



HCV ADVOCATE EASL 2007 NEWS REVIEW

[EASL 2007 Index](#)

Update - April 16th 2007

Hepatitis C

- [Analysis: Shorter therapy for hepatitis C?](#)
- [Achillion Presents Positive Data on Novel Mechanism for Treating HCV at EASL Annual Meeting](#)
- [Psychiatric Disorders No Reason to Exclude Hepatitis C Patients From Peginterferon-Alfa2b Plus Ribavirin Treatment: Presented at EASL](#)
- [Hepatitis C Patients With Advanced Kidney Disease Benefit From Peginterferon-Alfa-2a: Presented at EASL](#)

Hepatitis B

- [Adefovir And Lamivudine Combo Is Effective In Lamivudine-Resistant Hepatitis B Patients](#)
- [Liver Cirrhosis Linked to Hepatitis B Virus Genotypes and Mutants: Presented at EASL](#)

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Analysis: Shorter therapy for hepatitis C?

By ED SUSMAN

<http://www.sciencedaily.com>

BARCELONA, Spain, April 15 (UPI) -- Hepatitis C virus patients today face a

yearlong, grueling treatment regimen in hopes they can achieve a virtual cure of the disease, but preliminary trial results indicate a drug in development could allow a dramatically shorter treatment course.

"The result of this study has elevated our hopes that we can reduce the time of treatment for this disease," Ira Jacobson, chief of gastroenterology and hepatology at Weill Medical College of Cornell University, New York, told United Press International.

Jacobson was one of the investigators who treated hepatitis C patients with the oral drug telaprevir, an investigational small molecule that inhibits the protease enzyme of the virus, preventing reproduction.

The interim results of the study were presented at the weekend's conclusion of the 42nd annual meeting of the European Association for the Study of the Liver, attended by more than 5,600 clinicians in Barcelona, Spain.

The encouraging results with telaprevir were presented by John McHutchison, professor of medicine at Duke University Medical Center in Durham, N.C., who said that a "highly significant" number of patients were able to achieve complete viral suppression -- undetectable levels on the most sensitive assay -- within four weeks of treatment.

"About 79 percent or 138 of 175 patients infected with genotype 1 hepatitis C virus -- the most common and most difficult to treat form of the disease -- were able to achieve undetectable levels of the virus after four weeks of therapy with telaprevir plus pegylated interferon alfa-2a and ribavirin compared to 11 percent of patients treated with just pegylated interferon alfa-2a and ribavirin," he told UPI.

The current standard of care for hepatitis C virus infection is 48 weeks of interferon - a once-a-week injection, plus twice daily oral ribavirin. "By the time a patient gets to the second 24 weeks of this treatment, he or she is often really miserable," Jacobson said. The drugs have flu-like symptom side effects.

McHutchison said that an equally important part of the interim results was a small study of 20 patients who tested the theory that they if they could get the virus under control rapidly -- by four weeks -- and then continued on medication for 12 weeks they could stop taking all medication.

He said nine patients achieved the criteria for stopping, and 20 weeks after discontinuation of medicine six of those patients remained with undetectable virus

levels.

"Even though the number of patients who were able to achieve this was small, we believe we have achieved proof of concept that we can shorten the treatment period using telaprevir," McHutchison told UPI.

"We have to realize that these are interim results and we have to wait to see if this rapid viral response does indeed become a sustained viral response," he said. A sustained viral response - undetectable virus six months after ending treatment -- has been shown to be tantamount to a durable cure.

"We agree that the data is very encouraging," said Frank Duff, executive director for virology at Roche in Nutley, N.J., who was not involved in the trial. Roche makes pegylated interferon and ribavirin (Copegus) used in the trial.

"These are still early results," he said. "We still need to run the data and see how this pans out over the 48 weeks and that it does result in a sustained viral response. But this is all going into a very positive direction."

