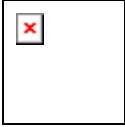


A February 15th 2002 thru March 15th 2002 Review of HCV, HBV and HIV/HCV Coinfection Related News and Highlights

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1. On February 15th, 2002 based upon an article published in the N Engl J Med 2002;346:469-475,522-523.the press reported that in patients with chronic renal failure treated with recombinant human erythropoietin, the formation of neutralizing anti erythropoietin antibodies can result in the development of pure red-cell aplasia,

European investigators report in The New England Journal of Medicine for February 14. Dr. Nicole Casadevall, of the Hopital Hotel-Dieu in Paris, and colleagues identified 13 chronic dialysis patients who developed severe transfusion-dependent anemia between 1998 and 2000 following an initial hematological response to epoetin. The diagnosis of red-cell aplasia was based on the absence of erythroid cells in bone marrow or of circulating reticulocytes.

Twelve of the patients had been treated with epoetin-alpha and one with epoetin-beta. The severe anemia developed after 3 to 67 months of treatment.

After epoetin treatment was discontinued, six patients recovered some erythropoietic function of their own after being treated with immunosuppressants or a renal allograft. Three remain dependent on transfusions more than 2 years later. The remaining four patients also still require transfusions, but their follow-up has been too short to determine their clinical course.

Tests of the patients' serum demonstrated neutralizing antibodies with a high affinity and specificity for the protein moiety of epoetin and for native erythropoietin, Dr. Casadevall and her colleagues report. After treatment was discontinued, the antibody titers slowly decreased.

In an accompanying editorial, Dr. H. Franklin Bunn, of Brigham and Women's Hospital in Boston, points out that at least 25 other patients in Europe have developed the same complication during the same time period. This immune response is the only serious adverse effect of the recombinant human protein to have occurred when it was administered under appropriate medical supervision, he notes.

"This state of affairs raises the question whether the antigenicity of the European product has been slightly enhanced by a change in the manufacturing process that has altered either the formulation or the carbohydrate structure of epoetin," Dr. Bunn suggests.

This possibility is of concern, he adds, because a new preparation of epoetin, darbepoetin-alfa, has been developed by adding new glycosylation sites, for the purpose of prolonging its half-life. It may be that this new preparation will also engender cross-reacting antibodies, he warns.

2. On February 17th 2001 the press released an article titled “High proportion of untreated chronic hepatitis C patients suffers emotional distress” based upon data that is reported in the March issue of the Journal of Hepatology

Approximately 35% of patients with chronic hepatitis C, who are not receiving antiviral therapy, suffer from clinically significant emotional distress, claim researchers from Ann Arbor, Michigan, USA.

The team determined the prevalence, type, and severity of emotional distress in a large group of consecutive chronic hepatitis C (CHC) patients not receiving antiviral therapy.

A brief symptom inventory, together with a questionnaire, was used to study 220 outpatients with compensated CHC.

Of the participants, 35% reported significantly elevated global severity index (GSI) T-scores, compared to an expected frequency of 10% in population controls.

In addition, significantly elevated depression, anxiety, somatization, psychoticism, and obsessive-compulsive subscale T-scores were reported in 28-40% of subjects.

Subjects with an active psychiatric co-morbidity had significantly higher GSI and subscale T-scores, compared to subjects with active medical co-morbidities and subjects without medical or psychiatric co-morbidities.

However, patients with CHC alone were also found to have a higher frequency of elevated GSI T-scores compared to population controls (20% versus 10%).

Broad array of psychological symptoms are observed in chronic hepatitis C sufferers.

Robert J. Fontana, of the University of Michigan Medical School, Ann Arbor, said on behalf of his colleagues, “Clinically significant emotional distress was reported in 35% of chronic hepatitis C patients not receiving antiviral therapy”.

“In addition to depression, a broad array of psychological symptoms was observed.”

“Further investigation into the etiopathogenesis and treatment of emotional distress in chronic hepatitis C patients is warranted,” he concluded.

3. On February 18th 2002 the press released an article titled “Rheumatologic Symptoms Often Associated with Hepatitis C Infection” based upon an article published in the Journal of Medical Virology 2002; 66:200-203.

Chronic hepatitis C virus (HCV) infection with mixed cryoglobulinemia is often accompanied by rheumatologic symptoms, Italian investigators report. They recommend that HCV be considered in the differential diagnosis of rheumatologic symptoms of unknown origin.

Dr. Nicola Leone, of Molinette Hospital in Turin, and colleagues found that of 114 patients with HCV and cryoglobulinemia, 51 (44.7%) had rheumatological symptoms. These often comprised "an intermittent, generally non-erosive oligoarthritis involving large and medium-sized joints," the investigators write in the Journal of Medical Virology for February.

Sero-negative arthritis was present in 16.6% of subjects, carpal tunnel syndrome in 6%, Raynaud's phenomenon in 3.5%, and symptoms of Sjogren's syndrome in 8.7%. Rheumatoid arthritis meeting the American College of Rheumatology criteria was diagnosed in 9.6%. Except for Raynaud's phenomenon, all manifestations were more common in patients whose HCV infection had progressed to cirrhosis.

In an interview with Reuters Health, Dr. Leonard Calabrese, Chief of Clinical Immunology at the Cleveland Clinic in Ohio, commented that "while the percentages may differ, we believe that HCV represents a major cause of undetected rheumatologic symptomatology, and is now a major focus of education for rheumatologists."

He noted that such symptoms as painful joints, muscle aches, fatigability and vasculitis can be sentinel events in patients with HCV. "Mixed cryoglobulinemia is relatively rare," he added, and it has been only in the past 10 years that clinicians have recognized that "virtually all cases are associated with HCV." Cryoglobulinemia presents with a vasculitic skin rash, skin ulcers, neuropathies, renal problem, and the aches and pains associated with arthritis.

"There are a large number people with bona fide rheumatoid arthritis who have HCV," Dr. Calabrese stated. "These patients pose a particular challenge for therapy since so many of the drugs used to treat the arthritis are metabolized by the liver." He recommends that drugs such as methotrexate not be initiated without screening patients for HCV first.

