that about 1,200 of the state's 23,000 inmates are infected. But many who study prison health care question that figure, both because the state has not tested broadly for the virus and because it sets the state's inmate infection rate at 5 percent, drastically lower than the national average, 18 percent.

Until last month, New Jersey was the only one of the 10 most populous states that did not treat prisoners for hepatitis C. But after articles in The Philadelphia Inquirer last July about the spread of hepatitis among prison inmates, state officials announced that New Jersey would begin to pay for hepatitis treatment, which can cost as much as \$25,000 per inmate.

That treatment, which often involves a combination of the drugs interferon and ribavirin, can curb the virus in as many half the cases, according to figures from the centers. But there is no vaccine for hepatitis C, and the drugs can have adverse side effects.

The state also offered Correctional Medical Services a 10-month extension on its contract. Before the extension was granted, the company, which according to court papers holds a contract with New Jersey worth nearly \$100 million, said that hepatitis C treatments should not be considered part of its basic health care contract and that the state should pay extra for them. The state differed, but agreed to pay the costs for the next 10 months.

Mr. Fields, spokesman for the company, said each inmate's physician would consider treatment options case by case.

Mr. Bennett said that he was considering treatment options with a private physician and that he and his wife, Rita, had struggled with the impact of his illness. "She was angry at me at first, but then she realized that it wasn't my fault," he said.

His wife added: "They could have said something to him. Ten years in prison, they could have said something to him."

Seronegative HCV Infection Found in One of Five HIV-Infected Subjects

Whole blood testing for hepatitis C virus (HCV) RNA in HIV-infected, HCV antibody-negative patients yielded an incidence of 20% in a prospective study conducted at the University of Iowa College of Medicine in Iowa City.

HCV infection in the absence of antibody formation was more likely in patients whose HIV infection was acquired through sexual contact rather than through parenteral risk factors, Dr. Jack T. Stapleton and colleagues found. This group also had initial CD4+ cell counts and ALT levels that were lower than were those of HCV antibody-positive patients.

Dr. Stapleton's group tested blood samples from 131 HIV-infected patients attending their institution's HIV clinic and 102 HIV-negative persons attending a diabetes clinic. The HIV-positive subjects were all being treated with effective antiretroviral therapy and *Pneumocystis carinii* prophylaxis. Thirty-one (23.7%) HIV-positive patients and two (2.0%) patients with diabetes were positive for HCV antibodies.

When the clinicians used a proprietary method of assessing HCV RNA in whole blood, 20 (20%) of the HIV-positive, HCV antibody-negative patients, but none of the diabetic patients who lacked HCV antibody, tested positive for HCV RNA. RNA results for 19 of the 20 HIV-infected subjects were confirmed in additional blood samples by other methodologies, the Iowa research team notes, and the remaining patient showed strong evidence of viremia.

There were significant differences in initial CD4+ cell counts among the HIV-infected subjects, with a mean of 392 cells/L among the HCV-seropositive patients, followed by 299 cells/L among those with no evidence of HCV infection and 225 cells/L among the seronegative HCV-infected individuals.

The patients with HCV antibodies also had higher ALT values than the antibody-negative patients ($p = 0.002$). Commenting on this last finding, the authors write in the *Journal of Acquired Immune Deficiency Syndromes* for October 1, "As HCV-related liver disease is mediated at least in part by host cellular immune function, the higher ALT values observed in the HCV-seropositive group may reflect a more effective immune response to HCV."

"It seems prudent to consider HCV infection in HIV-positive persons who test negative for HCV antibody, especially those with elevations in liver-associated enzymes," Dr. Stapleton and his associates advise. They also suggest implementation of specific therapy for HCV and avoidance of alcohol if significant fibrosis is found in a liver biopsy.

J Acquir Immune Defic Syndr 2002;31:154-162.

December 2nd, 2002

Syringe bleach disinfection may stem hepatitis C

By Alan Mozes

Injection drug users who disinfect their syringes with bleach before each use all or some of the time are at a significantly lower risk of infection with the hepatitis C virus (HCV), according to researchers.

"While the best ways to prevent the spread of hepatitis C are by either stopping injection drug use or using new sterile needles, these preliminary results do indicate that additional studies are warranted to evaluate the efficacy of bleach disinfection as part of a comprehensive prevention program to reduce hepatitis C transmission," study lead author Farzana Kapadia told Reuters Health. Kapadia is the project director in the Center for Urban Epidemiologic Studies at the New York Academy of Medicine in New York City.

Bleach disinfection has primarily been studied for its value in preventing the spread of HIV. To investigate whether bleach has any effect on HCV, a more common infection among injection drug users, Kapadia and her colleagues reviewed data collected between 1997 and 1999 during the Second Collaborative Injection Drug Users Study funded by the Centers for Disease Control and Prevention (CDC). The study explored blood-borne infections, sexual history and drug use behavior among almost 2,200 male and female injection drug users. All participants were between the ages of 18 and 30 and lived in Los Angeles, New Orleans, New York, Baltimore or Chicago.

The participants were asked whether they shared syringes as well as other paraphernalia used in preparing drugs, such as drug cookers, cotton and water. All were also asked if they ever disinfected their syringes with bleach, water, rubbing alcohol or peroxide.

In the current issue of *Epidemiology* (*Epidemiology* 2002;13:738-741), the researchers report that blood

samples taken at 6-month intervals found that of the roughly two thirds of participants who were not infected with hepatitis C at the onset of the study, 78 became infected by the end of the 2-year period.

Hepatitis C infection was more common among those who shared needles, cotton, water and cookers, or used drugs in a public place, Kapadia and her team found.

However, the risk of contracting hepatitis C was 65% lower among those who said they always disinfected their syringes with bleach. Among those who disinfected their syringes some of the time, infection risk was 24% lower.

The authors conclude that syringe bleach disinfection--a relatively inexpensive process that they say is socially acceptable to most injection drug users--is a potential way to halt hepatitis C spread among this high-risk population.

And for the youngest users, who are at greatest risk of infection, the disinfection method could prove to be more practical than either syringe exchange or drug treatment programs, the researchers state. Young users, they note, are often reluctant to seek out such programs in the first place.

Kapadia emphasized that syringe bleaching offers an additional tool in the battle to halt hepatitis C infections not only in the US, but also in other countries--such as China, India and the republics of the former Soviet Union--where the rate of transmission is currently very high.