He noted that Roche is also investigating ways of shortening the treatment period. He pointed out that patients infected with genotypes 2 and 3 of hepatitis C virus already have a shortened 24-week therapy.

McHutchison said that in his trial, adverse side effects that were associated with telaprevir included rash, nausea, pruritus, diarrhea, anemia and vomiting. He noted that these are the same side effects seen with ribavirin so there maybe some interaction between the two medications.

In the study, now being replicated in Europe and the Americas, researchers randomly assigned 80 patients to the standard of care and 180 other patients to various treatment schedules involving telaprevir plus interferon and ribavirin.

The drug is being co-developed by Vertex of Cambridge, Mass., and Tibotec, Cork, Ireland.

Achillion Presents Positive Data on Novel Mechanism for Treating HCV at EASL Annual Meeting

<http://www.prnewswire.com/>

-NS4A Antagonist Demonstrates Clinical Activity, a Novel Mechanism of Action

and In Vitro Compatibility with other HCV Inhibitors-

NEW HAVEN, Conn., April 16 /PRNewswire-FirstCall/ -- Achillion Pharmaceuticals, Inc. (Nasdaq: ACHN) today announced the presentation of data validating the clinical antiviral activity of one of Achillion's NS4A antagonists, ACH-806, for the treatment of hepatitis C virus (HCV) infection at the 42nd Annual Meeting of the European Association for the Study of the Liver (EASL). In three separate presentations, Achillion researchers discussed the potent antiviral activity in HCV-infected subjects, synergy with other classes of HCV inhibitors, and the unique mode of action of a NS4A antagonist. Achillion has shown that blocking NS4A, a viral protein that binds to a portion of HCV protease, inhibits HCV replication. This program is part of a collaboration and exclusive license agreement with Gilead Sciences for the research, development and commercialization of compounds for the treatment of chronic HCV.

In a late-breaker session on April 14th at 5:00 PM, John Pottage, M.D., Senior Vice President and Chief Medical Officer at Achillion, discussed clinical data in a presentation titled, "Short-term Antiviral Activity and Safety of ACH-806 (GS-9132), an NS4A Antagonist, in HCV Genotype 1 Infected Individuals." The randomized, double-blind, placebo-controlled dose-escalation trial measured the antiviral activity, safety and pharmacokinetics of 300 mg of ACH-806 or placebo, dosed orally twice daily as a monotherapy over 5 days. The mean change in HCV RNA (log₁₀) at day 5 was a decrease of 0.91 from baseline for treated subjects versus an increase of 0.05 for control subjects. Elevations in serum creatinine (a marker of kidney function) were observed in ACH-806 treated subjects and were reversible after completion of dosing.

"This study provides the first demonstration of human antiviral activity of an NS4A antagonist for HCV," said Dr. Pottage. "While we and our partner Gilead decided to discontinue development of ACH-806 based upon the increase in serum creatinine levels, we do not believe this effect was target-related. The antiviral activity of the compound validates NS4A as a novel therapeutic target and therefore supports our continued work with Gilead to identify and evaluate next-generation compounds with the same mechanism of action."

A second presentation on April 12 at 6:30 PM, titled "In Vitro Evaluation of Combination Treatment of ACH-806 with Interferon, VX-950 and NM 107," was led by Mingjun Huang, Ph.D., Senior Director of Virology at Achillion, who discussed in vitro evaluations of ACH-806 in combination with interferon, a protease inhibitor, and a polymerase inhibitor. The data revealed that the NS4A antagonist did not show in vitro cross-resistance with agents from these other HCV

therapeutic classes, and that NS4A antagonism appears to have a synergistic antiviral effect in combination in vitro with the HCV protease inhibitor VX-950 and the polymerase inhibitor NM 107.

Finally, in a third presentation on April 12 titled "ACH-806: A Potent Inhibitor of HCV Replication with a Novel Mechanism of Action," Dr. Huang described the novel mechanism of action of NS4A antagonists. Achillion's studies demonstrated that these antagonists block the formation of functional viral replication complexes, thereby preventing HCV replication independent of protease or polymerase inhibition.