In addition, interferon used to treat HCV can itself cause arthritis, neuropathy, and delayed wound healing, he pointed out. "HCV and rheumatologic symptoms present a very complex matrix of decision-making," he emphasized, which should be done by those knowledgeable in both areas.

4. On February 20th, 2002 an article was published in Ann Intern Med 2002; 136: 288-92 titled, “Surprisingly small effect of antiviral treatment in patients with hepatitis C”

The majority of patients with hepatitis C virus infection are not candidates for interferon-based antiviral therapies, finds a study published in the latest issue of the Annals of Internal Medicine.

A team from Cleveland, Ohio, USA, determined the applicability and usefulness of interferon-based antiviral therapy in a metropolitan clinic population of persons with hepatitis C virus (HCV) infection.

A total of 327 patients, referred to the liver clinic after a positive result for antibody against HCV on enzyme-

linked immunosorbent assay, were included in the study.

Treatment rates, and reasons for non-treatment, were noted.

Some 34 patients had no detectable HCV RNA. Only 23% of patients with HCV were treated with antiviral therapy. Of the remaining 293 patients, 72% were not treated for several reasons.

The reasons were as follows: 37% did not adhere to evaluation procedures, 34% had medical or psychiatric contraindications, and 13% had ongoing substance or alcohol abuse.

In addition, 11% preferred no treatment, and 5% had normal liver enzyme levels.

Only 83 patients (28%) were treated. The researchers found that, of these, 13% had a sustained viral response.

Dr Yngve Falck-Ytter, of the MetroHealth Medical Center and Case Western Reserve University, Cleveland, concluded on behalf of fellow authors, "Most patients with HCV infection are not candidates for interferon-based therapies. "Alternative interventions should be sought for these patients."

5. On February 21st, 2002 based upon an article in the American Journal of Epidemiology 2002:155:323-331, the press released an article titled "Heavy Drinking Raises Risk of Liver Cancer".

Drinking high volumes of alcohol each day is associated with a greater risk of developing liver cancer, a team of Italian researchers' reports.

"The quantity of alcohol consumed is the most important determinant of the risk of having liver disease due to alcohol," study author Dr. Francesco Donato, a professor of epidemiology and public health at the University of Brescia in Italy, told Reuters Health. "Drinking a large amount of alcohol for a few years is a risk-taking behavior, whereas drinking a low-to-moderate amount for many years is probably safe for an individual."

Alcohol use is known to be a major cause of liver diseases such as cirrhosis and liver cancer. The researchers hoped to determine what amount of alcohol is considered safe to consume and what amount was most associated with this increased risk.

Donato and colleagues studied 464 Italian men and women diagnosed with hepatocellular carcinoma, the most common form of liver cancer, and 824 patients with no liver damage. All were asked to report their lifetime drinking history. The study results are published in the February 15th issue of the American Journal of Epidemiology.

The researchers found that for both men and women, drinking more than 60 grams of alcohol a day, equivalent to around four to five glasses of wine, was associated with an elevated risk of developing liver cancer, while drinking between 40 and 60 grams of alcohol daily, the equivalent of three to four glasses of wine, was associated with a moderate risk.

"Drinking up to 40 grams per day is probably not dangerous for the liver of a healthy individual," Donato noted, "and may (even) be beneficial to his or her cardiovascular system".

Because most of the patients were primarily wine drinkers, the investigators could draw no conclusions about the effects of different types of alcohol.

The researchers also found that the risk of developing liver cancer was even greater for patients who had been diagnosed with either hepatitis C or hepatitis B. "The risk of (liver cancer) in subjects with a viral hepatitis infection approximately doubles if he or she also drinks alcohol regularly," Donato noted. "Prudently, they should totally abstain from drinking alcohol."

6. On February 22nd, 2002 the press released the following article, “Maternal Injection Drug Use Increases Risk of Vertical Hepatitis C Transmission” in response to information published in the Journal of Infectious Diseases 2002; 185:567-572.

Maternal injection drug use, but not co-infection with HIV, significantly increases the risk of hepatitis C virus (HCV) transmission to a fetus, according to results of a multi-center, prospective study conducted in Italy.

A total of 1372 consecutive, unselected mothers positive for HCV antibody and their infants were identified in 24 medical centers. Ninety-eight of the offspring were infected with HCV.

Gestational age, birth weight, breast-feeding, and method of delivery were unrelated to transmission rates, Dr. Massimo Resti, of the University of Florence and Pediatric Hospital A. Meyer, and associates report in March 1st issue of The Journal of Infectious Diseases. Multivariate analysis showed that only injection drug use was significantly associated with HCV transmission ($p = 0.0002$).

Transmission rates were similar for mothers who were seropositive or seronegative for HIV. However, the investigators note that "maternal HIV -1 positivity and history of injection drug use appear to be strictly related ($p < 0.000001$). This finding could account for previous reports suggesting that HIV seropositivity increases the risk of HCV vertical transmission.

It made no difference in outcome whether the mother continued injecting drugs during pregnancy or quit prior to becoming pregnant. Dr. Resti's group suggests that mononuclear cell infection by HCV is higher in those who inject drugs. Another explanation they offer is that individuals who inject drugs are subject to repeated super infections with different HCV variants, some of which may have selective advantages in the infection of offspring.

The investigators conclude, "All anti-HCV-positive women with a history of past or active drug addiction should be advised that, independently of HIV -1 co-infection, they are at higher risk of infecting their offspring."

7. On February 25th Hep C Alert launched a National Low-Cost Hepatitis C Testing Program

Starting today, Hep-C ALERT, a national nonprofit organization, is offering low-cost hepatitis C antibody blood tests to the public anywhere in the United States.

Hep-C ALERT's first announcement of their national low- cost hepatitis C antibody testing program in March 2000, captured the interest of patients, health departments

and nonprofit organizations throughout the country. Andi Thomas, Hep-C ALERT's executive director explained, "We were surprised at the response from health and nonprofit organizations. We discovered that these providers needed expanded hepatitis C testing options for their clients."