Schering-Plough Announces Peg-Intron(R) And Rebetol(R) Surpasses 150,000 Patients Treated Mark In United States

Schering-Plough Corporation today announced that the U.S. launch of PEG-INTRON(R) (peginterferon alfa-2b) Powder for Injection and REBETOL(R) (ribavirin, USP) Capsules combination therapy represents the most successful new product introduction in the company's history, measured in terms of product sales. Since its introduction in October 2001, more than 150,000 hepatitis C patients in the United States have been treated with the combination therapy.

"As a result of the advances we have made in hepatitis C treatment in the last 10 years, we are providing a therapy that was effective in the majority (52 percent) of patients studied. We are extremely pleased with the rapid acceptance by physicians and patients of PEG-INTRON and REBETOL combination therapy," said Richard W. Zahn, president of Schering Laboratories. "We believe this combination therapy has transformed the treatment of hepatitis C, providing established therapeutic value to patients as well as economic value to the U.S. health care system. The proven safety and efficacy of PEG-INTRON, along with its convenient once-weekly dosing, has resulted in more U.S. patients starting treatment in the past year than during any previous period."

An estimated 4 million Americans are infected with the hepatitis C virus (HCV), which contributes to approximately 8,000 to 10,000 deaths each year, according to the Centers for Disease Control (CDC). This toll is expected to triple by the year 2010. The CDC has reported that HCV-associated end-stage liver disease is the most frequent indication for liver transplantation among adults. It is predicted that direct U.S. medical costs to treat HCV-related disease will exceed \$13 billion for the years 2010 through 2019, according to a study published in the American Journal of Public Health.

"Along with our extensive clinical development program involving U.S. studies, the real-world treatment experience we've gained with PEG-INTRON and REBETOL in U.S. patients allows physicians to prescribe this combination therapy with confidence," said Robert J. Spiegel, M.D., senior vice president of medical affairs and chief medical officer, Schering-Plough Research Institute. "This deep knowledge base is especially significant given that U.S. patients often have disease characteristics that make them a more difficult group to treat successfully than patients in other countries." American patients with hepatitis C have a higher incidence of genotype 1 virus, which is the most difficult to treat, and typically are older, more cirrhotic and generally have greater body weight, all factors known to negatively affect treatment outcome.

"We designed the clinical study program for PEG-INTRON and REBETOL combination therapy to be consistent with the demographics of the U.S. hepatitis C patient population," Spiegel said. "You can't change a patient's viral genotype, age or degree of cirrhosis, but one factor that a physician can address during treatment is patient body weight, by adjusting dosing accordingly. This gives physicians the flexibility to tailor the appropriate dose of PEG-INTRON to the patient to remove the impact of patient weight on sustained virologic response rates and help achieve consistent treatment outcomes."

PEG-INTRON is approved by FDA for dosing according to body weight, whether used as monotherapy or in combination therapy with REBETOL for up to 48 weeks. Data from a large, randomized, controlled clinical study, which served as the basis for U.S. approval of PEG-INTRON and REBETOL combination therapy (*Manns et al., Lancet 2001*), demonstrated that once weekly administration of weight-based PEG-INTRON (1.5 mcg/kg) in combination with daily REBETOL (800 mg) achieved consistent sustained viral response (SVR) rates across all patient weights. In this study, 68 percent were U.S. patients and, of these, 73 percent weighed more than 75 kg (165 lbs.). Among U.S. patients weighing more than 75 kg, those treated with weight-based PEG-INTRON and REBETOL achieved a 47 percent SVR versus 39 percent of patients who received standard INTRON(R) A (interferon alfa-2b, recombinant) Injection three times weekly in combination with daily REBETOL (1,000-1,200 mg). These results were consistent with the overall SVR rates seen in U.S. patients in this study (49 vs. 39 percent, respectively).

PEG-INTRON, the only weight-based alpha interferon product, is approved for use in the United States as monotherapy or in combination therapy with REBETOL 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.

Continuing Clinical Research

Schering-Plough is conducting a comprehensive investigational clinical study program with PEG-INTRON and REBETOL involving more than 10,000 U.S. patients that is designed to maximize treatment benefits and improve outcomes for a variety of patient populations with HCV. Ongoing studies include defining the optimal dose and duration of PEG-INTRON and REBETOL combination therapy in all HCV virus genotypes; evaluating the safety and efficacy of this combination therapy in African-American patients, patients on methadone and HIV/HCV co-infected patients; the effect of treatment on liver cirrhosis; and long-term maintenance therapy in patients who are non-responders to previous combination therapy.

Commitment to Hepatitis C Patients

In addition to ongoing investments in research and development, Schering-Plough is continuing its extensive commitment to support hepatitis C patients in the United States with education and service programs as well as financial assistance for patients in need. The company's U.S. patient assistance programs are among the most comprehensive in the industry, providing 24-hour support and guidance to patients from the time of diagnosis through treatment, and ensuring that all eligible patients have access to the company's HCV products.

Twenty-five percent of all hepatitis C patients in the United States currently treated with PEG-INTRON are enrolled in the company's Commitment to Care program, which provides free therapy and/or reimbursement assistance. The market value of assistance and treatment provided to hepatitis C patients through this program was more than \$80 million in 2001, and in 2002 is expected to exceed \$100 million.

Schering-Plough's Be In Charge hepatitis C patient-support program has enrolled more than 55,000 U.S. patients to date, with more than 25,000 patients enrolling in 2002 alone. This U.S. program is designed to assist patients in managing the side effects associated with HCV therapy through the use of educational materials and telephone contact with trained nurses skilled in the management of HCV. Patients involved in this program have demonstrated a higher pharmacy refill rate with their treatment regimen at the end of six months of therapy as compared to those patients who do not participate in the program.

PEG-INTRON is a longer-acting form of INTRON A that uses proprietary PEG technology developed by Enzon, Inc. of Piscataway, N.J. Schering-Plough holds an exclusive worldwide license to PEG-INTRON.

INTRON A is a recombinant version of naturally occurring alpha interferon, which has been shown to exert

both antiviral and immunomodulatory effects. Schering-Plough markets INTRON A for 16 major antiviral and anticancer indications worldwide.

REBETOL is an oral formulation of ribavirin, a synthetic nucleoside analog. Schering-Plough has exclusive worldwide rights to market oral ribavirin for hepatitis C through a licensing agreement with Ribapharm Inc. of Costa Mesa, Calif.