"The high mutation rate of HCV necessitates the combination use of drugs with complimentary mechanisms of action in order to suppress viral resistance. Therefore, the possibility that candidates with the unique NS4A antagonism mechanism may be complementary to protease and polymerase inhibitors will be an important benefit in treating HCV infection," stated Pottage.

About Hepatitis C

Hepatitis C is a viral liver disease, caused by infection with the hepatitis C virus. Globally, it is estimated that more than 170 million people have chronic hepatitis C, including about three million in the United States. Chronic hepatitis C is a leading cause of cirrhosis, a common cause of hepatocellular carcinoma, and is the leading cause of liver transplantation in the United States.

About Achillion

Achillion is a biopharmaceutical company focused on the discovery, development and commercialization of innovative treatments for infectious diseases. Achillion is currently developing treatments for HIV infection, chronic hepatitis C infection and serious hospital-based bacterial infections. For more information on Achillion Pharmaceuticals, please visit the company's web site at <http://www.achillion.com> or call Achillion at 1-203-624-7000. ACHN-G

This press release includes forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995 that are subject to risks, uncertainties and other factors, including statements with respect to completion and success of Achillion's preclinical studies and clinical trials of Achillion's drug candidates. Among the factors that could cause actual results to differ materially from those indicated by such forward-looking statements are: unexpected regulatory actions or delays; uncertainties relating to results of clinical trials, including additional data relating to ongoing clinical trials; Achillion's ability to obtain additional funding required to conduct its research, development and

commercialization activities and Achillion's dependence on its collaboration with Gilead Sciences. These and other risks are described in the reports filed by Achillion with the U.S. Securities and Exchange Commission, including its Annual Report on Form 10-K for the year ended December 31, 2006.

All forward-looking statements reflect Achillion's expectations only as of the date of this release and should not be relied upon as reflecting Achillion's views, expectations or beliefs at any date subsequent to the date of this release. Achillion anticipates that subsequent events and developments may cause these views, expectations and beliefs to change. However, while Achillion may elect to update these forward-looking statements at some point in the future, it specifically disclaims any obligation to do so.

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Psychiatric Disorders No Reason to Exclude Hepatitis C Patients From Peginterferon-Alfa2b Plus Ribavirin Treatment: Presented at EASL

By Jill Stein
<http://www.docguide.com>

BARCELONA, SPAIN -- April 16, 2007 -- A history of psychiatric disorders should not be a contraindication to treatment with peginterferon-alfa2b plus ribavirin in patients with genotype 2 or 3 hepatitis C, according to data presented here at the European Association for the Study of the Liver (EASL).

Jean-Philippe Lang, MD, chief, psychiatry service, Centre Hospitalier Erstein, Erstein, France, reported results in 641 patients infected with G2/G3 virus who were treated with peginterferon alpha-2b plus ribavirin.

"Clinical trial data indicate that adherence differentially affects response to therapy depending on hepatitis C genotype," Dr. Lang said in his presentation on April 14th. For patients with genotype 1, adherence is closely related to treatment outcome, with higher sustained virological response (SVR) rates reported in adherent patients.

For genotype 2 or 3 patients, SVR rates are similar among G2/G3 patients who meet the 80:80:80 rule and among those who are less adherent.

With the 80:80:80 rule, at least 80% of the planned peginterferon-alfa and 80% of planned ribavirin doses are taken for at least 80% of the duration of the planned treatment.

Overall, 460 patients had no prior psychiatric disorders, and 181 had prior psychiatric disorders. The 2 groups were similar with respect to most baseline demographic, virological, and histological characteristics.