Accordingly, Hep-C ALERT is launching its low-cost testing program with the development of strategic partnerships in mind. Their goal is to enhance, rather than duplicate existing hepatitis C community efforts by specializing in this unique service. "We've found Hep-C ALERT's service to be a great benefit to our clients and look forward to working closely with them as partners," said Ann Jesse, Executive Director of Hep C Connection, a patient support organization in Denver, CO.

One or more of every fifty people in the United States is infected with the hepatitis C virus. The infection can linger without symptoms for decades while causing serious liver damage. Risk factors that indicate the need for prompt screening include:

- ◆ Blood transfusion or solid organ transplant before 1992
- ◆ Treatments with blood clotting products before 1987

- ◆ Long-term kidney dialysis.
- ◆ Shared drug needles; drug straws; body piercing needles; tattoo needles and inks
- ◆ Accidental needlesticks; blood contact with the eyes, nose, mouth or broken skin
- ◆ Unprotected sex with multiple partners or history of sexually transmitted disease
- ◆ Elevated liver blood tests or rejection from a blood bank after donating blood
- ◆ Previous diagnosis of non-a non-b hepatitis, hepatitis B or HIV
- ◆ Born to a mother who had hepatitis C.
- ◆ Unexplained fatigue; joint and muscle pain; night sweats; or discomfort under the lower right ribcage

People with any of the above risks can call HEP-C ALERT directly at 877-HELP-4-HEP (877-435-7443) for a confidential health-risk assessment and information about the blood test.

8. On February 27th it was announced by the press that “Roche says Pegasys U.S. approval on track for Q4, 2002”

Roche Holding AG ROCZg.VX expects U.S. regulators to approve its Pegasys drug for treating hepatitis-C late this year, chairman and chief executive Franz Humer said on Wednesday.

He said Roche ROCZg.VX had generated additional data on the manufacturing process for Pegasys, which is Roche's main product launch this year.

"We are therefore confident that the product will be approved, as planned, in the fourth quarter of this year," he said in remarks prepared for delivery at a news conference on the 2001 results.

9. On February 27th, 2002 the press announced that the Supreme Court will Hear Case on Workplace Health Risks under ADA; Hepatitis, HIV Advocates 'Closely Following' Case

The Supreme Court will hear arguments today in a case that will determine whether the Americans with Disabilities Act allows companies or employees "to decide whether a workplace represents a danger to a worker's health," the Los Angeles Times reports. The case centers on Mario Echazabal, a Los Angeles man who worked for a private contractor at a Chevron Corp. oil refinery beginning in 1972. In 1995, Echazabal was hired in a full-time position by Chevron, pending the results of a physical exam. When a company doctor discovered that Echazabal had hepatitis C, Chevron withdrew its offer and barred him from the plant, "claiming that exposure to chemicals and solvents there could endanger his health." A federal judge rejected a lawsuit brought by Echazabal alleging that Chevron's actions violated the ADA by discriminating against him because of his condition. But the 9th U.S. Circuit Court of Appeals overturned that decision, noting that the ADA states that businesses cannot discriminate against a "qualified individual with a disability" except when the prospective employee would represent a "direct threat" to others.

HIV and hepatitis advocates are closely following the case. They say that individuals with medical conditions, including HIV or heart ailments, should not be excluded from employment based on employer fears that the workplace could expose them to harm. Every job involves some risks, and the question is: "Do we let people make those risk assessments for themselves, or do we let employers decide?" Matthew Coles, head of the ACLU's Lesbian and Gay Rights Project, asked. Employers, on the other hand, believe that a Supreme Court ruling in Echazabal's favor could open them up to liability if a worker's condition deteriorates, despite assurances from Echazabal's attorneys that businesses that take "all reasonable steps" to warn an employee of a possible health risk cannot be held at fault if that employee later becomes ill or dies. "This puts employers in a terrible dilemma. No matter what they say, employers are going to look guilty if they put someone in a job who later suffers severe injury," Fred Alvarez, a California attorney who filed a brief on behalf of the Employers Group, a coalition of California companies, said.

In January, the court ruled that people must have "substantial limitations" on activities "central to daily life," not only in the workplace, to qualify as disabled under the ADA. The decision made it more difficult for workers to

demonstrate that they are entitled to an accommodation by their employer under the law.

10. On February 28th, 2002 the FDA OKs Blood Bank Fingerprint Test

The government approved sophisticated genetic fingerprinting tests Thursday for blood banks to use to reduce the risk of the AIDS or hepatitis C viruses slipping into transfusions.

The vast majority of transfusions are infection-free. But blood banks have been performing this nucleic acid testing, called NAT, as part of a nationwide experiment since 1999 to see if the more sophisticated method can make the blood supply even safer.

Thursday's approval by the Food and Drug Administration validates NAT testing as adding that extra layer of safety.

In the three-year study, the new test caught seven blood donations tainted with HIV and 88 tainted with liver-destroying hepatitis C that otherwise would have slipped into the blood supply, the FDA said.

"Blood is already remarkably safe," said FDA blood chief Dr. Jay Epstein. "However, the public wants the safest achievable blood supply and these are technological innovations which do make blood safer."

NAT can detect tiny amounts of HIV or hepatitis C before the blood donor's body has even recognized the infection. That's because viral genes spread through blood faster than the immune system begins forming antibodies to fight them, a reaction that may not occur for weeks, even months after the person is infected.

Yet until now, blood testing has depended largely on tests that detect antibodies in an infected donor. So newly infected donors occasionally slip through.

Nucleic acid testing closes much of that "window period," cutting off about a week for HIV and a stunning 57 days for hepatitis C. In practical terms, that means NAT can prevent up to 50 cases of hepatitis C every year, and cut the HIV risk to 1 in 2 million transfusions, Epstein said.

"We're very excited," said Jim McPherson of America's Blood Centers, whose member blood banks collect half of the nation's supply. "This exceedingly powerful tool is now recognized as improving blood safety."

"As we continued to do it and identify donors who were positive on NAT but not detectable on other tests, it became clearer and clearer" the new testing was valuable, added Dr. Jerry Squires of the American Red Cross, which supplies the other half of the nation's blood. "This is, we think, a significant step."