Interleukin-12 restores antigen-specific response to hepatitis B virus

By Sonia Nichols, senior medical writer of NewsRx.com

Interleukin-12 may be beneficial for restoring antigen-specific response in patients infected with hepatitis B virus (HBV).

Researchers think weak dendritic cells may be one reason that some people with HBV cannot raise sufficient T-cell response to their infections. They have proposed that exogenous interleukin (IL)-12 may enable patients to overcome that problem.

University of Mainz researchers in Germany carried out a series of laboratory studies investigating autologous dendritic cells, T-cell activity, and other components of antigen-specific response to HBV using the cells of individuals with chronic hepatitis B infections.

"Proliferative CD4+ T-cell response and specific cytokine release were analyzed in cocultures of dendritic cells pulsed with HBV surface and core antigens or tetanus toxoid and autologous CD4+ T cells," described H.F. Lohr and colleagues.

Researchers cultured all sets of cells under the same conditions, according to study data.

Laboratory results showed those with acute resolved hepatitis B, as well as healthy study volunteers, had strong antigen-specific response, whereas chronic hepatitis B carriers had weak antigen-specific response. Both T-cell activity and interferon gamma production were weaker among chronic HBV carriers. Despite weak antigen-specific response to HBV in those patients, response to tetanus toxoid antigen remained normal.

Lohr's team learned they could boost antigen-specific activity in cell cultures from each study group by pretreating the cells with IL-12. The data is published in *Clinical and Experimental Immunology*, 2002;130(1):107-114).

The failure of dendritic cells to stimulate T cells properly may be one reason for poor immune system response to HBV in some patients, the researchers theorized. "Immunostimulation by IL-12 restored the HBV antigen specific T-cell responses and could have therapeutical benefit to overcome viral persistence," they said.

Key points reported in this study include:

- ◆ Weak dendritic cell stimulation may be one reason T cells fail to develop an antigen-specific response to hepatitis B virus (HBV) in chronic HBV carriers
- ◆ Sets of cells preincubated with exogenous interleukin (IL)-12 demonstrated heightened antigen-specific response to HBV
- ◆ IL-12 could be a useful therapy for those who are chronic HBV carriers

Hepatitis Virus Seen in Sweat of Chronically Infected Patients

Hepatitis C virus (HCV) replicates in sweat glands and is released into the sweat of those with chronic HCV infection, Spanish researchers report in the December issue of the *Journal of Medical Virology* (*J Med Virol* 2002;68:529-536).

Dr. Vicente Carreno of the Fundacion para el Estudio de las Hepatitis Virales, Madrid, and colleagues note that it is known that HCV replicates in the salivary glands of such patients, suggesting that it "may replicate in other exocrine glands."

To investigate, the researchers examined skin and sweat samples from 15 patients with chronic hepatitis C and 10 anti-HCV negative controls with chronic liver disease.

Both positive and negative HCV RNA strands were seen in the epithelial sweat gland cells of all of the patients with HCV. None were seen in controls.

HCV RNA was also detected in sweat samples from all of the 10 HCV patients who were tested. Findings were negative in all of the 8 controls who were tested. Furthermore, "HCV RNA of both polarities as well as HCV core protein were found in the keratinocytes of the basal, spinous and granular layers from all patients with chronic hepatitis C," but not in controls, the researchers report.

Nevertheless, the investigators point out that overall, relatively few cells were infected, indicating that "HCV replication in eccrine sweat glands and epidermal cells is unlikely to contribute significantly to HCV viremia."

Dr. Carreno also told Reuters Health that there "are no data supporting the hypothesis of the transmission of HCV infection by sweat and we believe that this type of transmission is very unlikely."

Platelet levels reversible in hepatitis C patients on consensus interferon

By Sonia Nichols, senior medical writer of NewsRx.com

Consensus interferon can lower platelet counts and increase serum thrombopoietin in individuals with chronic hepatitis C, but those changes are typically reversible, researchers say.

Researchers across the world are presently evaluating consensus interferon (CIFN) for use as monotherapy or in combination with ribavirin as a treatment for chronic hepatitis C. Interferon therapy is linked to the evolution of thrombocytopenia, or low platelet counts in the serum of patients infected with hepatitis C virus (HCV). Even so, medical investigators in Taiwan have announced changes in platelet counts and serum thrombopoietin levels are reversible with CIFN.

According to Chen-Wei Chu and colleagues, Veterans General Hospital-Taipei, investigators enrolled 75 patients with chronic hepatitis C into a randomized trial of thrice-weekly doses of 9 micrograms CIFN, 3 micrograms CIFN, or a placebo. Researchers administered therapy to the patients for 24 weeks and then monitored them for changes in liver histology and serum and blood markers an additional 24 weeks.

"The results showed a significantly higher degree of decrease in platelet counts and elevated serum thrombopoietin (TPO) in patients receiving CIFN 9 or 3 microgram as compared with placebo at week 12 and week 24 of treatment, respectively," said Chu and coauthors.

Researchers detected the greatest changes in platelet and TPO levels in patients given 9 micrograms of CIFN.

"Both the decrease of platelet counts and elevated serum TPO levels returned to baseline values after patients stopped CIFN therapy," Chu and coauthors commented.

Higher levels of serum TPO in patients who developed thrombocytopenia were indicative of sustained response to CIFN. Reduced liver fibrosis, lower HCV RNA levels before treatment, and HCV genotypes other than 1b were also associated with higher TPO levels during CIFN therapy.

In addition, being younger than 45 years old and having serum TPO values that had risen above 50% of baseline by week-12 of the trial were significantly associated with sustained response. The data is published in *Hepatology Research*, 2002;24(3):236-244).

"The serum TPO response to CIFN-induced thrombocytopenia may serve as a marker for the degree of liver fibrosis, and also as a parameter for predicting therapeutic response," Chu and colleagues suggested.

Key points reported in this study include:

- ◆ Consensus interferon was responsible for reduced platelet levels and higher thrombopoietin levels in patients with chronic hepatitis C
- ◆ The highest doses of consensus interferon produced the greatest changes in platelet and thrombopoietin levels
- ◆ Consensus interferon-induced thrombocytopenia is reversible in patients with chronic hepatitis C

December 3rd, 2002

FDA Approves Pegasys(R) (peginterferon alfa-2a) in Combination with Copegus (TM) (ribavirin) for the Treatment of Hepatitis C: New Treatment Offers Dosing Regimen Based on Hepatitis C Virus Strain

Roche announced today that the U.S. Food and Drug Administration (FDA) has approved combination therapy with Pegasys(R) (peginterferon alfa-2a), a pegylated interferon, and Copegus(TM) (ribavirin) for the treatment of adults with chronic hepatitis C who have compensated liver disease and have not previously been treated with interferon alpha. Patients in whom efficacy was demonstrated included patients with compensated liver disease and histological evidence of cirrhosis (Child-Pugh class A).