Mean duration of treatment (28.4 vs 29.4 weeks, $P = .87$), rate of early treatment cessation (13% vs 13%, $P = .89$), adherence to ribavirin plus peginterferon at month 6 (54% vs 51%, $P = .566$) and SVR (92% vs 83%, $P = .151$) did not differ significantly between the groups with past psychiatric disorders and the group without past psychiatric disorders.

Dr. Lang said that the study is the first prospective, community-based investigation to assess treatment adherence among patients with G2/G3 HCV infections.

The study was supported by Roche.

[Presentation title: A Prospective, Multicenter, Observational Study on Adherence With Viral Hepatitis C treatments (CHEOBS) Study: Impact of Past Psychiatric Disorders on Sustained Virologic Response (SVR). Abstract 607]

Adefovir And Lamivudine Combo Is Effective In Lamivudine-Resistant Hepatitis B Patients

<http://www.medicalnewstoday.com/>

Jill Stein

Long-term treatment with adefovir dipivoxil (ADV, HepseraR) and lamivudine provides multiple benefits in lamivudine-resistant patients with chronic hepatitis B,

researchers announced at the 42nd Annual Meeting of the European Association for the Study of the Liver (EASL).

The results, reported by an Italian group, showed that the combination decreased the risk of genotypic resistance to adefovir and prevented both virological rebound and clinical resistance for up to three years.

Long-term therapy with lamivudine is initially effective but genotypic hepatitis B resistance develops in about 25% of patients at one year and in 71% by four years, principal investigator Professor Pietro Lampertico, who is an assistant professor of gastroenterology at the University of Milan, said.

Add-on ADV therapy has been established as an effective treatment strategy for patients developing lamivudine resistance but the long-term risk of genotypic resistance to ADV and the impact of ADV combined with lamivudine on the progression of cirrhosis has not been known, he added.

In the trial, 145 patients received 10 mg/d of adefovir as add-on therapy to ongoing lamivudine treatment.

HBV DNA was assessed every two months, and drug resistance was assessed annually in viremic patients.

Most patients achieved a virological and biochemical response (80% and 84%) for up to three years. None developed a virological or clinical breakthrough regardless of the degree of viral suppression.

No patient developed genotypic resistance for rtA181V and rtN236T. Three patients developed the rtA181T mutation as a mixed viral population with rtA181A while responding to therapy.

Combination therapy prevented clinical decompensation in all cirrhotic patients.

Professor Lampertico concluded that the data demonstrate that the adefovir-lamivudine combination is an effective and safe treatment strategy for lamivudine-resistant patients for at least three years.

Approximately one million individuals are infected with the hepatitis B virus in Europe every year. Of these, roughly 90,000 become chronically infected carriers.

The study was sponsored by Gilead. www.gilead.com

Liver Cirrhosis Linked to Hepatitis B Virus Genotypes and Mutants: Presented at EASL

<http://www.docguide.com>:

By Jill Stein

BARCELONA, SPAIN -- April 16, 2007 -- Hepatitis B virus (HBV) genotype C and A1762/G1764A mutants are independent risk factors for liver cirrhosis, according to data reported here at the 42nd Annual Meeting of the European Association for the Study of the Liver (EASL).

Y. L. Chen, MD, consultant, division of hepatology, National Taiwan University, Taipei, Taiwan, and colleagues investigated the effects of genotype, pre-core and basal core promoter (BCP) mutants of HBV, independently and interactively, on the progression of liver cirrhosis.

"Reported risk factors for chronic hepatitis b virus-related cirrhosis include active viral replication, presence of hepatitis B e antigen (HBeAg), advanced age, increased alanine aminotransferase level, and coinfection with the hepatitis delta virus," Dr. Chen said in a presentation on April 13th.

"It has been shown that patients with genotype C are more often HBeAG positive and have more active viral replication than genotype B patients, and genotype C results in a more advanced liver disease and a lower response rate to antiviral therapy," he added.

There have been some reports that the BCP and precore mutants result in a loss of HBeAg. However, the effects of these mutants on the development of liver cirrhosis remains unclear, he said.