But McPherson said the FDA's approval means the cost of NAT will reach \$15 or \$20 a donation, up from the lower research cost of \$8 a donation.

That's partly because NAT is an intensive process to perform, requiring a specially vented and cleaned laboratory to prevent contamination, extra preparation of blood samples and more time. The test materials will also cost more.

Chiron Corp. makes the newly approved test, which it developed with Gen-Probe Inc. and sells under the brand name Procleix.

A competitor, Roche Diagnostics, is seeking FDA approval of a slightly different version of NAT, which remains in testing at a number of blood banks. It will take the FDA about a year to order all blood banks to begin using a licensed version of NAT instead of the research version, time in which either Roche's competing test could be approved or banks would have to switch to Chiron's.

11. On February 28th, 2002 reports from the 2002 Retrovirus Conference in Seattle state that

Pegasys (Pegylated interferon alfa-2a) Improves Hepatitis C Outcome in HIV+ Patients

Pegasys (Pegylated interferon alfa-2a) plus ribavirin leads to a significantly better treatment response compared with conventional interferon alfa-2a (IFN) plus ribavirin in patients infected with HIV and hepatitis C virus (HCV).

While the superiority of the PEG-IFN formulation has been reported in patients with HCV, it has not before been documented in HCV patients who also have HIV infection. At the 9th Conference on Retroviruses and Opportunistic Infections, Dr. Ray Chung, of Massachusetts General Hospital in Boston, presented results from the first large randomized, controlled trial comparing the safety and efficacy of the two regimens in co-infected patients.

Dr. Chung and colleagues, at the NIAID/NIH AIDS Clinical Trials Group in Bethesda, Maryland, conducted a multi-center, open-label trial with 133 dually infected patients who were randomized to one of two treatment groups.

Both groups received ribavirin doses of 600 mg/d, increasing to a maximum of 1 g/d. One group received PEG-IFN 180 mcg per week during the 48-week study, and the other group received IFN 6 MIU three times a week for 12 weeks and then 3 MIU for the remainder of the study period.

Dr. Chung presented 24-week data. He reported that 44% of the PEG-IFN-treated patients had a virologic response compared with 15% in the conventional IFN group. When virologic response was combined with histologic data obtained from liver biopsy, Dr. Chung's group found that 53% of the PEG-IFN-treated patients compared with 37% of the IFN-treated patients responded to treatment.

In both treatment arms, total CD4 cell counts declined, but no adverse effects on HIV RNA were noted. The PEG-IFN arm experienced more grade 4 toxicities, but discontinuation of treatment was not significantly different between the two groups. Overall, both regimens were well tolerated.

12. On Friday March 1st, 2002 the press announced that “ICN Pharmaceuticals are defending the Ribavirin Patent”

ICN Pharmaceuticals, Inc released the following response regarding potential infringement on its ribavirin patent:

There have been questions raised in recent days about our patent position with respect to the use of ribavirin in combination with interferon alpha or pegylated interferon for use in the treatment of hepatitis C.

Last year three companies filed Abbreviated New Drug Applications challenging ribavirin patents. Other challenges could come forward. Lawsuits have been filed against two of the companies that will not come to trial for thirty months from filing at the earliest. If other challenges come forward, similar lawsuits will be filed.

ICN holds a very strong intellectual property position. There is no NDA for ribavirin alone. There are broad method of use and related patents held by ICN, and for combination therapy with interferon, by Schering-Plough, which extend to 2015-17. (In the EU and Japan, ICN has applied for extensions for important patents to about 2010.) In our license agreement with Schering-Plough, they are prohibited from licensing ribavirin to other companies either for mono or combination therapy.

ICN has not licensed ribavirin to any other company, nor are they obliged to, for use in combination therapy with interferon. Any such use would be deemed a patent infringement and would be treated as such and responded to vigorously.

ICN's legal position is formidable, and we will vigorously resist attempts to weaken our market position by anyone claiming otherwise.

ICN is an innovative, research-based global pharmaceutical company that manufactures markets and distributes a broad range of prescription and non-prescription pharmaceuticals under the ICN brand name. Its therapeutic focus is on anti-infectives, including anti-virals, dermatology and oncology.

13. Additionally on March 1st, the press stated that Achillion is Starting Phase II Study of Its Lead Hepatitis B Product Candidate

The phase II study is designed to help identify the optimal dose of ACH-126,443 (Beta-L-Fd4C) to treat patients chronically infected with hepatitis B virus (HBV), defined as the dose which most effectively suppresses hepatitis B DNA levels (viral load) while providing the best safety profile.

The double-blind study will evaluate several doses of ACH-126,443 administered once a day to patients with chronic HBV infection, compared with lamivudine (3TC), and placebo. The study will be conducted in multiple centers across central and eastern Europe under Achillion's Investigational New Drug application filed with the FDA.

“In two years from the launch of Achillion, we have advanced ACH-126,443 from early preclinical testing into phase II efficacy trials. This rapid entry into clinical development underscores the value of the experience of our team to deliver major milestones successfully,” said William GRice, Achillion's CEO, in a media release.

“Chronic hepatitis B infection is a silent epidemic with an enormous need for additional and superior therapeutics. With existing treatments, the medical needs of patients are often not met due to adverse side effects or loss of efficacy because of viral resistance,” Mr Rice continued.

Achillion Pharmaceuticals, a privately held pharmaceutical company focused on the discovery, development and commercialization of innovative anti-infective agents, today announced the commencement of a Phase 2 clinical study with the Company's lead product candidate, ACH-126,443 (Beta-L-Fd4C) in patients with chronic hepatitis B infection.

This phase 2 study (Study 443-003) will help identify the optimal dose of ACH-126,443 to treat patients chronically infected with hepatitis B virus (HBV), defined as the dose which most effectively suppresses hepatitis B DNA levels (viral load) while providing the best safety profile. This double-blind study will evaluate several doses of ACH-126,443 administered once a day to patients with chronic HBV infection, compared with lamivudine (3TC), and placebo. The 443-003 study will be conducted in multiple centers across central and eastern Europe under Achillion's Investigational New Drug application (IND) filed with the US Food and Drug Administration.