Pegasys and Copegus combination therapy was granted priority review designation by the FDA. Pegasys was approved as monotherapy for the treatment of adults with chronic hepatitis C on October 16, 2002. Currently, 2.7 million Americans are chronically infected with hepatitis C.

"Roche has taken a leadership role in advancing hepatitis C therapy by researching approaches to reduce the duration of treatment with Pegasys and Copegus and the dose of Copegus therapy for certain patients," said George B. Abercrombie, President & Chief Executive Officer -- Hoffmann-La Roche Inc. "Today, Roche can proudly offer Americans with hepatitis C a new treatment choice-Pegasys and Copegus combination therapy."

"Different genotypes of the hepatitis C virus need to be approached differently. Certain genotypes of the hepatitis C virus are easier to treat while others are stubborn and more difficult to treat," said Pegasys investigator, David Bernstein, MD, Director of Hepatology at North Shore University Hospital, Manhasset, NY. "With Pegasys combination therapy, we can now tailor the dose and duration of a patient's therapy to the genotype of the virus."

Pivotal Studies

Pegasys and Copegus combination therapy was granted approval based on the results of two pivotal Phase III clinical trials that demonstrate it is an effective treatment for patients with chronic hepatitis C.

The pivotal study completed most recently evaluated the effects of the duration (24 weeks compared to 48 weeks) of Pegasys 180mcg as a subcutaneous injection once weekly and Copegus treatment (24 weeks compared to 48 weeks) and the daily dose of Copegus (800mg compared to 1000 for patients weighing less than 75kg and 1200 for patients equal to or more than 75kg) in patients with chronic hepatitis C. The number of patients who received medication in the study was 1,284.

The study showed that patients with strains of the hepatitis C virus known as genotype non-1 (predominantly 2 and 3) achieved similar sustained virological response rates when treated with a 24-week regimen of

Pegasys and 800mg Copegus compared to a 48 week regimen of Pegasys and 1000-1200 Copegus. Genotype non-1 (predominantly 2 and 3) patients who were treated with the 24-week lower Copegus dose regimen experienced fewer side effects. Sustained virological response refers to a patient's continued undetectable serum hepatitis C RNA levels 24 weeks after finishing a course of treatment.

Genotype 1 patients who were treated with the 48 week regimen of Pegasys and 1000-1200 Copegus had higher sustained virological response rates compared to those treated with the 24 week lower Copegus dose regimen.

Sustained virological response rates for these groups treated with Pegasys and Copegus therapy were:

- ◆ Genotype 1: 48 week duration with 1000 - 1200mg Copegus: 51 percent
- ◆ Genotype non-1: 24 week duration with 800mg Copegus: 82 percent

The other pivotal study was published in the September 26, 2002 New England Journal of Medicine and showed that Pegasys 180mcg and Copegus 1000 -- 1200mg combination therapy is a more effective treatment for chronic hepatitis C than interferon alfa-2b 3 MIU as a subcutaneous injection three times a week and 1000 -- 1200mg ribavirin. The sustained virological response rate in the Pegasys and Copegus treated patients was 53 percent compared to 44 percent in the interferon alfa-2b and ribavirin group. The number of patients who received medication in the study was 1,121.

In both studies, virus genotype was clearly the strongest predictor of whether or not a patient achieved a sustained virological response.

Pegasys, a premixed solution, is dosed at 180mcg as a subcutaneous injection once a week. Copegus, available as a 200mg tablet, is administered at 800 to 1200mg taken twice daily as a split dose. Pegasys is currently available at pharmacies. Copegus will be available in early 2003. The two products will be sold separately.

About Pegasys

Pegasys is supported by the most extensive development program ever undertaken for a hepatitis C treatment. Pegasys has been studied in a variety of patient populations, including those with the most difficult to treat form of the disease -- patients with genotype 1 and with cirrhosis (scarring of the liver).

Pegasys is made when interferon alfa-2a undergoes the process of pegylation in which one or more chains of polyethylene glycol, also known as PEG, are attached to another molecule.

In Pegasys, a large, branched, mobile PEG is bound to the interferon alfa-2a molecule and provides a selectively protective barrier. Pharmacokinetic behavior of the end product depends on the length of the PEG and the nature of the link between the PEG and the protein. The high molecular weight (40 kilodalton) branched PEG in Pegasys has been shown to provide sustained pegylated interferon alfa-2a exposure at clinically effective levels over the one-week dosing period.

Pegasys has been approved for use in more than 50 countries, including all European Union countries.

Pegasys and Copegus Adverse Events

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

Copegus may cause birth defects. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients taking Pegasys and Copegus combination therapy. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in worsening of cardiac disease. Ribavirin is genotoxic, mutagenic, and should be considered a potential carcinogen.

Pegasys is contraindicated in patients with hypersensitivity to Pegasys or any of its components, autoimmune hepatitis, and decompensated hepatic disease prior to or during treatment with Pegasys. Pegasys is also contraindicated in neonates and infants because it contains benzyl alcohol. Benzyl alcohol has been reported to be associated with an increased incidence of neurological and other complications in neonates and infants, which are sometimes fatal. Pegasys and Copegus therapy is additionally contraindicated in women who are pregnant, men whose female partners are pregnant and patients with hemoglobinopathies (eg, thalassemia major, sickle-cell anemia).

The most common adverse events reported for Pegasys and Copegus combination therapy, observed in clinical studies to date (n=451), were fatigue/asthenia (65%), headache (43%), pyrexia (41%), myalgia (40%), irritability/anxiety/nervousness (33%), insomnia (30%), alopecia (28%), neutropenia (27%), nausea/vomiting (25%), rigors (25%), anorexia (24%), injection site reaction (23%), arthralgia (22%), depression (20%), pruritus (19%) and dermatitis (16%).