The trial included 3,573 untreated individuals, who were hepatitis B surface antigen (HbsAg) positive and anti-HCV-seronegative.

Serum samples in these individuals were tested for HBV viral load and genotype.

A subcohort of 1,477 individuals with HBV DNA levels greater than or equal to 3104 copies/mL was tested for precore (G1896A) and BCP mutants (A1762T/G1764A).

The incidence rates of liver cirrhosis per 100,000 person-years for participants

infected with HBV genotype B and C were 746.9 and 1532.04, respectively.

The incidence rates for persons infected with wild and mutant type HBV precore stop codon 1896 were 1915.1 and 862.4, respectively.

For individuals infected with wild and typical mutant type HBV BCP 1762/1764, rates were 885.3 and 2146.8, respectively.

The effects of precore mutant on liver cirrhosis risk was most significant in HBeAg negative subjects and in subjects with HBV DNA levels less than 106 copies/mL, while the effect of BCP mutants was predominant in HBeAg-positive subjects.

"Taking subjects with wild type on both precore and BCP as referent, subjects with precore wild type and BCP mutant had a significantly higher risk of developing liver cirrhosis, while those with pre-core typical mutant and BCP wild type had a significantly lower risk," Dr. Chen said.

[Presentation title: Risk of Liver Cirrhosis Associated With Genotype and Mutants of Hepatitis B Virus. Abstract 222]

Hepatitis C Patients With Advanced Kidney Disease Benefit From Peginterferon-Alfa-2a: Presented at EASL

<http://www.docguide.com>:

By Jill Stein

BARCELONA, SPAIN -- April 16, 2007 -- Low-dose peginterferon-alfa-2a is effective in patients with chronic hepatitis C virus (HCV) infection who are undergoing haemodialysis for end-stage renal disease (ESRD), according to the interim results of an ongoing trial.

Markus Peck-Radosavljevic, professor, division of gastroenterology and hepatology, University of Vienna, Vienna, Austria, presented these results here on April 14th at the 42nd Annual Meeting of the European Association for the Study of the Liver (EASL).

"Patients with ESRD and chronic HCV are at increased risk of disease progression and decreased graft survival after transplantation," Dr. Peck-Radosavljevic explained.

The preliminary results were from 80 non-cirrhotic, interferon-naïve patients with

chronic HCV and ESRD who were undergoing dialysis and were randomised to peginterferon alfa-2a (40KD) 135 mcg/week or 90 mcg/week for a total of 48 weeks of treatment.

The primary endpoint was sustained virological response, defined as undetectable serum HCV RNA (<50 IU/mL) 24 weeks after the end of treatment.

The 2 treatment groups were similar with respect to gender, mean age, mean body weight, mean level of alanine aminotransferase (ALT), ALT quotient, HCV genotype, mean HCV RNA and mean number of dialysis sessions per week.

Results at 12 weeks showed that in patients receiving peginterferon alfa-2a 135 mcg/week, there were significantly more virological responders at week 12 than in the group receiving 90 mcg/week (61% vs 37%, respectively). However, a significant difference was not observed at week 24.

Only in the difficult-to-treat patients with high viral loads was a clinically relevant difference still present between the 2 dose groups at week 24 (45% vs 25%).

The frequency of adverse events and laboratory abnormalities was similar in the 2 treatment arms.

"These interim results show that treatment with peginterferon-alfa 2a (40 KD) is effective and has acceptable tolerability in chronic HCV patients who have ESRD and are undergoing haemodialysis," Dr. Peck-Radosavljevic said.

The study was supported by Roche.

[Presentation title: Use of Low-Dose Peginterferon Alfa-2a (40KD) (Pegasys) to Treat Hepatitis C-Infected, End-Stage Renal Disease Patients undergoing Hemodialysis: Interim Results from a Randomized Study. Abstract 628]