Background:

ACH-126,443 is an L-nucleoside antiviral agent administered orally once daily that has demonstrated in vitro activity against both wild-type and lamivudine-resistant strains of HBV. Clinical studies are planned in 2002 to evaluate the efficacy of the agent in patients with lamivudine-resistant strains of HBV. Chronic HBV infection is a life-threatening disease that affects more than 350 million individuals worldwide. It is a common cause of liver damage and the leading cause of liver cancer. The World Health Organization lists chronic HBV as the ninth leading cause of death worldwide.

Pre-clinical studies have also demonstrated that ACH-126,443 effectively inhibits HIV, including lamivudine-resistant and multi-drug resistant strains. Achillion is also conducting studies to evaluate ACH-126,443 in patients with HIV infection. Over 36 million people worldwide were estimated by the National Institutes of Health to be living with HIV/AIDS at the end of 2000, with approximately 5.3 million new infections having occurred in 2000. Through

2000, the HIV/AIDS epidemic had resulted in over 20 million deaths worldwide.

Achillion is a privately held pharmaceutical company focused on the discovery, development and commercialization of innovative small molecule drugs that combat drug resistance in infectious diseases, with a particular emphasis on antiviral drugs to treat diseases caused by hepatitis B and C viruses (HBV and HCV), HIV and herpes viruses. Achillion's drug development pipeline is led by the product candidate, ACH- 126,443 (Beta-L-Fd4C), which is currently in human clinical trials for the treatment of chronic hepatitis B and HIV infections. Achillion's drug discovery expertise embodies both a conventional medicinal chemistry approach directed at classic anti-infective molecular targets, and its novel Zinc Finger Targeting (ZFT) drug discovery technology developing small molecules that target zinc finger motifs unique to particular pathogens.

14. On March 3rd, 2002 the press reported that a Hepatitis C Injection program is linked to HCV epidemic in Egypt

Scientists have found the strongest link yet between Egypt's unusually high prevalence of hepatitis C and a mass injection program conducted 20 or 30 years ago to treat schistosomiasis, a waterborne tropical disease caused by a parasite. Egypt has a high rate of liver disease, mostly due to chronic infection with the hepatitis C virus, which can go unnoticed until decades after the infection, when liver damage becomes evident. Hepatitis C is easily spread through blood contact.

About 15-20 percent of the population in Egypt has hepatitis C antibodies, according to a study published this week in The Lancet medical journal that compares to a hepatitis C infection rate of about 1.5 percent in the United States. The study of 8,499 people found that within all regions of the country, the prevalence of hepatitis changed most dramatically between those who were old enough to have participated in the mass injection program and those who were too young to have been exposed to it and were instead treated with pills.

Liver experts have noted the link before, but the latest study provides the strongest evidence yet to explain the hepatitis epidemic in Egypt. "It wasn't the schistosomiasis drug, it was contamination of the injection equipment," said Christina Frank, an epidemiologist at the University of Maryland who led the study. "In those days they used reusable needles and syringes, not sterile. They didn't know that boiling them for two minutes was not enough."

The Egyptian Ministry of Health and Population and the World Health Organization were also involved in the study. The findings help explain the origin of similar hepatitis C Outbreaks elsewhere in the world, said Dr. David Thomas, an infectious disease specialist at Johns Hopkins University, who was not connected with the research.

The Egyptians should not be accused of any past sloppiness, Frank said, because at the time the injection program was running, scientists did not know what they know today about how to sterilize equipment properly and the danger of exposure to blood.

Egypt is a unique case when it comes to hepatitis because it had, and still has one of the highest incidences of schistosomiasis and was one of the few countries afflicted with the disease that had the money to initiate a mass treatment program, Frank said.

15. On March 4th, 2002 the press announced that "Maxim says drug can stop liver damage from alcohol"

U.S.-Swedish biotech Maxim Pharmaceuticals said on Monday an animal study showed that its drug Ceplene could completely reverse damage to the liver caused by alcohol.

Pre-clinical testing showed that rats injected with ethanol and the company's drug Ceplene sustained no liver damage, while rats given only ethanol developed symptoms related to alcohol abuse, the company said.

"We've shown we could completely reverse the damage made by the alcohol," Maxim Chief Scientific Officer Kurt Gehlsen told analysts at a meeting in Stockholm.

Maxim expects clinical testing of Ceplene against alcoholic liver disease and non-alcoholic steatohepatitis to start this year. Any drug must go through three different phases of clinical trials, which typically take several years, before being approved for sale to the public.

In the United States one out of 10 people suffer from chronic liver diseases such as cirrhosis and fatty liver, Maxim said.

Ceplene, with the scientific name histamine dihydrochloride, is also in clinical trials for use against hepatitis C and different forms of cancer.

"Hepatitis C is a two billion dollar market, but this is way bigger ... I have to say we are pretty enthusiastic for the prospects of Ceplene against chronic liver diseases," Maxim Chief Executive Larry Stambaugh said.

The company's shares rose 3.7 percent to \$5.94 in early U.S. trading, while they gained 3.3 percent to 62.50 Swedish crowns (\$5.99) in Stockholm on Monday.

The company would not disclose any further details of the animal study, which will be presented at the EASL conference for liver studies in Madrid starting April 18.

In late 2000, the U.S. Food and Drug Administration rejected Maxim's application to market Ceplene, then called Maxamine, for treatment of skin cancer.

The company's shares then plunged 92 percent from levels above \$60 in late 2000 to a low of \$5.

16. Additionally on March 4th, 2002 the following news was released: Hepatitis C Study; Results Indicate New Drug Therapy Improves Adherence and Cure Rate”

If you have a serious disease that is curable by medication, you take the medication. That should go without saying, but it often is not the case with hepatitis C, a blood-borne virus that affects the liver. The side effects with the standard therapy (interferon in combination with ribavirin) are so unpleasant that patients frequently abandon treatment, even though when left untreated hepatitis C is a life-threatening illness.

An investigational drug, PEGASYS(R), promises improved quality of life over the standard therapy, which could increase the likelihood that patients adhere to the one-year course of therapy necessary for treatment success, according to a study published this month in Hepatology. The study's lead author is David Bernstein, MD, of North Shore University Hospital (NSUH) in Manhasset, New York.