Serious adverse events include neuropsychiatric disorders (suicidal ideation and suicide attempt), serious and severe bacterial infections, bone marrow toxicity (cytopenia and rarely, aplastic anemia), cardiovascular disorders (hypertension, arrhythmias and myocardial infarction), hypersensitivity (including anaphylaxis), endocrine disorders (including thyroid disorders and diabetes mellitus), autoimmune disorders (including psoriasis and lupus), pulmonary disorders (dyspnea, pneumonia, bronchiolitis obliterans, interstitial pneumonitis and sarcoidosis), colitis (ulcerative and hemorrhagic/ischemiccolitis), pancreatitis, and ophthalmologic disorders (decrease or loss of vision, retinopathy including macular edema and retinal thrombosis/hemorrhages, optic neuritis and papilledema).

The complete package inserts for Pegasys and Copegus are available at www.pegasys.com, or by calling 1-877-PEGASYS.

About Hepatitis C

Hepatitis C, a blood-borne infectious disease of the liver, the leading cause of cirrhosis and liver cancer and the number one reason for liver transplants in the U.S., is transmitted through body fluids, primarily blood or blood products, and by sharing needles. In many patients, the mode of transmission is unknown. Unfortunately, most people infected with hepatitis C are unaware of it because it may take years for symptoms to develop. Hepatitis C chronically infects an estimated 170 million people worldwide (three percent of the world's population), with as many as 180,000 new cases occurring each year. It is estimated that less than 30 percent of all cases are diagnosed. If left untreated, hepatitis C can be fatal for some patients.

About Roche

Roche Molecular Diagnostics, a business unit of the Roche Group, manufactures the COBAS AMPLICOR (TM) HCV Test, v2.0 test for the detection of hepatitis C virus in clinical specimens.

Hoffmann-La Roche Inc. (Roche), based in Nutley, N.J., is the U.S. prescription drug unit of the Roche Group, a leading research-based health care enterprise that ranks among the world's leaders in pharmaceuticals and diagnostics. Roche discovers, develops, manufactures and markets numerous important prescription drugs that enhance people's health, well-being and quality of life. Among the company's areas of therapeutic interest are: dermatology; genitourinary disease; infectious diseases, including influenza; inflammation, including arthritis and osteoporosis; metabolic diseases, including obesity and diabetes; neurology; oncology; transplantation; vascular diseases; and virology, including HIV/AIDS and hepatitis C.

For more information on the Roche pharmaceuticals business in the United States, visit the company's website at: <http://www.rocheusa.com>.

December 4th, 2002

Entecavir is superior to lamivudine in reducing hepatitis B virus DNA

A team of international researchers find entecavir has potent antiviral activity against HBV, and is superior to lamivudine in chronically infected patients.

Entecavir is a novel and selective nucleoside analogue with potent activity against hepatitis B virus (HBV).

In this study, published in the December issue of *Gastroenterology* (*Gastroenterology* 2002; 123(6): 1831-8, 2135-9), the safety and efficacy of entecavir (0.01 mg/day, 0.1 mg/day, or 0.5 mg/day orally) were compared with lamivudine (100 mg/day orally).

The research team performed a 24-week, double-blind, randomized, multicenter, phase II clinical trial.

The team assessed 169 patients, chronically infected with HBV (hepatitis B e antigen [HBeAg]-positive and -negative).

Overall, entecavir was found to be well tolerated.

When compared with lamivudine, the team found that entecavir reduced HBV DNA by an additional 0.97 log₁₀ at the 0.1-mg/day dose and an additional 1.28 log₁₀ at the 0.5-mg/day dose. They observed a clear dose-response relationship for entecavir, with the higher doses showing significantly greater viral suppression.

Furthermore, in patients treated with entecavir 0.5 mg/day, 84% had an HBV-DNA level below the lower limit of detection of the Quantiplex branched DNA (bDNA) assay. This figure was 58% in patients treated with 100 mg/day lamivudine. However, by week 22 few patients achieved HBeAg loss and/or seroconversion, in either treatment arm.

The team found that more patients treated with the 0.1-mg/day and 0.5-mg/day doses of entecavir had normalization of alanine transaminase levels at week 22.

Overall the researchers found entecavir to be well tolerated. Most adverse events were mild to moderate, transient, and comparable in all study arms.

Dr Ching-Lung Lai's team concluded, "This study showed that entecavir has potent antiviral activity against HBV at 0.1-mg/day and 0.5-mg/day doses, both of which were superior to lamivudine in chronically infected HBV patients".

In a related editorial in the same publication, Dr Tim Shaw and colleagues also discuss chemotherapy for hepatitis B.

They conclude by questioning whether, "Future research will eventually produce solutions to the problem of eradication of intrahepatic HBV DNA...[and whether this would] lead to...improved quality of life and extended life expectancy".

"Could the achievement of this goal be regarded as a real "cure"?"

Liver Fibrosis Progression Slow in Most HCV-Infected Renal Transplant Patients

For most patients with hepatitis C virus (HCV) with moderate liver disease who receive renal transplantation, the progression of liver fibrosis is slow, French researchers report.

Dr. Laurent Alric from Pavillon Dieulafoy, CHU Purpan, Toulouse, and colleagues compared 30 renal transplant patients with 30 HCV-infected hemodialysis patients and 30 HCV-infected patients who were not receiving hemodialysis or transplantation.

Based on the results of liver biopsies performed at baseline and at two 37-month intervals, HCV-infected patients who underwent renal transplantation showed significantly slower progression of liver fibrosis compared with HCV-infected patients who did not undergo hemodialysis or transplantation, the researchers

report in the November issue of *Gastroenterology* (Gastroenterology 2002;123:1494-1499).

"Our prospective study suggests that in most patients infected by HCV, progression of liver fibrosis after renal transplantation is slow, at least within 7 years of follow-up," Dr. Alric's group concludes.

While these findings are encouraging, "baseline histologic staging remains an important recommendation in the HCV-infected candidate for renal transplantation," Drs. Ana M. Contreras and Raymond T. Chung from Massachusetts General Hospital, Boston, comment in an editorial.

"Consideration should be given to attempts to treat HCV prior to renal transplantation in view of the clear beneficial effects of viral eradication on the natural history of liver disease," they add.

FDA Approval of Pegasys Combo for Hepatitis Sets Stage for Challenge to Peg-Intron

By Michael Shields

The US Food and Drug Administration on Tuesday approved Roche's Pegasys (pegylated interferon alfa-2a) in combination with ribavirin to treat hepatitis C.

Roche Holding AG said on Wednesday that regulators gave Pegasys the marketing ammunition it needs to take on Schering-Plough's top-selling rival, long-acting interferon called Peg-Intron (peginterferon alpha-2b).

"We believe that we have a very good position here. We got a quite strong [wording for the] package insert and a quite strong label, putting us in a very good start position to now start fighting for market share," a Roche spokesman said.

Pegasys's effectiveness in treating patients with liver cirrhosis, a short course of therapy for easier-to-treat patients, a relatively short period to test if it is likely to work and variability of ribavirin dosages may give it a leg up, although there have been no head-to-head studies of the drugs.

Pegasys is given once-a-week by injection, and is combined with daily doses of Copegus, Roche's version of the ribavirin pill.

The FDA in October gave Pegasys clearance as a stand-alone treatment for hepatitis C, but approval for the combination is crucial for Roche to compete with Schering-Plough.

Patients flocked to Schering-Plough's Peg-Intron/ribavirin dual therapy (sold in the US under the brand-name Peg-Rebetron) after it was launched in October 2001 because it is more effective and causes fewer side effects than the company's older treatment using an interferon that had to be taken three times a week.

Pegasys has already received European approval for use alone or in combination with ribavirin.

December 5th, 2002

NAFLD may be a common underlying disease in patients with hepatocellular carcinoma

Researchers in the December issue of *Hepatology* find that hepatitis C and cryptogenic liver disease are the most common etiologies of diseases in patients with hepatocellular carcinoma, but NAFLD (Non alcoholic fatty liver disease) accounts for at least 13%.

The incidence of hepatocellular carcinoma (HCC) in the United States is increasing. However, the clinical characteristics of American patients with HCC have not been well described. 50% of patients with

cryptogenic cirrhosis had features associated with nonalcoholic fatty liver disease.

In this study, researchers sought to determine the etiology of liver disease and short-term outcome among HCC patients presenting to a single center in the United States.

The research team studied 105 consecutive patients with HCC. Their mean age was 59 years, 67% were men, and 76% were non-Hispanic white. They identified the most common etiologies of liver disease as hepatitis C (51%) and cryptogenic cirrhosis (29%).

However, half the patients with cryptogenic cirrhosis had histologic or clinical features associated with nonalcoholic fatty liver disease (NAFLD). Of the patients in the study, 50% patients had HCC detected during surveillance (group I), whereas the remaining 50% had symptomatic tumors (group II). Overall, patients in group I had smaller tumors, were more likely to be eligible for surgical treatment, and had a better median survival, compared with patients in group II.

The team also found that patients with cryptogenic cirrhosis were less likely to have undergone HCC surveillance. These patients had larger tumors at diagnosis.

Dr Jorge Marrero's team at the University of Michigan, USA, concluded, "Hepatitis C and cryptogenic liver disease are the most common etiologies of diseases in our patients with HCC".

However, "NAFLD accounted for at least 13% of the cases".

"Patients who underwent surveillance had smaller tumors and were more likely to be candidates for surgical or local ablative therapies".

"Because of the increasing incidence of NAFLD, further studies are needed to determine the risk of HCC in patients with NAFLD".

The date is published in *Hepatology* 2002; 36(6): 1349-54

December 6th, 2002

High Prevalence of Hepatitis C Virus in Spinal Cord Injuries

Author: NewsRx.com via Screaming Media

The prevalence of hepatitis C virus (HCV) infections among people with spinal cord injuries may be higher than suspected, according to a team of researchers in the United States. Researchers from several institutions in California recently completed a study indicating HCV prevalence among patients with spinal cord injury is higher than in the general population. They urged clinicians who care for such patients to be vigilant in monitoring for the infection.

Over 50 spinal cord injury patients who received care at an urban rehabilitation center in California participated in the government-funded study. According to Tse-Ling Fong, Rancho Los Amigos National Rehabilitation Medical Center, Downey, California, doctors performed routine evaluations of each patient that included tests for HCV serum markers and liver enzyme levels. "Seventeen percent of the cohort was anti-HCV reactive (HCV positive)," said Fong and colleagues.

Among patients who had spinal cord injuries before 1990, HCV prevalence was 21%, whereas among those injured after 1990, HCV prevalence was 7%. Investigators noted that the period in which injury was sustained, in addition to patient age, were the sole risk factors for demonstrating HCV positivity. The data is published in *Archives of Physical Medicine and Rehabilitation*, 2002;83(11):1620-1623).

Alanine aminotransferase, a liver enzyme, was elevated in 30% of the HCV-positive spinal cord injury

patients, and in 10% of the HCV-negative patients. "Individuals who were HCV-positive were more likely to be hepatitis B core antigen-reactive compared with those who were HCV-negative," researchers stated. Given a high HCV prevalence among the spinal cord injured and the possibility that liver enzyme levels can remain normal in the HCV-infected, practitioners should consider checking for HCV infection in patients with spinal cord injury, Fong and colleagues indicated.

Key points reported in this study include:

- ◆ HCV prevalence was 21% and 7%, respectively, among spinal cord injury patients who sustained injuries before 1990 and after 1990.
- ◆ HCV prevalence was higher among people with spinal cord injury than among the general population
- ◆ Because liver enzyme levels may not change in spinal cord injured patients with HCV, clinicians are urged to consider the possibility of infection anyway

Hepatitis C Causes Genes to Line up Differently, Says Study

NewsRx.com via Screaming Media

Researchers have identified genetic rearrangements in people with hepatitis C virus (HCV)-linked cryoglobulinemia that may explain cancer formation. "HCV infection is strictly associated with mixed cryoglobulinemia, a benign B-cell lymphoproliferative disorder that may evolve to lymphoma," said A.L. Zignego, the coauthor of a study done at the University of Florence in Italy.

The researchers evaluated the prevalence of Bcl-2 gene rearrangements in HCV-positive patients with (n7) and without (n1) mixed cryoglobulinemia, explaining that it is highly prevalent in people with HCV. The Bcl-2 gene blocks apoptosis, and is overexpressed in some malignancies.

Investigators detected Bcl-2 rearrangements in 75.7% of HCV-positive patients with mixed cryoglobulinemia and in 37.6% of HCV-positive patients without the lymphoproliferative disease. "Overexpression of Bcl-2 protein and a high ratio of Bcl-2 to Bax were observed in samples from patients with Bcl-2 rearrangements," Zignego and colleagues reported. In at least two patients with viral clearance, genetic rearrangements within their peripheral blood cells also cleared. The data is published in *Annals of Internal Medicine*, 2002;137 (7):571-580).