The study is significant because hepatitis C is viewed by many as “the new epidemic”, unless it can be controlled, it threatens to overwhelm the U.S. healthcare system.

PEGASYS is a pegylated interferon. To define this term simply, there is a strand of an inert, synthetic polymer called polyethylene glycol (PEG) attached to the interferon molecule. This PEG strand sweeps around like a tail and keeps the medication from being broken down too quickly. That means it can be administered once a week as compared with three times. And, most important, the PEG seems to help keep the drug at a fairly constant level in the patient's bloodstream, preventing “peaks and valleys” which have been linked to negative side effects.

In Dr. Bernstein's study, entitled “Relationship of Health-Related Quality of Life to Treatment Adherence and Sustained Response in Chronic Hepatitis C Patients,” PEGASYS was compared to standard interferon in

over 1,400 patients from 11 countries, including the United States. Based on health surveys and fatigue severity scales administered to these patients at five points during their treatment, they had more energy, less fatigue, less bodily pain and fewer problems doing their job than patients taking standard interferon. In addition to being better tolerated, PEGASYS has the highest overall efficacy of any hepatitis C medication and provides an early indication (at three months) of whether the patient might or might not succeed on therapy. Of patients on PEGASYS plus ribavirin for whom success was projected based on early response, 75 percent who adhered to the full course of therapy had virus below the limits of detection after finishing their course of therapy.

It is estimated that 2.7 million people are infected with hepatitis C, many of them still undiagnosed, according to Dr. Bernstein, who is director of hepatology of the Division of Gastroenterology and Hepatology at NSUH in Manhasset, one of the cornerstone hospitals of the North Shore-Long Island Jewish Health System. He starts seeing patients at 6:30 a.m. in his hospital office to get through his caseload (92 percent diagnosed with hepatitis C).

"The practices of most hepatologists I know are bursting at the seams," he said. "Cirrhosis may occur in 20 to 30 percent of cases within 20 years. Hepatitis C is the leading predisposing factor for liver cancer and liver transplant. It's already overburdening our transplant facilities. And we're seeing just the leading edge. There's no way our medical system can handle this epidemic."

Hepatitis C patients represent all socioeconomic classes and have been infected in a variety of ways, including intravenous or intranasal drug use, blood transfusion prior to 1992, when procedures were put in place to safeguard the U.S. blood supply, and other less risky-seeming procedures such as manicures, tattooing and body piercing. Patients can be symptom free for decades, while the disease progresses, which is part of the adherence problem.

"Maybe they're diagnosed as a result of a blood test performed by an insurance company, but they feel fine," said Dr. Bernstein. "Then they start on the medication and they feel terrible. I find that 80 to 90 percent of my patients suffer some side effects: flu-like symptoms, irritability, depression, thyroid problems. They find it hard to do their jobs or take care of their children. It affects their relationships -- they know that the therapy can cure them, but their quality of life is so seriously diminished that they quit, even though it's their only chance for a cure." Studies show that between 4 and 27 percent of patients discontinue conventional therapy within 24 weeks.

"Hepatitis C is the only virus known that can be cured by medication, and interferon is the only medication known that can cure it," Dr. Bernstein said. "PEGASYS is likely to be our mainstay for quite some time because of its effect on adherence, although I expect it to be used in combination with other antiviral agents as they are developed. And as the number of cures increases, the spread decreases. I view PEGASYS as a significant advance on the hepatitis C front."

PEGASYS has been approved for use in 13 countries to date. Approval for use in additional countries, including the United States, is expected to be granted in the coming months.

17. On March 6th, 2002 Hepatitis Weekly Editors released the following information: DNA Array Gives New Information about HCV & Genes following the publishing of an article titled Insights into the pathobiology of hepatitis C virus-associated cirrhosis in the American Journal of Pathology, February 2002;160(2):641-654.

With the advent of microarray technology in recent years, studying genetics has become a less difficult proposition. Using cDNA array analysis, scientists in Australia have gleaned new information about the relationship between human genes and hepatitis C virus (HCV)-associated cirrhosis.

In the analyses, Nicholas A. Shackel and colleagues, the University of Australia, Sydney compared three types of samples, HCV-associated cirrhosis, autoimmune hepatitis, and control, nondiseased liver tissue samples using a cDNA array that could identify 874 genes.

“Genes upregulated in HCV-associated cirrhosis were predominantly associated with a Th1 immune response, fibrosis, cellular proliferation, and apoptosis,” described Shackel and coworkers.

Investigators detected genes for several factors typically related to fibrosis, including EMMPRIN and discoidin domain receptor 1, as well as apoptosis, including apoptosis-related protein 3, during their evaluations of virally infected tissues.

“Real-time quantitative reverse transcriptase-polymerase chain reaction confirmed the increased expression of 15 genes,” Shackel and coauthors reported.

The nature in which genes linked to apoptosis were expressed in autoimmune hepatitis was markedly different from the way in which they were expressed in viral hepatitis. For example, samples from patients with autoimmune hepatitis expressed pro- and antiapoptotic genes, but those from HCV-positive patients tended to express mostly proapoptotic genes.

“HCV-associated cirrhosis was characterized by a proinflammatory, profibrotic, and proapoptotic gene expression profile,” Shackel and coworkers concluded. The corresponding author for this study is Nicholas A. Shackel, The University of Sydney, Sydney, Australia.

Key points reported in this study include:

- ◆ New gene identification technologies have provided insight into the way genes are expressed in HCV-associated cirrhosis
- ◆ Genes for fibrosis, apoptosis, cell proliferation, and Th1 immune response are significantly expressed in liver tissues of patients with HCV-related cirrhosis
- ◆ Genetic profiles differed between those with autoimmune hepatitis and those with hepatitis-associated cirrhosis

18. On March 8th, 2002 the press released the following article: “Vaccinating chronic hepatitis C patients against hepatitis A reduces morbidity and mortality” based upon a study published in the February issue of the American Journal of Gastroenterology

Vaccination would reduce number of hepatitis A cases by 63-72% and therefore vaccinating chronic hepatitis C patients against hepatitis A reduces morbidity and mortality in all age groups.

A team from Alexandria, Virginia, USA, evaluated the cost-effectiveness of vaccinating chronic hepatitis C patients against hepatitis A.

A Markov model was used to assess cost-effectiveness from the health system and societal perspectives.

Costs of hepatitis A screening and vaccination were compared with savings from reduced hepatitis A treatment and work loss. These were used to determine net costs of a "screen and vaccinate" strategy.

The researchers compared net costs with longevity gains, to assess cost-effectiveness.

Based on hypothetical cohorts of 100,000 patients, it was found that vaccination would reduce the number of hepatitis A cases by 63-72%, depending on patient age.

Screening and vaccination costs of \$5.2 million would be partially offset by \$1.5-\$2.8 million reductions in hepatitis A treatment costs and \$0.2-\$1.0 million reductions in work loss costs.

From the health system perspective, vaccination would cost \$22,256, \$50,391, and \$102,064 per life-year saved for patients vaccinated at ages 30, 45, and 60 years, respectively.

The team found that cost-effectiveness ratios improved when work loss prevention was considered.

Author R. J. Jacobs, of Capitol Outcomes Research, in Alexandria, said on behalf of the group, "Hepatitis A vaccination of chronic hepatitis C patients would substantially reduce morbidity and mortality in all age groups examined."

"Consistent with other medical interventions for chronic hepatitis C patients, cost-effectiveness is most favorable for younger patients," it was concluded.

19. On March 8th, 2002 it was announced that a "Hormone may treat type 2 diabetes". Researchers reported their findings in an article published in the March 9th issue of the Lancet 2002; 359:824-830.

A lab-engineered version of a natural intestinal hormone has shown early promise in treating type 2 diabetes, Danish researchers report.

The hormone, glucagon-like peptide 1 (GLP-1), is released in response to food intake, helping to regulate blood levels of sugar, or glucose.

Type 2 diabetes is marked by poorly controlled blood glucose levels and arises from the body's inability to properly use the pancreatic hormone insulin, the body's key blood-sugar regulator. The disease is often related to excessive body weight and is typically managed with diet, exercise, oral drugs to control blood glucose and sometimes insulin therapy.

According to the authors of the new study, GLP-1 treatment was able to lower patients' glucose levels and improves functioning in the insulin-producing beta cells of the pancreas.

"The treatment nearly normalizes the ability of the patients' own beta cells to respond to glucose again," co-author Dr. Jens Juul Holst, of the University of Copenhagen in Denmark has been reported as saying.

If further research confirms these findings, GLP-1 could eventually be used alone to treat type 2 diabetes, according to Holst.

The study included 20 type 2 diabetes patients, half of whom were given GLP-1 infusions over 6 weeks. The infusions were given via a portable insulin pump, which provide patients with a continuous supply of the synthetic hormone. The other 10 patients were given infusions of saline, for comparison purposes.

After 6 weeks, the treated patients' blood glucose levels had decreased, on average, and their sensitivity to insulin and beta-cell functioning both improved, the researchers report.

GLP-1 had, in other research, been shown to slow the emptying of food from the stomach and control appetite--both of which were seen in patients in this study. On average, treated patients lost 1.9 kilograms, or about 4 pounds.

Holst said his team is about to start a larger, longer-term study of the hormone therapy. He noted that animal research has shown GLP-1 to promote growth of beta cells, and it will be "interesting" to see if this occurs in humans as well.

20. On March 11th, 2002 the press released the following news story "High-dose interferon with ribavirin may be suitable for non-responders to conventional interferon mono-therapy for hepatitis C". The data is published in the March 12th issue of Aliment Pharmacol Ther 2002; 16(3) 381-388

High-dose interferon with ribavirin may be suitable for non-responders to conventional interferon mono-therapy for hepatitis C, according to a report published in the March issue of Alimentary Pharmacology and

Therapeutics.

Conventional interferon mono-therapy fails to achieve virological clearance in most hepatitis C-infected patients.

The use of high-dose induction regimens has been suggested to improve the initial clearance of virus, while the addition of ribavirin appears to improve the rates of sustained response once clearance is achieved.

The efficacy and safety of re-treatment with an induction regimen of high-dose interferon alpha-2b, with or without ribavirin, in chronic hepatitis C patients who have not responded to standard dose interferon mono-therapy was assessed by Dr A.H. Malik and colleagues.

The research group, based at the Division of Digestive and Liver Diseases at the University of Texas Southwestern Medical Center in Dallas, Texas, USA, recruited previous virological non-responders to standard dose interferon (3-5 MU three times weekly for 12 weeks).

These patients were randomized into two groups, A and B.

Group A received, unblind, 10 MU interferon alpha-2b daily for 10 weeks, then 5 MU daily for 74 days, then 5 MU three times weekly for 24 weeks (total 36 weeks)

Interferon alpha-2b plus ribavirin - 33% sustained response rate.

The second group received the above regimen with the addition of ribavirin, 1000-1200 mg/day, at day 11 (group B).

All patients were followed up for 24 weeks after completion of therapy.

At the end of treatment, the virological response was noted in one of ten (10%) patients in group A and in 8 of 15 (54%) patients in Group B.

The sole end treatment responder in Group A and three in Group B relapsed on follow-up.

The apparent improvement in response in Group B compared to Group A nearly reached statistical significance (Group B 5/15 vs. Group A 0/10; $P=0.06$).

The research group concluded that a 36-week high-dose induction interferon mono-therapy did not yield sustained responses in previous non-responders to standard dose interferon.

However, the same regimen with ribavirin yielded a 33% sustained response rate, nearly reaching statistical significance.

Dr Malik, speaking on behalf of his fellow authors, commented, "The therapy was well tolerated, despite the higher doses of interferon used and the addition of ribavirin.

He concluded, "High-dose interferon with ribavirin appears to be a therapeutic option for non-responders to conventional interferon mono-therapy."