"The high ratio of Bcl-2 to Bax in patients with Bcl-2 rearrangement and disappearance of the rearrangement with antiviral therapy suggest that the translocation is associated with the antiapoptotic function of Bcl-2 and that HCV infection is linked to inhibition of B-cell apoptosis," Zignego and coauthors concluded.

Key points reported in this study include:

- ◆ Bcl-2 rearrangements are common among people infected with hepatitis C virus (HCV)
- ◆ Bcl-2 rearrangements were nearly twice as prevalent among HCV-infected patients with mixed-cryoglobulinemia
- ◆ HCV positivity contributes to Bcl-2-linked inhibition of B-cell apoptosis in lymphoproliferative disease

December 9th, 2002

Enzyme not indicative of sustained response after interferon

By Sonia Nichols, senior medical writer of NewsRx.com

Delayed normalization of the enzyme alanine aminotransferase (ALT) does not necessarily mean chronic hepatitis C patients won't respond to therapy.

Physicians usually prescribe interferon and ribavirin combination therapy for patients who are hepatitis C

virus (HCV)-positive. In most instances it is beneficial and yields a sustained virological response.

Doctors use ALT values to assess a patient's liver activity during the course of therapy. However, medical researchers in Japan caution that ALT values that remain high during therapy do not rule out the likelihood of sustained virological response down the road.

Their study looked at more than 103 chronic hepatitis C patients who were prescribed combination therapy for 24 weeks.

Nearly 70% of patients developed a sustained virological response after completing therapy, according to Chao-Hung Hung and coauthors, who work at Kaohsiung Chang Gung Memorial Hospital in Kaohsiung, Taiwan. "There was no significant difference in the sustained viral response (SVR) between patients with or without early normalization (week 12) of ALT level (69% vs. 56%)," noted Hung and colleagues. In fact, they said, over 10% of those with abnormal ALT values at the twelfth week of therapy went on to develop a SVR. The data is published in the *Journal of Gastroenterology and Hepatology*, December 2002;17(12):1307-1311).

"Nine of the 12 patients (75%) with abnormal ALT and negative HCV-RNA at week 12 had a SVR compared with none of 4 patients who had positive HCV-RNA at week 12 ($p=0.0192$)," researchers stated. Study data suggests HCV-RNA at 12 weeks, but not ALT, can predict the eventuality of SVR, Hung's team concluded.

Key points reported in this study include:

- ◆ Doctors use ALT values as an indicator for interferon effectiveness in chronic hepatitis C
- ◆ More than 10% of patients with abnormal ALT at the twelfth week of therapy eventually developed a sustained virological response
- ◆ ALT is not a reliable marker for the eventuality of sustained virological response in chronic hepatitis C patients on interferon

Roche Pegasys/Copegus Phase IV To Evaluate Higher Doses, Shorter Duration - THE-PINK-SHEET

Roche will conduct a pilot study to assess the safety and tolerability of higher doses of Pegasys and Copegus in hepatitis C patients with poor prognostic factors as part of its postmarketing commitments.

The study will evaluate the effect of Pegasys 180 mcg or 270 mcg in combination with Copegus 1,200 mg or 1,600 mg on viral kinetics, week 12 virological response, and safety and tolerability in 160 patients who have genotype 1, a high viral load and weigh over 85 kg, the Dec. 3 approval letter states.

FDA cleared Pegasys (peginterferon alfa-2a) for combination use with Copegus (ribavirin) for the treatment of adults with chronic hepatitis C who have compensated liver disease and have not been previously treated with interferon alpha.

The study protocol is to be submitted by May 2003 with patient accrual completed by June 2004. The study should be completed by October 2004 and a summary of the data submitted by December 2004.

In clinical trials, "treatment response rates were lower in patients older than 40 years (50% vs. 66%), in patients with cirrhosis (47% vs. 59%), in patients weighing over 85 kg (49% vs. 60%), and in patients with genotype 1 with high vs. low viral load (43% vs. 56%)," Pegasys labeling states.

"If the results of the pilot study suggest an acceptable risk/benefit profile for any of the doses evaluated, a larger study will be conducted, in 900 evaluable patients equally randomized to two treatment arms for 48 weeks," the approval letter states.

The draft protocol for the larger study should be submitted by December 2004 with enrollment completed by

January 2006. The study is to end by August 2007 and the final report, data sets and modified labeling to be submitted by November 2007.

The recommended dose of Pegasys used alone or in combination with Copegus is 180 mcg once weekly. Pegasys monotherapy was approved Oct. 16 ("The Pink Sheet" Oct. 21, p. 10). "The recommended dose of Copegus and duration for Pegasys/Copegus therapy is based on viral genotype," labeling states.

For patients with HCV genotype 1 or 4, the recommended dose of Pegasys is 180 mcg and 1,000 mg/day for Copegus if the patient's weight is less than 75 kg, or 1,200 mg/day for patients weighing equal to or more than 75 kg for 48 weeks.

The recommended dose for patients with genotype 2 or 3 is Pegasys 180 mcg and Copegus 800 mg for 24 weeks. Data on patients with genotypes 5 or 6 were insufficient to make dosing recommendations, labeling notes.

FDA's Antiviral Drugs Advisory Committee recommended Nov. 14 that Pegasys/Copegus be dosed according to virus genotype to optimize the product's risk/benefit ratio ("The Pink Sheet" Nov. 25, p. 13).

A second postmarketing study will evaluate the safety and efficacy of Pegasys/Copegus given for 16 weeks compared to 24 weeks to 1,400 genotype 2/3 patients.

The protocol is to be submitted by March 2003 with patient accrual completed by August 2004. The study should be completed by September 2005 and the final study report, data sets and modified labeling submitted by December 2005.

Another postmarketing study will assess the safety and efficacy of Pegasys monotherapy and Pegasys/Copegus in 112 pediatric patients. The protocol was submitted Sept. 27 and patient accrual is to be completed by June 2004. The study is scheduled to end by June 2006 and the final report, data sets and modified labeling are due by December 2006.

Roche will also submit data on an ongoing study in 400 African American and Caucasian genotype 1 patients. Patient accrual for the National Institutes of Health-sponsored VIRAHEP-C study began in September and should be completed by August 2003.