21. On March 13th, 2002 it was announced that Boston AIDS Activist Dunn had died

An HIV-infected woman who raised money for a new liver for herself after her insurance company refused to pay for the procedure died Tuesday following two unsuccessful transplants.

Belynda Dunn, a 51-year-old AIDS activist, died at the University of Pittsburgh Medical Center.

Dunn underwent a transplant procedure March 5, but the liver did not function and was removed, hospital spokeswoman Lisa Rossi said. She received another transplant Friday.

While the second liver apparently functioned, an obstruction formed in her lung and she died of multi-organ failure. Her doctors said the obstruction could have been a complication of the surgery.

Dunn never regained consciousness from either transplant, Rossi said.

Her case stirred debate over the wisdom of giving an organ transplant to someone with HIV - a procedure that has become more common in recent years with medical advances against the AIDS virus.

Dunn suffered from liver damage caused by Hepatitis C, but her health maintenance organization, Neighborhood Health Plan, refused to cover it on grounds that the procedure is experimental for those who have the AIDS virus.

She campaigned to convince insurers that HIV does not make liver transplants any riskier.

Dunn had to raise money for her procedure, which normally costs about \$208,000. Mayor Tom Menino stepped forward to lead the campaign, which netted about \$275,000, including \$100,000 from Neighborhood Health Plan.

"I am very saddened to hear of the passing of Belynda," the mayor said. "She fought a valiant battle not only for her own life but for countless others with HIV and Hepatitis C."

Neighborhood Health Plan had no immediate comment.

Dunn said she contracted Hepatitis C 30 years ago when she received a blood transfusion while giving birth. She said she contracted HIV through sex in 1991.

She founded AIDS Action's Who Touched Me Ministry, which provides HIV education and prevention through black churches in Boston.

Five years ago, doctors and insurers routinely rejected AIDS patients for transplants, in part because of their lower life expectancies. Since transplant recipients must take drugs to suppress the immune system and prevent it from rejecting the new organ, doctors assumed the medication would worsen problems in HIV patients.

But in the past few years, as new drugs have saved the lives of HIV patients, doctors are beginning to perform more transplants. In 1999, five transplants were reported to the United Network for Organ Sharing. In 2000, there were 11.

However, some doctors and insurance companies still do not support transplants for HIV patients.

22. On March 13th, 2002 SciClone Pharmaceuticals announced that Thymalfasin Plus Interferon is Successful in Phase II Hepatitis B Study.

SciClone Pharmaceuticals said on Wednesday that a combination therapy of interferon and its immune-enhancing drug Zadaxin (thymalfasin) demonstrated a 71% sustained response rate in hepatitis B patients, based on 12-month follow-up data from an independent phase II study in Turkey. The response rate for the combination therapy compared with just a 10% sustained response for patients who received interferon monotherapy. Investigators presented the follow-up data at the World Congress of Gastroenterology in Bangkok.

In the original study, 21 patients with anti-HBe-positive chronic hepatitis B received 26 weeks of Zadaxin plus interferon followed by 26 weeks of interferon monotherapy. Another 10 patients in the study received 52

weeks of interferon monotherapy alone. The treatment phase for each arm ended in late 2000.

At the end of a 6-month, treatment-free follow-up period, 76% of patients receiving Zadaxin plus interferon showed a sustained response, as measured by normalization of ALT and the disappearance of hepatitis B virus DNA. In comparison, only 40% of patients receiving interferon monotherapy showed a sustained response.

But it was the 12-month follow-up results that identified the real responders, SciClone Medical Director Dr. Eduardo Martins told Reuters Health, noting the sustained response rate in the interferon monotherapy group plunged to 10% after 12 months.

"Relapses are the critical problem in treating hepatitis B and other viral diseases," said Dr. Martins. "The significance [of the data] is the ability to evaluate the use of the combination therapy down the line."

SciClone officials said Zadaxin is under review for approval in Turkey as a hepatitis B treatment and that a phase III trial may not be necessary to gain approval. A research group in Turkey initiated the phase II study, with SciClone providing the drug for the investigation.

Earlier this month, SciClone reported that a preliminary analysis of a 319-patient randomized phase III trial in Japan revealed that 24% of the study group demonstrated a successful interruption of hepatitis B virus replication after receiving Zadaxin monotherapy. Patients in the phase III trial had been receiving one of two doses of Zadaxin for 6 months, followed by 12 months of observation.

SciClone is also testing Zadaxin in a phase III trial with Roche's Pegasys (pegylated interferon alfa-2a) as a combination therapy for hepatitis C.

23. On March 14th, 2002 the press released an article titled: US Panel Advises Tattooed and Pierced Not Give Blood

U.S. health advisers voted on Thursday to continue a policy that requires people who have been pierced or tattooed to put off donating blood for a year after the procedure, but said those who have received acupuncture can safely give blood.

The advisers to the Food and Drug Administration (news - web sites) (FDA) said they were concerned that loose regulation of tattoo and piercing establishments meant non-sterile procedures might be used, increasing the potential for transmission of viruses.

"In a non-sterile environment, I have very serious concerns about tattooing and body piercing," said panelist James Allen of Scientific Technologies Corp. of Phoenix, Arizona.

The panelists recommended that blood banks try to verify if tattoos or piercings were performed at a licensed facility.

The FDA usually follows the advice of its panels.

Currently, people who have received a tattoo, a piercing, or acupuncture in a non-sterile environment must wait a year before donating blood. As a result, about 100,000 people are turned away from donating each year, blood banks estimate.

The concern is that these people may have contracted viruses such as hepatitis B or hepatitis C through dirty needles or reused tattoo inks, and that these infections may be too recent to be picked up by blood screening. That worry has grown with the increased popularity of tattooing and piercing.

One study of New York state university students found that half had body piercings, and 23 percent had tattoos.

Miriam Alter, of the viral hepatitis division of the U.S. Centers for Disease Control and Prevention, told the committee that based on available studies, tattoo and piercing recipients are not at increased risk for viruses. CDC is recommending against a routine ban on donations from people with tattoos or body piercings.

Blood banks also said that new testing procedures now catch these viruses early in the infection process, which means contaminated blood can be discarded.

But panelists said there still is a risk of contamination.