The study is set to end by March 2006 and the final report, data sets and modified labeling are due by September 2006. Along with the report, Roche will submit a protocol and schedule for a study to optimize treatment response in African Americans.

"The factors associated with resistance to antiviral therapy in African Americans with chronic hepatitis C, which are selected for evaluation will be based upon the outcomes of the VIRAHEP-C study," the approval letter states.

Roche plans to submit analysis of markers of interferon activity for Pegasys/ribavirin to European authorities to explore whether individualized dosing would be appropriate. The combination was approved in Europe in June. The study is not a formal postmarketing commitment ("The Pink Sheet" July 22, p. 17).

Pegasys combination therapy will launch in early 2003 when Copegus is expected to be available in pharmacies. Pegasys and Copegus will be sold as separate products, Roche said.

Approval was based on a Phase III 1,284-patient trial in which participants received Pegasys with one of four ribavirin regimens: 800 mg or 1,000 mg/1,200 mg for 24 or 48 weeks.

For genotype 1 patients, "treatment for 48 weeks with Pegasys and 1,000 mg or 1,200 mg of Copegus resulted in higher [sustained virological response] (51%) compared to shorter treatment and/or 800 mg Copegus," labeling states.

For patients with genotype non-1, "treatment for 24 weeks with Pegasys and 800 mg of Copegus resulted in a similar SVR (82%) compared to longer treatment and/or 1,000 mg or 1,200 mg of Copegus."

However, "among the 36 patients with genotype 4, response rates were similar to those observed in patients with genotype 1," labeling states.

In a 48 week, 1,211-patient Phase III trial, Pegasys/Copegus 1,000 mg/1,200 mg produced a SVR of 53% compared to 44% for Schering-Plough's Rebetron (interferon alfa-2b/ribavirin).

Schering's pegylated interferon Peg-Intron (peginterferon alfa-2b) and ribavirin (Rebetol) was approved in August 2001 with virologic response rates of 52% compared to 46% for Rebetron ("The Pink Sheet" Aug. 20, 2001, p. 24).

Roche, which utilized a free sampling program for Pegasys monotherapy to help prepare the market for the combo therapy, will still face the challenge of introducing Pegasys/Copegus into an established market. Schering announced Dec. 2 that PEG-Intron/Rebetol was the "most successful product introduction in company history," with more than 150,000 hepatitis C patients treated since October 2001.

December 12th, 2002

Increased risk of chronic hepatitis in children with cancer

Hepatitis B and C infections are serious causes of morbidity and mortality in children with cancer, find researchers in the latest issue of *Medical and Pediatric Oncology* (Med Pediatr Oncol 2002; 40(2): 104-10).

There is a risk of viral hepatitis for children with cancer.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections cause major problems in the management of cancer patients.

In this study, researchers from Turkey evaluated the incidence of HBV and HCV infections in children with malignant diseases, receiving chemotherapy. The team screened 198 children with cancer (mean age = 7.5 years) and 100 healthy children (control) for HBV and HCV. They monitored liver function tests, the number of transfusions, HBV and HCV serology, regularly. 48% of children infected with hepatitis B virus developed chronic hepatitis. In seropositive children, HBV-DNA and HCV-RNA were measured. Chronic hepatitis was defined as having an alanine aminotransferase (ALT) level 3 times of upper normal limit, positive HBV and HCV antigenemia for longer than 6 months. The team performed biopsies in all children with chronic hepatitis. They then analyzed the relationship between the chronic hepatitis and study parameters.

HBsAg positivity, anti-HCV, and mixed (HBV and HCV) infection were found in 12%, 6%, and 2% of children, respectively.

The team found that 48% of the HBV infected children developed chronic hepatitis, while 26 and 22% became carriers and immune, respectively. In addition, 1 died of acute fulminant HBV hepatitis.

Of HCV infected children, 64% also had positive HCV-RNA.

The 4 children with mixed infection all progressed to chronic hepatitis.

The team observed chronic hepatitis in 58% of the HCV infected children. The majority had leukemia and lymphoma.

Furthermore, the researchers found that children with HBsAg antigenemia developed chronic hepatitis in a significantly shorter time than HCV positive children.

Dr Betul Sevinir's team concluded, "We observed an increased incidence of chronic hepatitis and even mortality due to HBV infection".

"This suggests that HBV and HCV infections are serious causes of morbidity and mortality in children with cancer".

December 13th, 2002

Impact of smoking on histological liver lesions in chronic hepatitis C

Smoking could aggravate the histological activity of chronic hepatitis C find researchers in the January issue of *Gut* (Gut 2003; 52: 126-9).

In this study, a research team from France examined the association between smoking and histological liver lesions in chronic hepatitis C. The team studied 244 consecutive patients (152 men, 92 women; mean age 45.9 years) with histologically proven chronic hepatitis C. They recorded daily tobacco consumption (number of cigarettes smoked daily) during the 6 months preceding liver biopsy. While lifetime tobacco consumption was recorded as the number of cigarette packs smoked per year. In addition, the researchers graded liver biopsy specimens for histological activity and fibrosis using the METAVIR scoring system.

The research team found that the proportion of patients with moderate (A2) or marked (A3) activity increased gradually from 62% in non-smokers, to 82% in patients who smoked more than 15 cigarettes per day. Furthermore, a similar relationship was observed for total lifetime tobacco consumption.

Patients with moderate to marked histological activity:

- ◆ Non-smokers = 62%
- ◆ Smokers = 82%

The team found that 59% of patients who had never smoked had grade A2 or A3 disease activity, compared with 85% of patients who smoked more than 20 packs per year.

Multivariate analysis showed that age over 50 years (odds ratio (OR) 5.4), alcohol intake exceeding 20 g/day (OR 2.75), and tobacco consumption of more than 15 cigarettes/day (OR 3.6) were independently related to the histological activity score.

The researchers found no relationship between the severity of fibrosis, and either daily tobacco consumption, or total lifetime tobacco consumption.

Multivariate analysis showed that only age over 50 years (OR 8.8), daily alcohol intake exceeding 30 g/day (OR 3.4), and histological activity score (OR 7.9) were independently related to the fibrosis score.

Dr Hézode's team concluded, "This study suggests that smoking, independent of alcohol, could aggravate the histological activity of chronic hepatitis C".

"Patients with chronic hepatitis C virus infection should be advised to reduce or stop smoking."